Muscle, Fat and Performance during Androgen Deprivation for Prostate Cancer

By

Patrick James Owen
B Ex Sp Sci (Hons)

Submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy

Deakin University

February, 2018

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Contribution statement

I developed the initial study concepts (cross-sectional study and randomised controlled trial) with A/Prof Steve Fraser (PhD supervisor; Deakin University, Australia) and Prof Robin Daly (PhD supervisor; Deakin University, Australia). A/Prof Fraser and Prof Daly secured internal (Deakin University) and external (Omniblend, Ostelin and YMCA Victoria; in-kind) funding. Significant input into the development of these protocols was also provided by Prof Patricia Livingston (PhD supervisor; Deakin University, Australia), Ms Niamh Mundell (PhD candidate and Accredited Exercise Physiologist; Deakin University, Australia) and Mr Jack Dalla Via (PhD candidate; Deakin University, Australia). Development of the clinician referral-based recruitment pathways was aided by A/Prof Jeremy Millar (referring clinician; The Alfred, Australia). I was primarily responsible for obtaining ethics for these studies in accordance with Deakin University and Alfred Health Human Research Ethics Committee; which included six separate amendments. I registering the randomised controlled trial with the Australian and New Zealand Clinical Trials Registry and the nutritional supplement under the Clinical Trial Notification Scheme of the Therapeutics Goods Administration of the Australian Government. I developed all standardised documentation used in these studies and obtained author/organisation approval, when applicable, for the use of all outcome measures. I operated as project manager for these studies from inception until write up of this thesis, with Mr Dalla Via then assuming this role. This role included participant screening, organisation of testing sessions (participant and researcher coordination), dissemination of results to participant and clinicians and compliance with Deakin University and Alfred Health Human Research Ethics Committee annual reports and adverse event reporting. Whilst in this role, I led all recruitment via the pathways mentioned in this thesis with assistance from Ms Mundell and Mr Dalla Via. As part of recruitment, I developed promotional material, organised and conducted prostate cancer support group presentations and sent email and mail correspondence. I performed and analysed all radiological scans presented in this thesis in consultation with Dr Timo Rantalainen (University of Jyväskylä, Finland) and Prof Daly. Assistance with the collection of performance outcomes was provided by Ms Mundell, Mr Dalla Via and Mr Stephen Foulkes (Honours candidate; Deakin University). Ms Mundell implemented and oversaw the exercise training intervention examined in the randomised controlled trial. I entered all data presented in this thesis, performed all statistical analyses and

interpreted all results under the guidance of A/Prof Fraser, Prof Daly and Prof Livingston. My contributions as lead author for the three manuscripts emanating from this thesis are detailed in Authorship Statement A, B and C.

Full Name: Patrick James Owen

Signed:

Date: 05/02/2018

Authorship statement A

1. Details of publication and executive author

Title of Publication		Publication details
Efficacy of a multi-component exercise program and nutritional supplementation on musculoskeletal health in men treated with androgen deprivation therapy for prostate cancer [IMPACT]: Study protocol of a randomized controlled trial		Trials. 18(1), 451.
Name of executive author	School/Institute/Division if based at Deakin; Organisation and address if non-Deakin	Email or phone
Mr Patrick J Owen	Institute for Physical Activity and Nutrition (IPAN), School of Exercise and Nutrition Sciences	p.owen@deakin.edu.au

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Mr Patrick J Owen	Institute for Physical Activity and Nutrition (IPAN), School of Exercise and Nutrition Sciences	Muscle, Fat and Performance during Androgen Deprivation for Prostate Cancer
If there are multiple authors, give a full description of HDR thesis author's contribution to the publication (for example, how much did you contribute to the conception of the project, the design of methodology or experimental protocol, data collection, analysis, drafting the manuscript, revising it critically for important intellectual content, etc.)		
PJO (and RMD, SFF) developed the study concept and initiated the project. PJO (and RMD, PML, NLM, JDV, JLM, SFF) provided significant input into the development of the protocol. PJO drafted the manuscript. PJO (and NLM, JDV, JLM) will implement the protocol and oversee collection of the data. PJO (and RMD, PML, NLM, JDV, JLM, SFF) read, contributed and approved the final manuscript.		
<i>I declare that the above is an accurate description of my contribution to this paper, and the contributions of other authors are as described below.</i>	Signature and date	11/01/2018

4. Description of all author contributions

Name and affiliation of author	Contribution(s) (for example, conception of the project, design of methodology or experimental protocol, data collection, analysis, drafting the manuscript, revising it critically for important intellectual content, etc.)
Mr Patrick J Owen ¹	As above
Prof Robin M Daly ¹	As above
Prof Patricia M Livingston ²	As above
Ms Niamh L Mundell ¹	As above
Mr Jack Dalla Via ¹	As above
A/Prof Jeremy L Millar ³	As above
A/Prof Steve F Fraser ¹	As above

¹ Deakin University, Geelong, Australia, Institute for Physical Activity and Nutrition (IPAN), School of Exercise and Nutrition Sciences. ² Deakin University, Geelong, Australia, Faculty of Health. ³ Alfred Health Radiation Oncology, The Alfred, Melbourne, Australia.

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Mr Jack Dalla Via		11/01/2018
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The role of exercise training in men with prostate cancer		Topics in Geriatric Rehabilitation. 31(4), 246-250.
Name of executive author	School/Institute/Division if based at Deakin; Organisation and address if non-Deakin	Email or phone
Mr Patrick J Owen	Institute for Physical Activity and Nutrition (IPAN), School of Exercise and Nutrition Sciences	p.owen@deakin.edu.au

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Mr Patrick J Owen	Institute for Physical Activity and Nutrition (IPAN), School of Exercise and Nutrition Sciences	Muscle, Fat and Performance during Androgen Deprivation for Prostate Cancer
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PJO drafted the manuscript. PJO (and SFF) read, contributed and approved the final manuscript.		
<i>I declare that the above is an accurate description of my contribution to this paper, and the contributions of other authors are as described below.</i>	Signature and date	11/01/2018

4. Description of all author contributions

Name and affiliation of author	Contribution(s) (for example, conception of the project, design of methodology or experimental protocol, data collection, analysis, drafting the manuscript, revising it critically for important intellectual content, etc.)
Mr Patrick J Owen ¹	As above
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Title of Publication		Publication details
Lifestyle guidelines for managing adverse effects on bone health and body composition in men treated with androgen deprivation therapy for prostate cancer: An update		Prostate Cancer and Prostatic Diseases. 20(2), 137-145.
Name of executive author	School/Institute/Division if based at Deakin; Organisation and address if non-Deakin	Email or phone
Mr Patrick J Owen	Institute for Physical Activity and Nutrition (IPAN), School of Exercise and Nutrition Sciences	p.owen@deakin.edu.au

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As above	Institute for Physical Activity and Nutrition (IPAN), School of Exercise and Nutrition Sciences	Muscle, Fat and Performance during Androgen Deprivation for Prostate Cancer
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PJO drafted the manuscript. PJO (and RMD, PML, SFF) read, contributed and approved the final manuscript.		
<i>I declare that the above is an accurate description of my contribution to this paper, and the contributions of other authors are as described below.</i>	Signature and date	11/01/2018

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Mr Patrick J Owen ¹	As above
Prof Robin M Daly ¹	As above
Prof Patricia M Livingston ²	As above
A/Prof Steve F Fraser ¹	As above

¹ Institute for Physical Activity and Nutrition, School of Exercise and Nutrition Sciences, Deakin University, Geelong, Australia. ² Faculty of Health, Deakin University, Geelong, Australia.

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Acknowledgements

I would like to express my sincere gratitude to:

A/Prof Steve Fraser, for first introducing me to the world of research and providing a mentorship that allowed me to produce this thesis and achieve the goals I set at the start of candidature.

Prof Robin Daly, for sharing your wealth of knowledge and helping develop my skills as a researcher. Your guidance has vastly improved my ability to write scientifically, think critically and conduct research to a high standard. Moreover, your work ethic and dedication to research has served as a constant inspiration.

Prof Patricia Livingston, for your attention to detail when reviewing my writing, as well as your insights into designing, conducting and reporting clinical trials.

Niamh Mundell, for all your dedication in the conducting of the IMPACT study. Most notably, without your coordination and facilitation of the exercise training intervention, the trial would not have been feasible.

Jack Dalla Via, for your contributions to participant coordination, data collection and recruitment with the IMPACT study.

Steve Foulkes, for your assistance with the IMPACT study during and following your Honours year.

Dr Timo Rantalainen, for sharing your expertise and enthusiasm of soft tissue analysis.

A/Prof Daniel Belavy, for giving me the opportunity to contribute to various projects over the past year that furthered my skills as a researcher and for your invaluable counsel whenever required.

Dr Shane McIver and Natalie Hakman, for providing countless teaching opportunities that allowed me to support myself throughout candidature and develop my teaching skills.

My fellow postgraduate students at Deakin University, both past and present, for your continued friendship and support: Dr Daniel van den Hoek, Dr Sarah Hall, Matthew Clarkson, Dr Christopher Latella, Anthony May, Dr Brianna Larsen, Dr Christopher Brandner, Dr Clint Miller, Dr Grace Vincent and Dr Daniel Wundersitz. I wish you all the best with your future endeavours.

Sue and Paul Owen, for your love and support.

Shane Jurgenstein and Jarryd 'Sauce' Moss, for your friendship and banter.

The referring clinicians and participants involved in our study, for dedicating your valuable time to support our research.

Thank you.

List of publications and presentations emanating from this thesis

Journal articles

[Chapter 3] Owen PJ, Daly RM, Livingston PM, Mundell NL, Dalla Via J, Millar JL & Fraser SF. Efficacy of a multi-component exercise program and nutritional supplementation on musculoskeletal health in men treated with androgen deprivation therapy for prostate cancer [IMPACT]: Study protocol of a randomized controlled trial. *Trials*. 2017;18(1), 451.

[Chapter 2] Owen PJ, Daly RM, Livingston PM & Fraser SF. Lifestyle guidelines for managing adverse effects on bone health and body composition in men treated with androgen deprivation therapy for prostate cancer: an update. *Prostate Cancer and Prostatic Diseases*. 2017;20(2), 137-145.

[Chapter 2] Owen PJ & Fraser SF. The role of exercise training in men with prostate cancer. *Topics in Geriatric Rehabilitation*. 2015;31(4), 246-250.

Conference presentations

Owen PJ, Daly RM, Mundell NM, Dalla Via J, Livingston PM & Fraser SF. Are current definitions of (pre)sarcopenia suitable for older men treated with androgen deprivation therapy for prostate cancer? Deakin University School of Exercise and Nutrition Sciences Research Symposium, 2016. Melbourne, Australia. Published: *Australasian Journal on Ageing*. 2018;37(Suppl. S1), 43-44.

Owen PJ, Daly RM, Mundell NL, Dalla Via J, Foulkes SJ, Livingston PM & Fraser SF. 2017. Does use of androgen deprivation therapy increase the risk of sarcopenia? 18th Asia-Pacific Prostate Cancer Conference, 2017. Melbourne, Australia. Published: *BJU International*. 2017;120(Suppl. S1), 13-18.

Owen PJ. Symposium: Sarcopenia in cancer. The role of exercise training in cancer patients with sarcopenia. First Australia and New Zealand Conference on Sarcopenia and Frailty, 2017. Melbourne, Australia. Published: *Australasian Journal on Ageing*. 2017;36(Suppl. S1), 17-22.

Owen PJ, Daly RM, Livingston PM, Mundell NM, Dalla Via J & Fraser SF. Effects of androgen deprivation for prostate cancer on muscle health. Deakin University School of Exercise and Nutrition Sciences Higher Degree by Research School Research Symposium, 2016. Melbourne, Australia.

Mundell NL, Foulkes SJ, Owen PJ, Daly RM & Fraser SF. Case studies of exercise programming modifications to reduce falls and fracture risk in elderly men with prostate cancer treated with androgen deprivation therapy. Research to Practice (Exercise & Sports Science Australia), 2016. Melbourne, Australia.

Dalla Via J, Daly RM, Owen PJ, Mundell NL & Fraser SF. Risk of sarcopenia in prostate cancer survivors treated with androgen deprivation therapy. Research to Practice (Exercise & Sports Science Australia), 2016. Melbourne, Australia.

Owen PJ, Daly RM, Livingston PM & Fraser SF. Improving Musculoskeletal Health during Prostate Cancer Androgen Deprivation Therapy [IMPACT Study]. Deakin University School of Exercise and Nutrition Sciences Higher Degree by Research School Research Symposium, 2014. Melbourne, Australia.

Owen PJ, Livingston PM, Daly RM & Fraser SF. Musculoskeletal health in prostate cancer patients treated with androgen deprivation therapy: A review of current practice guidelines. Prostate Cancer World Congress, 2013. Melbourne, Australia. Published: *BJU International*. 2013;112(Suppl. S1), 54-65.

Community presentations

Owen PJ. 2017: Prostate cancer information evening (hosted by Box Hill Prostate Cancer Support Group and Prostate Cancer Foundation of Australia). Prostate cancer research at Deakin.

Owen PJ. 2016: Prostate cancer awareness evening (hosted by Ringwood Prostate Cancer Support Group Inc. and Prostate Cancer Foundation of Australia). The role of exercise training for prostate cancer survivors.

Owen PJ. 2016: Lions Club of Box Hill. The role of exercise training and nutritional supplementation for older adults.

Owen PJ. 2015: Prostate cancer awareness evening (hosted by Box Hill Prostate Cancer Support Group and Prostate Cancer Foundation of Australia). The role of exercise training for prostate cancer survivors.

Owen PJ. 2015: Rotary Club of Frankston. The role of exercise training and nutritional supplementation for older adults.

Owen PJ. 2014-15: Various prostate cancer support groups affiliated with the Prostate Cancer Foundation of Australia (Geelong, Mornington Peninsula, Heidelberg, Essendon, Bayside Kingston, Diamond Valley, Westgate, Melbourne and Ringwood). The role of exercise training and nutritional supplementation for prostate cancer survivors.

Research support for this thesis

Australian Postgraduate Award (APA) scholarship (2013-2016)

Centre for Physical Activity and Nutrition Research, School of Exercise and Nutrition Sciences, Deakin University, Australia (2013-2016)

Institute for Physical Activity and Nutrition, School of Exercise and Nutrition Sciences, Deakin University, Australia (2016-2018)

Omniblend, Australia (2013-2018)

Ostelin, Australia (2013-2018)

YMCA Victoria, Australia (2013-2018)

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Abstract

Introduction: Prostate cancer (PCa) is one of the most frequently diagnosed male cancers worldwide. One treatment, androgen deprivation therapy (ADT), is commonly prescribed and has been shown to increase survival in appropriately selected patients. However, the treatment-induced hypogonadism is often accompanied with a myriad of adverse effects, including those that negatively impact muscle, fat and performance outcomes. Therefore, ADT-treated men may be living longer, but are at risk of both age- and treatment-related complications. The overall aim of this thesis was to quantify outcomes of muscle, fat and performance in men treated with ADT when compared to PCa (men diagnosed with PCa, not treated with ADT) and healthy controls (men not diagnosed with PCa), and assess the feasibility of implementing a multi-component exercise program combined with protein, calcium and vitamin D supplementation (Ex+ProCaD) compared to usual care in ADT-treated men.

Methods: This thesis presents two studies that form part of a larger 52-week randomised controlled trial (RCT), which examined the efficacy of Ex+ProCaD compared to usual care in men treated with ADT for PCa. The first study presented was a nested cross-sectional study performed parallel to the baseline assessment of the RCT and examined differences in muscle, fat and performance outcomes between men treated with ADT when compared to PCa and healthy controls. The second study presented examined the feasibility of implementing the first 26 weeks of the RCT.

Results: The cross-sectional study showed that height, weight, body mass index and diet were similar between the three groups, but ADT-treated men were four years older and tended to be less physically active (23-30%; $P=0.054$). After adjusting for age and physical activity, total body fat mass was 3.3-5.0 kg ($P < 0.05$) greater in men treated with ADT compared to PCa controls, but there was no difference in total body and regional lean mass. When adiposity was considered, ADT-treated men had 10-12% ($P < 0.05$) lower appendicular lean mass adjusted for body mass index and 5.6-6.4% ($P < 0.05$) lower forearm percent muscle cross-sectional area compared to controls. Absolute muscle strength was similar between groups, but when expressed relative to body weight, men treated with ADT had 13-21% ($P < 0.05$) lower muscle strength compared to controls. Whilst only two ADT-treated men had sarcopenia, these men had a higher proportion ($P < 0.001$) of pre-sarcopenia when appendicular lean mass

was adjusted for body mass index (42%) compared to PCa (15%) and healthy (7%) controls. These differences were not observed when appendicular lean mass was adjusted for height alone. Men treated with ADT had 15-36% ($P < 0.05$) greater storage of fat within subcutaneous depots when compared to controls, whereas visceral and intermuscular fat was similar. The majority of subcutaneous fat depots (excluding android region) were shown to be positively associated with ADT duration ($P < 0.05$). Forearm muscle density was shown to negatively correlate with ADT duration ($P < 0.05$). The RCT had a high participant retention rate (96%). Adherence was high for the supplement (mean, 92-93%) and modest for the exercise program (mean, 60%). A relatively high proportion (81%) of men in the intervention group reported an adverse event, although only 16% were confirmed to be related to the intervention and the vast majority (97%) were determined to be mild or moderate in terms of severity. Across the ten separate recruitment pathways considered, clinician referral (43%) and PCa support groups (29%) yielded the greatest proportion of enrolled participants. A total of 149 potential participants were screened, which resulted in 42 participants at the time of write up for this thesis. Among the first 28 participants to complete the 26-week intervention, 21-50% were unable to complete at least one measure of muscle strength due to pre-existing comorbidities. Data from the initial 28 participants tended to show that when compared to usual care, Ex+ProCaD led to net improvements in lean mass (0.2-1.4 kg), fat mass (-0.1 to -0.9 kg), muscle strength (8.0-19%), functional muscle power (8.6%) and functional capacity (12-14%).

Conclusions: The following key themes emerged from this thesis and may be used to guide clinical practice guidelines and future research: 1) Men treated with ADT for PCa had greater amounts of fat when compared to non-ADT counterparts; therefore, muscle-based outcomes should be considered relative to body size or adiposity in these men, 2) Current definitions of sarcopenia and sarcopenic obesity were limited in men treated with ADT for PCa; thus, the development of additional risk stratification tools specific to this clinical population group are warranted, 3) The greater amounts of fat observed in men treated with ADT for PCa tended to be stored in subcutaneous depots and supersede age-related plateaus/losses; hence, the long-term risk associated with this pattern of fat accumulation should be explored in these men, 4) The recruitment of men treated with ADT for PCa into a lifestyle intervention was challenging; therefore, future trials should consider including clinician referral and PCa support groups to ensure sample size targets are met in a timely manner, and 5) Men treated

with ADT for PCa tended to respond positively to a multi-modal exercise training combined with multi-nutrient supplementation; thus, the incorporation of similar interventions into usual care for this susceptible population group should be considered pending results of the larger 52-week RCT.

List of abbreviations

One-repetition maximum.....	1-RM
Three-repetition maximum.....	3-RM
Areal bone mineral density.....	aBMD
Activity of daily living.....	ADL
Androgen derivation therapy.....	ADT
Appendicular lean mass.....	ALM
Appendicular lean mass adjusted for body mass index.....	ALM _{BMI}
Appendicular lean mass adjusted for height and fat mass.....	ALM _{HFM}
Appendicular lean mass index.....	ALMI
Analysis of covariance.....	ANCOVA
Bioelectrical impedance analysis.....	BIA
Bone mineral density.....	BMD
Body mass index.....	BMI
Confidence interval.....	CI
Cross-sectional area.....	CSA
Computed tomography.....	CT
Coefficient of variation.....	CV
Dual-energy x-ray absorptiometry.....	DXA
European Working Group on Sarcopenia in Older People.....	EWGSOP
Multi-component exercise program combined with protein, calcium and vitamin D supplementation.....	Ex+ProCaD
Foundation for the National Institutes of Health.....	FNIH
Gonadotropin-releasing hormone.....	GnRH
Homeostatic model assessment of insulin resistance.....	HOMA-IR
Hazard ratio.....	HR
Intraclass correlation coefficient.....	ICC
International Working Group on Sarcopenia.....	IWGS
Low-density lipoprotein.....	LDL
Magnetic resonance imaging.....	MRI
Odds ratio.....	OR
Prostate cancer.....	PCa
Peripheral quantitative computed tomography.....	pQCT
Progressive resistance training.....	PRT

Prostate-specific antigen.....	PSA
Randomised controlled trial.....	RCT
Rating of perceived exertion.....	RPE
Relative risk.....	RR
Spearman's rho.....	r_s
Whey protein concentrate 80%.....	WPC80

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Chapter 1

General introduction

1.1 Introduction

Prostate cancer (PCa) is one of the most frequently diagnosed male cancers in developed countries ^[1]. Similarly, PCa accounts for a substantial proportion of male cancer-related deaths worldwide ^[1]. However, advancements in diagnostics and treatment options have led to five-year relative survival rates approaching 100% internationally ^[2]. Therefore, men diagnosed with PCa are now living longer, but may be at risk of both age- and treatment-related complications.

One treatment, androgen deprivation (hormone) therapy (ADT), is commonly prescribed to men with both metastatic ^[3] and non-metastatic PCa ^[4] and has been shown to increase survival in appropriately selected patients ^[5-9]. The aim of this treatment is to suppress androgens to castration levels in an attempt to slow the growth and spread of PCa ^[3, 10]. However, despite potential benefits to survival in appropriately selected men, the treatment-induced hypogonadism is often accompanied with a myriad of adverse effects ^[11-14], including those that negatively impact muscle (lean mass and muscle cross-sectional area [CSA] ^[15-21]), fat (fat mass and CSA ^[17-23]) and performance (muscle strength and functional capacity [the performance outcome of a muscle or muscle group, whether independent or inclusive of other domains of functional capacity ^[24] ^[25-34]). Moreover, the interplay between these adverse effects may hinder muscle quality (the intricate muscular structural changes associated with muscle function ^[35]) ^[15]. However, the true extent to which muscle and performance may be compromised in this susceptible population group is unknown due to methodological inconsistencies and the lack of assessment of these components concurrently within the same sample ^[15-23, 25-34, 36-38].

In addition to muscle, ADT-induced region-specific changes in fat are poorly understood ^[17-23], which limits the ability to assess the influence of these changes on cardiometabolic risk and other potential health complications. There is also a general lack of available data quantifying muscle quality (intermuscular fat infiltration) in men treated with ADT ^[15]. This limits the ability to determine why physical performance may alter at rates non-parallel to changes in muscle mass, size or strength within this population group; a phenomenon in healthy older adults commonly suggested to be partially due to the accumulation of intermuscular fat mass ^[39]. Understanding this relationship is of increased interest in men treated with ADT, due to the accelerated accumulation of fat associated with this treatment, and the further complications that

may occur when fat infiltration of muscle occurs ^[40]. Therefore, future research should ensure multiple components of muscle, fat and performance are quantified in men treated with ADT, due to the potential musculoskeletal, cardiometabolic and functional complications associated with these outcomes when compromised. Moreover, there is a need to ensure that valid and reliable assessment methods are utilised, and known confounding variables (e.g. age, disease status, physical activity and diet) are accounted for during analyses.

Once appropriately quantified, there is also a need to assess the risk of further adverse events with ongoing treatment due to any potential alterations to muscle, fat and performance outcomes. Collectively, any such compromises may predispose these men to an increased risk of falls, fractures, cardiometabolic disease, functional impairment and mortality ^[41-49] and partially explain the substantial economic burden of PCa on the Australian healthcare system ^[50]. Although in their infancy, the application of pre-defined syndromes, such as sarcopenia ^[51-53] and sarcopenic obesity ^[54, 55], may assist in quantifying the risk of adverse health outcomes in these men; thus potentially allowing for those at the greatest risk to be identified and addressed. To date, no studies have applied composite definitions of sarcopenia (those including measures of both muscle and performance) or sarcopenic obesity in an attempt to quantify the consequences in men treated with ADT, and future research would benefit clinical practice via this investigation and stratification of risk.

Given the potential ADT-induced negative alterations to muscle, fat and performance outcomes, as well as the possible risk of further adverse events, interventions are warranted within this susceptible population group. There is emerging evidence that lifestyle interventions, such as exercise training and to a lesser extent nutritional supplementation, may improve or maintain muscle, fat and performance outcomes in men treated with ADT, which may in turn reduce the likelihood of further clinical complications ^[14, 56-59]. To date, previously evaluated interventions have been limited to singular modalities (e.g. exercise training only) and due to the severity and breadth of ADT-induced adverse effects, including those beyond the scope of this thesis (e.g. compromised bone health, sexual dysfunction and psychological distress ^[60]), these men may benefit from a multifactorial approach that includes a combination of various modalities of exercise training in conjunction with nutritional supplementation. To

date, no studies have examined this type of approach and thus there is a need to assess the feasibility and efficacy of such interventions.

1.2 Experimental design

This thesis presents two studies that form part of a larger 52-week randomised controlled trial (RCT), the IMPACT study (Owen et al. 2017. *Trials*. 18(1), 451; Appendix A), which was designed to examine the efficacy of a multi-component exercise program combined with protein, calcium and vitamin D supplementation compared to usual care in men treated with ADT for PCa. The first study presented in this thesis includes data from a nested cross-sectional study performed parallel to the baseline assessment of the RCT which examined differences in muscle, fat and performance outcomes between men treated with ADT, PCa controls (men diagnosed with PCa, not treated with ADT) and healthy controls (men not diagnosed with PCa). The second study presented includes data from the first 26 weeks of the RCT in terms of the feasibility of conducting the trial.

1.3 Overall aims

The overall aim of this thesis was to quantify outcomes of muscle, fat and performance in men treated with ADT when compared to PCa and healthy controls (Chapters 4 and 5), and assess the feasibility of implementing a multi-component exercise program combined with protein, calcium and vitamin D supplementation compared to usual care in ADT-treated men (Chapter 6).

1.4 Specific aims

1. To compare lean mass (total body, appendicular, arm and leg; dual-energy x-ray absorptiometry [DXA]) and muscle CSA (forearm [66% radius] and lower leg [66% tibia]); peripheral quantitative computer tomography [pQCT]) in men treated with ADT to PCa and healthy controls (Chapter 4).
2. To compare fat mass (total body, arm, leg, android, gynoid, abdominal visceral and abdominal subcutaneous; DXA) and CSA (forearm [66% radius] and lower leg [66% tibia]; pQCT) in men treated with ADT to PCa and healthy controls (Chapter 4 and Chapter 5).
3. To compare muscle strength (handgrip strength and three-repetition maximum leg press, chest press and seated row), functional muscle power (30-second sit-to-stand) and functional capacity (timed up-and-go, four-square step test, four

metre walk and Berg balance scale) in men treated with ADT to PCa and healthy controls (Chapter 4).

4. To compare the prevalence of pre-sarcopenia, sarcopenia, obesity and sarcopenic obesity in men treated with ADT to PCa and healthy controls (Chapter 4).
5. To compare muscle density (forearm [66% radius] and lower leg [66% tibia]; pQCT) as a marker of intermuscular fat in men treated with ADT to PCa and healthy controls (Chapter 5).
6. To assess the influence of duration of ADT use on lean mass, muscle CSA, fat mass and CSA, muscle density, muscle strength, functional muscle power and functional capacity in men treated with ADT (Chapter 4 and Chapter 5).
7. To assess the feasibility (recruitment, attrition, adherence, data collection and safety) of a multi-component exercise program combined with protein, calcium and vitamin D supplementation when compared to usual care in men treated with ADT (Chapter 6).

1.5 Specific hypotheses

1. Lean mass and muscle CSA would be lower in men treated with ADT when compared to PCa and healthy controls (Chapter 4).
2. Fat mass and CSA would be greater in men treated with ADT when compared to PCa and healthy controls (Chapter 4 and Chapter 5).
3. Muscle strength, functional muscle power and functional capacity would be lower in men treated with ADT when compared to PCa and healthy controls (Chapter 4).
4. Pre-sarcopenia, sarcopenia, obesity and sarcopenic obesity would have a greater prevalence in men treated with ADT when compared to PCa and healthy controls (Chapter 4).
5. Muscle density (as a marker of intermuscular fat mass) would be lower in men treated with ADT when compared to PCa and healthy controls (Chapter 5).
6. Duration of ADT use would positively correlate with fat mass and CSA, and negatively correlate with lean mass, muscle CSA, muscle density, muscle strength, functional muscle power and functional capacity in men treated with ADT (Chapter 4 and Chapter 5).
7. The multi-component exercise program combined with protein, calcium and vitamin D supplementation when compared to usual care in men treated with

ADT would be feasible in terms of recruitment, attrition, adherence, data collection and safety (Chapter 6).

1.6 Significance

Given the impact of PCa as a significant global and Australian public health issue, and the continued use of ADT for managing this disease, understanding the severity of treatment-induced adverse effects on muscle, fat and performance outcomes is warranted. This is of further clinical importance given the potential musculoskeletal, cardiometabolic and functional consequences associated with these potential changes and the need to quantify risk in this susceptible population group. Furthermore, as men diagnosed with PCa are now living longer, there is increased importance on enhancing the quality of years lived, which may benefit from the quantification of risk factors and subsequent management via intervention. These interventions are imperative to reduce the burden of disease at the individual level, as well as at the public healthcare system level from an economical perspective. Therefore, the findings of this thesis will assist in the clinical management of treatment-induced adverse effects on muscle, fat and performance outcomes in men treated with ADT, by quantifying these adverse effects, evaluating means of risk stratification and presenting an evidence-based intervention within this clinical population group.

1.7 Organisation of the thesis

The thesis is organised around the specific research aims noted above. In Chapter 2, a review of the current literature relevant to the specific aims of the thesis is presented. Chapter 2 also integrates two recent review journal articles where the PhD candidate was the lead author (Owen et al. 2015. *Topics in Geriatric Rehabilitation*. 31(4), 246-250; Owen et al. 2017. *Prostate Cancer and Prostatic Diseases*. 20(2), 137-145; Appendix B and Appendix C, respectively). In Chapter 3, the general methods implemented in the cross-sectional study and RCT are presented. Chapter 3 also integrates a recently accepted protocol journal article where the PhD candidate was the lead author (Appendix A). In Chapter 4, results from the cross-sectional study regarding total body lean and fat mass, muscle strength and functional capacity are presented. In Chapter 5, results from the cross-sectional study regarding regional fat mass and CSA are presented. In Chapter 6, feasibility outcomes of the RCT are presented. In Chapter 7, a general discussion relevant to the specific aims of the thesis and outcomes of the cross-sectional study and RCT is presented.

Chapter 2

Literature review

2.1 Overview

This chapter will introduce the concept of prostate cancer (PCa) as both a significant global and Australian public health issue. One treatment for PCa, androgen deprivation therapy (ADT), and the commonly reported treatment-induced adverse health effects known to impact muscle, fat and performance outcomes, will then be discussed. This will be followed with a specific emphasis on quantifying the risk associated with these outcomes both individually and collectively using the concepts of sarcopenia and sarcopenic obesity. Finally, potential interventions to manage these adverse effects in men treated with ADT will be discussed. Two review journal articles emanating from the literature review in which the PhD candidate was the lead author will be incorporated within this chapter. The first focused on the specific role of exercise training in men with PCa (Appendix A), and the second discussed lifestyle guidelines, with a specific emphasis on exercise training and nutritional supplementation, for managing the adverse effects of ADT on muscle and fat outcomes (Appendix B).

2.2 The prostate gland and prostate cancer

The prostate gland is an accessory organ of the male reproductive system, located below the bladder and vas deferens ^[61]. The primary function of the prostate is to secrete an alkaline fluid that forms part of seminal fluid and facilitates male fertility ^[61]. PCa refers to a malignant tumour of prostatic cell origin ^[61]. Although potentially aggressive, PCa tends to progress slowly and may lead to symptoms similar to those associated with benign prostatic hyperplasia, such as impaired genitourinary function ^[61].

2.3 Prostate cancer epidemiology

Worldwide, PCa was the second most frequently diagnosed male cancer in 2012, estimated to account for greater than 1.1 million diagnoses; which was 15% of worldwide male cancer incidence ^[1]. Moreover, approximately 758,700 cases were estimated to occur in developed countries, and PCa was deemed the most commonly diagnosed male cancer across these regions ^[1]. Although incidence rates vary by more than 25-fold throughout different regions of the world, Australia and New Zealand have the greatest age-standardised PCa incidence ^[1], which has been attributed to the increased availability and use of prostate-specific antigen (PSA; an enzyme associated with prostate gland enlargement and inflammation ^[61]) testing ^[62]. In 2014, it was estimated that 17,050 new cases of PCa were diagnosed in Australia, accounting for

approximately 25% of total male cancer incidence ^[63]. Furthermore, the most recently reported 5-year prevalence for PCa in Australia was 86,207 cases, accounting for approximately 42% of active male cancer ^[63]. Therefore, PCa has both the greatest incidence and prevalence of any male cancer in Australia.

Globally, PCa accounted for the fourth most common cause of death from any male cancer in 2012, totalling 307,500 deaths; which was approximately 6.6% of worldwide male cancer-related deaths ^[1]. Moreover, in developed countries such as Australia, PCa was estimated to cause 3,390 male cancer-related deaths in 2014 ^[63]. This represents approximately 13% of male cancer-related deaths in Australia and ranks second only to lung cancer ^[63]. Furthermore, in 2011, PCa accounted for 4.4% of all male deaths in Australia, with an additional 1,803 deaths attributed to PCa as a contributing cause of death ^[50]. In 2011-12, PCa also accounted for 51,328 hospitalisations in Australia; 11% of all cancer-related admissions ^[50]. In addition, the most recent estimates from the Australian Institute of Health and Welfare ^[50] concluded that PCa costs the Australian health-care system \$349 million per year.

The five-year relative survival rate of PCa is now over 90% internationally, with developed countries such as the United States of America and Australia having reported 99% ^[2] and 93% respectively ^[63]. Specifically, Australia observed an increase in five-year relative survival rate from 59% in 1986 to 90% in 2007 (Figure 2.1). Hence, men diagnosed with PCa are now living longer, but may be at risk of age-related and treatment-related health issues.

Figure 2.1. Five-year relative survival rates of prostate cancer in Australia from 1986 to 2007 (adapted from Australian Institute of Health and Welfare ^[50]).

2.4 Prostate cancer screening, diagnosis and treatment

PCa screening practices vary globally in terms of availability, utilisation and interpretation ^[62]. The most common forms include monitoring PSA levels over time and digital rectal examination ^[64]. Although these tests are informative and have been shown to correlate with PCa risk, they are not diagnostic, and suspicious outcomes will require transrectal ultrasound guided biopsies to acquire tissue for histopathological examination ^[64]. Once histologically confirmed, numerous treatment options, both passive and active, become available based on PCa stage and grade ^[64, 65]. The most commonly utilised treatments for localised PCa include active surveillance, radical prostatectomy (surgery) and radiotherapy ^[64]. ADT and chemotherapy are often reserved for advanced PCa ^[65]. The following section focuses on the therapeutic role and potential adverse effects of ADT for the treatment of PCa.

2.5 Androgen deprivation therapy

The aim of ADT is to reduce the activity and/or concentration of androgens, such as testosterone, to castration levels; which limits the growth and spread of PCa ^[3, 65]. This is most commonly attained pharmacologically, but may also be achieved via surgical orchiectomy ^[3, 65]. Despite the significantly lower cost of an orchiectomy, men are more often treated pharmacologically due to the reversible nature of the hypogonadism (impaired function of the testes ^[61]; clinically diagnosed with repeated fasting early-morning measures of testosterone < 8.0 nmol/L ^[66]) ^[67]. Pharmacological ADT is

achieved via gonadotropin-releasing hormone (GnRH) agonists and antagonists, anti-androgens or a combination of GnRH agonists and anti-androgens, known as combined androgen blockage ^[65]. Various modalities of ADT, including those administered neoadjuvant or adjuvant with other treatments, improve survival in appropriately selected men with PCa ^[5-9]. However, due to various assessments of survival, modalities of treatment and follow-up durations, an exact figure that represents the increased overall survival due to ADT does not exist. In contrast, the evidence that ADT prolonged survival in men with localised PCa remains limited and therefore debated ^[68-70]. Despite these findings, the use of ADT is commonly prescribed to men with both metastatic ^[3] and non-metastatic PCa ^[4]. In 2008-09, it was estimated that 23,500 Australian men received ADT via GnRH agonists ^[56]. Upon repeating this analysis for 2014-15, approximately 25,500 men were receiving ADT via GnRH agonists ^[71]. Thus, ADT remains the most common cause of severe male hypogonadism in Australia.

2.6 Adverse effects of androgen deprivation therapy

Despite potential benefits to overall survival in appropriately selected men, the hypogonadism induced via ADT has been associated with numerous adverse effects ^[11-14]. In healthy eugonadal men (fasting early-morning measures of testosterone > 12 nmol/L ^[66]), androgens, such as testosterone, assist in various metabolic processes which include maintaining musculoskeletal health, reducing cardiometabolic risk and improving aspects of health-related quality of life, including sexual function and cognition ^[72]. Therefore, men with ADT-induced hypogonadism may experience declines in the aforementioned aspects of health ^[11-14]. Given that these men are often of older age (mean age of diagnosis in Australia, 68 years ^[63]), have experienced the diagnosis of PCa and likely undergone additional non-hormonal treatment (e.g. prostatectomy or radiotherapy for curative intent upon diagnosis ^[64]), the compounded impact of these factors on the adverse effects of ADT should be considered ^[73-75].

The following sections focus on the age-related, PCa-related and ADT-related changes on the interconnected components of muscle, fat and performance, and the commonly utilised clinical measures used to quantify these measures. In addition to the definitions outlined in Chapter 1, the following definitions are used throughout the thesis:

- Lean mass: an areal assessment of tissue used as a measure of regional or total body muscle mass ^[76].

- Muscle cross-sectional area (CSA): a volumetric assessment of a slice of tissue used as a measure of regional muscle mass ^[77].
- Muscle density: a volumetric assessment of a slice of tissue used as a measure of intermuscular fat mass (any storage of lipids in adipocytes between muscle fibres, also referred to as intramuscular fat, or muscle groups located beneath the fascia of a muscle ^[40]; excluding intramyocellular lipids, which are stored within the muscle cells themselves and are not always harmful to the cell ^[78]) and therefore muscle quality (e.g. a decrease in muscle density suggests an increase in intermuscular fat mass) ^[77].
- Muscle strength: the ability of a muscle or muscle group to exert maximal force externally ^[24].
- Muscle power: the ability of a muscle or muscle group to exert force externally as quickly as possible ^[24].
- Functional capacity: the ability to perform activities of daily living (ADL) ^[79].
- Subcutaneous fat mass: the fat mass located beneath the skin within the hypodermis region ^[77].
- Visceral fat mass: the fat mass located within the abdominal cavity, between various organs (also known as intra-abdominal fat mass) ^[77].

2.6.1 Quantifying the risk associated with changes in muscle, fat and performance

Collectively, negative alterations to muscle, fat and performance may lead to additional complications beyond those associated with each individual factor, and thus an assessment of accumulated risk is warranted. Two potential concepts that may assist in quantifying accumulative risk are sarcopenia and sarcopenic obesity. The following sections will discuss these concepts and their components with regards to changes associated with ageing, PCa diagnosis and non-hormonal treatment and ADT.

Sarcopenia

Sarcopenia was initially described by Rosenberg ^[80] as the loss of lean mass associated with the ageing process. Since then, sarcopenia has been deemed a syndrome (with varying stages; Table 2.1) and evolved to include a decline of lean mass, muscle strength and functional capacity commonly associated with the ageing process ^[40, 53]. The cut-off points for lean mass, muscle strength and functional capacity for diagnosing sarcopenia in men are currently debated; with various groups having

proposed and adopted different criteria (Table 2.2) [51-53, 81-87]. To date, these definitions of sarcopenia are limited in that they do not include a measure of muscle density as a marker of muscle quality and future research would benefit from this investigation. Nonetheless, various definitions of sarcopenia have been associated with adverse health outcomes such as increased risk of falls [81, 88, 89], fractures [48, 88, 90], functional impairment [88, 91-94] and mortality [88, 91, 95, 96]; however, the true extent of risk associated with the diagnosis of sarcopenia is unknown due to the lack of universal consensus regarding its definition.

Table 2.1. Stages of sarcopenia.

Stage	Muscle mass	Muscle strength	Functional capacity
Pre-sarcopenia	↓		
Sarcopenia	↓	↓	OR ↓
Severe Sarcopenia	↓	↓	↓

Adapted from Cruz-Jentoft et al. [53].

Table 2.2. Proposed cut-off points for diagnosing sarcopenia in men.

Method	Authors	Lean mass	Muscle strength	Gait speed
EWGSOP	Baumgartner et al. [81]	ALMI, 2 SD below healthy young men ($\leq 7.26 \text{ kg/m}^2$)	-	-
Residual	Newman et al. [82]	Residual of ALM - ALM_{HFM} , $\leq 20^{\text{th}}$ percentile (-2.29)	-	-
Lowest quintile	Delmonico et al. [83]	ALMI, $\leq 20^{\text{th}}$ percentile ($\leq 7.25 \text{ kg/m}^2$)	-	-
EWGSOP	Cruz-Jentoft et al. [53]	ALMI, 2 SD below healthy young men ($\leq 7.26 \text{ kg/m}^2$)	Handgrip strength, $< 30 \text{ kg}$	Gait speed, $< 0.8 \text{ m/s}$
ESPEN-SIG	Muscaritoli et al. [85]	%LM, 2 SD below healthy young men ($\leq 37\%$)	-	Gait speed, $< 0.8 \text{ m/s}$
IWGS	Fielding et al. [52]	ALMI, $\leq 20^{\text{th}}$ percentile ($\leq 7.23 \text{ kg/m}^2$)	-	Gait speed, $< 1.0 \text{ m/s}$
SCWD	Morley et al. [86]	ALMI, 2 SD below healthy ethnicity-matched young men ($\leq 6.81 \text{ kg/m}^2$)	-	Gait speed, $< 1.0 \text{ m/s}$
AWGS	Chen et al. [87]	ALMI, 2 SD below healthy young men ($\leq 7.0 \text{ kg/m}^2$)	Handgrip strength, $\leq 20^{\text{th}}$ percentile ($< 26 \text{ kg}$)	Gait speed, $< 0.8 \text{ m/s}$
FNIH	Studenski et al. [51]	ALM_{BMI} , < 0.789	Handgrip strength, $< 26 \text{ kg}$	Gait speed, $< 0.8 \text{ m/s}$

%LM, percent lean mass; ALM, appendicular lean mass; ALM_{BMI} , appendicular lean mass adjusted for body mass index; ALM_{HFM} , appendicular lean mass adjusted for height and fat mass [$\text{ALM}_{\text{HFM}} (\text{kg}) = -22.48 + 24.14 \times \text{height (m)} + 0.21 \times \text{total fat mass (kg)}$]; ALMI, appendicular lean mass index; SD, standard deviation; AWGS, Asian Working Group for Sarcopenia; ESPEN-SIG, European Society for Clinical Nutrition and Metabolism Special Interest Groups; EWGSOP, European Working Group on Sarcopenia in Older People; FNIH, Foundation for the National Institutes of Health; IWGS, International Working Group on Sarcopenia; SCWD, Society on Sarcopenia, Cachexia and Wasting Disorders.

In an attempt to establish a universal consensus, studies have attempted to assess the validity of various definitions of sarcopenia and their ability to predict adverse health outcomes ^[88, 97]. Cawthon et al. ^[88] applied numerous definitions of sarcopenia in an attempt to predict recurrent falls (two or more self-reported falls within a year), hip fractures, functional limitation and mortality in healthy community-dwelling older men (n=5,934; age, ≥ 65 years) when compared to age as a predictor alone. The authors concluded that although associated with increased prediction of recurrent falls (odds ratio [OR], 1.09-2.23) and mortality (OR, 1.22-3.60), risk estimates commonly varied between definitions and did not improve upon age alone as a predictor when assessing the four outcomes of interest. As a result, it was suggested that the application of these current definitions would be limited within the clinical setting for healthy community-dwelling men ^[88]. Furthermore, Bischoff-Ferrari et al. ^[97] assessed falls risk in 445 community-dwelling older adults (mean age, 71 years) and concluded that the Baumgartner et al. ^[81] (OR, 1.54; 95% confidence interval [CI], 1.09-2.18) and European Working Group on Sarcopenia in Older People (EWGSOP ^[53]; OR, 1.82; 95%CI, 1.24-2.69) definitions produced the highest predictive validity of falls among sarcopenic versus non-sarcopenic participants when compared to other proposed criteria that diagnosed sarcopenia (OR, 0.61-1.66, all non-significant). Of note, both of these definitions utilised the same cut-off points for lean mass, whilst the EWGSOP ^[53] definition slightly differed with the addition of compromised muscle strength or functional capacity required for diagnosis (Table 2.2). The findings of this study suggested that adjusting for height alone when measuring lean mass is pragmatic within healthy community-dwelling older adults ^[97]. Moreover, these findings demonstrated the improved predictability of falls when the additional measures of muscle strength or functional capacity were incorporated; thus, the use of lean mass alone is limited in predicting fall risk ^[97]. Opposing definitions have noted that adjusting appendicular lean mass (ALM) for height (ALMI) alone may underestimate sarcopenic status ^[82] and that adjusting ALM for body mass index (BMI; ALM_{BMI}) is required, to account for the increased muscle mass associated with increased BMI and how this may impact functional capacity ^[51, 54]. However, this confounding relationship appeared to be more apparent in women than men, particularly when gait speed was assessed as a predictor of functional capacity, and thus adjusting ALM for height alone appeared to be acceptable when applying the definition of sarcopenia to

older men ^[51]; although whether this applies to men treated with ADT is currently unknown.

Sarcopenic obesity

Sarcopenic obesity refers to a syndrome in which sarcopenia and obesity are concurrently present and has gained attention due to the likely compromising effect of age-related adiposity on muscle health (Figure 2.2). The initial implementation defined sarcopenia as ALMI (ALM divided by height [m] squared) two standard deviation below the mean of healthy younger men ($\leq 7.26 \text{ kg/m}^2$) ^[81] and obesity as a total body percent fat mass $> 27\%$ ^[98]. While the authors used the term sarcopenia, definitions of compromised lean mass alone are defined as pre-sarcopenia within this thesis. Moreover, this definition is likely limited in its ability to predict risk, as consensus population measures of obesity in men, such as BMI ($\geq 30 \text{ kg/m}^2$ ^[99]) and total body percent fat mass ($> 30\%$ ^[100]), were not utilised. Of these two measures, a total body percent fat mass $> 30\%$ has been commonly suggested as a more appropriate indicator of obesity when compared to BMI ^[101]; thus, this cut-off should be utilised when available. Since the initial proposal of sarcopenic obesity, the cut-off points for both the sarcopenia and obesity components have been debated (Table 2.3). These definitions are limited by the aforementioned issues with current sarcopenia definitions, as well as the lack of inclusion of muscle strength and functional capacity outcomes, thus deeming these definitions of pre-sarcopenia and obesity concurrently ^[51-53, 85-87]. Additionally, these definitions do not consider the role of varying regions of fat mass, such as visceral fat mass which has been shown to be more deleterious to health outcomes than subcutaneous depots ^[102, 103], and all apply a global definition of obesity, rather than considering a central obesity approach, which has been shown to be more proinflammatory when compared to global obesity ^[104]. A previous study that applied the seven definitions of sarcopenic obesity from Table 2.3 to 4,984 older adults (49% men; mean age of men, 70 years) observed a 19-fold difference in the prevalence of sarcopenic obesity in men pending differing cut-offs (range, 4.4-84%) ^[105]; thus suggesting the need for further large-scale trials to determine a consensus criteria for sarcopenic obesity that is capable of valid and reliable predictions of morbidity and mortality.

Figure 2.2. Effects of ageing on muscle and fat (adapted from Zamboni et al. ^[54]).

Table 2.3. Proposed cut-off points for diagnosing sarcopenic obesity in men.

Authors	Sarcopenia*/pre-sarcopenia [#]	Obesity
Baumgartner et al. ^[98]	ALMI, 2 SD below healthy young men ($\leq 7.26 \text{ kg/m}^2$)	Total body fat percentage, greater than median in older men ($> 27\%$)
Davison et al. ^[106]	LMI, lower 2 quintiles in older men ($< 9.12 \text{ kg/m}^2$)	Total body fat percentage, upper 2 quintiles in older men ($> 37.16\%$)
Bouchard et al. ^[107]	ALMI, 2 SD below healthy young men ($< 8.51 \text{ kg/m}^2$)	Total body fat percentage, established values ($> 28\%$) ^[24]
Kim et al. ^[108] A	ALMI, 2 SD below healthy young men ($< 7.40 \text{ kg/m}^2$)	Total body fat percentage, upper 2 quintiles in older men ($> 20.2\%$)
Kim et al. ^[108] B	Total body lean mass percentage, 2 SD below healthy young men ($< 35.7\%$)	Total body fat percentage, upper 2 quintiles in older men ($> 20.2\%$)
Kim et al. ^[108] C	ALMI, lower 2 quintiles in older men ($< 8.81 \text{ kg/m}^2$)	Total body fat percentage, upper 2 quintiles in older men ($> 20.2\%$)
Levine et al. ^[109]	ALM percentage, 2 SD below health young men ($< 25.7\%$)	Waist circumference, established values ($> 102 \text{ cm}$) ^[110]

* as defined by authors; [#] as defined in this thesis. ALMI, appendicular lean mass index; LMI, lean mass index; SD, standard deviation.

2.6.2 Measuring muscle, fat and performance

Lean mass and muscle cross-sectional area

Computed tomography (CT) and magnetic resonance imaging (MRI) are recognised as the gold standard for acquiring measures of muscle with high accuracy [40, 77, 111, 112]. However, these techniques are limited in the clinical and research setting due to the high costs of scan acquisition and data processing, complications with claustrophobic and severely obese individuals ($\text{BMI} \geq 40 \text{ kg/m}^2$), and in the case of CT, high exposure to ionising radiation [76, 111]. Therefore, alternative measures, such as dual-energy x-ray absorptiometry (DXA) and peripheral quantitative CT (pQCT), have been suggested for use in these settings [77, 113]. Rationale for the use of these methods include the relatively low cost, decreased reliance on highly trained personnel and accessibility to equipment in both the research and clinical setting [77, 112, 113]. Bioelectrical impedance analysis (BIA), both single and multi-frequency, is another tool that may be used to estimate lean mass within the clinical and research setting, specifically due to its high portability [112]. However, due to the lack of robust reliability data when compared to DXA and the notable influence of age, sex, race, health status and hydration on results, more robust measures such as DXA should be utilised when available [112].

DXA assessments of muscle include areal total body and regional (arms, legs, trunk) lean mass (Figure 2.3) which can be used to calculate additional measures such as total body lean mass index (total body lean mass divided by height [m] squared), ALM (sum of arm and leg lean mass), ALMI (ALM divided by height [m] squared) and ALM_{BMI} (ALM divided by BMI) [77]. These adjusted calculations allow for comparisons independent of body size and are currently used in various definitions of sarcopenia [76]. Measures of lean mass via DXA are highly correlated with measures from CT and MRI ($r > 0.91$, both [112]) in older adults and can be performed at high precision with coefficients of variation (CV) ranging from 0.4% to 1.1% [114]. However, one limitation of DXA is that it does not provide a measure of muscle quality [77]. Despite this, DXA is an appropriate assessment technique for total body and regional lean mass in the clinical and research setting, but may need to be paired with a tool capable of quantifying muscle quality, such as pQCT.

Figure 2.3. Example of dual-energy x-ray absorptiometry total body scan with regions of interest defined ^[76]. A, android; G, gynoid; H_L, head left; H_R, head right; L_L, lower limb left; L_R, lower limb right; T_L, trunk left; T_R, trunk right; U_L, upper limb left; U_R, upper limb right.

Muscle measures obtained via pQCT include muscle CSA and muscle density (Figure 2.4) ^[77]. Muscle density measured via standard CT has been shown to highly correlate with simulated intermuscular fat within a phantom device ($R^2=0.995$; CV of 0.5%) ^[115]. Measures of muscle CSA via pQCT at the upper leg (50% femur) highly correlated with MRI results at the same site ($r=0.78-0.92$) ^[116]. Furthermore, high precision in measuring lower leg (tibia) and forearm (radius) muscle CSA and density via pQCT has been demonstrated with CV ranging from 2.1% to 5.3% and 0.7% to 3.2% respectively ^[117]. Despite this, pQCT measures are limited to the slices at lower leg (tibia), upper leg (femur), forearm (radius) and upper arm (humerus) sites, and thus are unable to quantify total body or larger regions of muscle CSA. Of note, high-resolution pQCT is also available, but more research utilising this tool is required before its ability to quantify muscle parameters can be compared to current gold standards ^[77]. Therefore, pQCT is a suitable assessment technique to pair with DXA to overcome muscle quality limitations and obtain additional measures of regional muscle CSA in the clinical and research setting.

Figure 2.4. (A) Peripheral quantitative computed tomography scanner (XCT 2000, Stratec Medizintechnik GmbH, Pforzheim, Germany) positioned for lower leg (tibial) scan; (B) cross-sectional scan obtained at the lower leg (66% tibia) with muscle borders manually drawn ^[77].

Fat mass and cross-sectional area

Similar to the acquisition of muscle outcomes, MRI and CT are the gold standard for the assessment of fat, yet due to the aforementioned limitations, may not be feasible in the clinical and research setting ^[40, 76]. Alternatively, DXA can measure total body and regional fat mass with high precision (CV of 0.9-4.4%) ^[118] and correlation compared to MRI ($r=0.990$) and CT ($r=0.979$) at the same sites ^[119]. Various DXA algorithms have also been developed to estimate additional regions of interest, including abdominal visceral fat mass and subcutaneous fat mass, with abdominal visceral fat mass estimates highly correlated to MRI visceral fat volume ($r=0.90$) and CT visceral fat CSA ($r=0.83$) in overweight older men (mean age, 62-66 years; mean BMI, 29.7-32.3 kg/m²) ^[120]. Furthermore, these algorithms have been shown to predict abdominal visceral fat mass with high precision in obese adults (CV of 5.1%; mean age, 35 years; mean BMI, 35.1 kg/m²), with no difference observed when compared to phantom measures (CV of 4.8%; $P=0.670$). However, DXA has been shown to significantly underestimate mean total body fat mass when compared to MRI and CT (-4.67 kg and -5.23 kg, respectively) ^[119], which may be further confounded by previously reported limitations of total body assessments in obese participants ^[121] and inter- and intra-manufacturer variations in DXA scanners and algorithms ^[122, 123]; thus highlighting the importance of using a singular DXA scanner when possible and strictly adhering to manufacturer guidelines when analysing scans (e.g. the use of the estimate function in severely obese participants ^[76]). Despite these limitations, DXA is a suitable tool for

the acquisition of total body and regional measures of fat mass in older men in the clinical and research setting.

Fat outcomes obtained via pQCT include fat CSA and intermuscular fat CSA ^[77]. Whilst fat CSA can be obtained with high precision at the lower leg (tibia) and forearm (radius) sites (CV of 2.4-6.4%), intermuscular fat CSA measured with pQCT at the same sites has been shown to have a CV of 3.3-4.2% ^[117]; thus muscle density is a more appropriate measure of intermuscular fat. Measures of fat CSA obtained with pQCT have been shown to not differ from those obtained with MRI ($P=0.97$) ^[116] and therefore provide a more feasible method to quantify regional fat CSA within the clinical and research setting.

Muscle strength and power

Muscle strength is a routinely implemented assessment of muscle performance in older adults ^[24]. Isokinetic dynamometry, typically of the lower limbs, is considered the gold standard for assessing muscle strength ^[124]. However, due to the high costs and lack of portability, measures of hand-held dynamometry, specifically handgrip dynamometer strength, have been suggested to be more feasible in the clinical and research setting ^[112, 124] and therefore has been incorporated into various definitions of sarcopenia ^[51, 53, 87]. Furthermore, in comparison to other standard muscle strength testing, such as the one-repetition maximum (1-RM) protocols, hand-held dynamometry quantified muscle strength has been associated with decreased physical demand for participants, and reduced risk of accumulated fatigue in older adults ^[24, 125]. However, 1-RM protocols and protocols that use equations to calculate 1-RM outcomes, such as various three-repetition maximum (3-RM) protocols, remain commonly utilised within the research setting in older adults capable of completing these without the aforementioned concerns ^[24]. Currently, the Jamar hand dynamometer (Lafayette Instrument Company, Indiana, United States of America) is considered the gold standard hand-held measurement tool due to having the most extensive normative data ^[126] and results shown to highly correlate with isokinetic dynamometry lower limb strength in older adults ($r=0.91$; mean age, 83 years ^[127]). Furthermore, the Jamar hand dynamometer has a CV of 6.3% when used within clinical populations similar to men treated with ADT, such as those with advanced lung and gastrointestinal cancer ^[128]. However, despite the prevalent use of handheld dynamometry in the research setting, there is at present a lack of standardised protocol for assessing handgrip strength, and

thus drawing comparisons between studies must be performed with caution at times ^[126]. Efforts have therefore been made in an attempt to standardise this measure, and future trials should consider adopting this protocol to ensure reproducibility and comparison between trials ^[126]. Thus, handgrip dynamometer strength assessment is a suitable measure of muscle strength in older men and allows for the prediction of risk associated with sarcopenia ^[53], particularly in those with known comorbidities that may affect a true measurements of muscle strength obtained via 1-RM or 3-RM protocols.

Although not included in definitions of sarcopenia, muscle power is another measure of muscle performance that may be used to predict risk of adverse health outcomes ^[129]. The current gold standard for quantifying muscle power in older adults is debated and previously implemented measures include varying jump-based protocols, dynamometers, stair climb tests and the Wingate cycle test ^[129]; some of which may be contraindicated in older adults ^[24].

One measure proposed to be suitable for estimating lower-limb muscle power in older adults is the 30-second sit-to-stand test ^[130], which has been shown to be reliable (intraclass correlation coefficient [ICC], 0.84). The quantification of muscle power via the 30-second sit-to-stand test, as opposed to muscle strength outcomes, showed good correlation with the Nottingham power rig ($r=0.6$ ^[131]); however, its use may be limited to an overall measure of functional capacity due to elements of muscle strength and endurance concurrently demonstrated during the test.

Functional capacity

Functional capacity is a clinically relevant and meaningful outcome in older adults, as it can be reflective of ADLs by combining aspects of muscle performance, sensorimotor and cognitive process ^[132]. There are numerous tools for assessing functional capacity depending on the domain to be assessed (e.g. balance, mobility, range of motion, dexterity), which vary in task, duration, physical demand and feasibility; most of which aim to emulate ADLs ^[24, 112]. Valid and reliable measures in older adults (age, ≥ 60 years) include those such as the timed-up-and-go (falls risk, sensitivity=87%, specificity=87%; interrater ICC=0.98-0.99 ^[133]), four-square step test (falls risk, sensitivity=89%, specificity=85%; interrater and test-retest ICC of 0.99 and 0.98, respectively ^[134]) and Berg balance scale (falls risk, $r=0.46$ -0.62 when

compared to caregiver global rating ^[135]; interrater and test-retest ICC of 0.98 and 0.97, respectively ^[136]). Whilst there is no consensus on what is considered the gold standard for assessing functional capacity overall, a previous systematic review that examined the various tools in community-dwelling older adults (≥ 60 years) concluded that gait speed assessment was a valid ($r=0.74-0.93$) tool for assessing mobility limitation and ADL disability in the clinical setting due to the simplicity of administration (when performed over short distances; e.g. four metres) ^[112]. Moreover, short distance gait speed (i.e. four metres) has been shown to have similar reliability (ICC=0.96-0.97 ^[137]) in healthy older adults when compared to distances ranging two metres to one kilometre (ICC=0.94 ^[112]). Therefore, these measures of functional capacity are feasible within the clinical and research setting, with short-distance gait speed also providing risk assessment as part of the criteria for sarcopenia ^[53].

2.6.3 The effects of ageing on muscle, fat and performance in men

Lean mass and muscle cross-sectional area

In healthy men, the ageing process is commonly accompanied by annual decreases in total body lean mass ranging from approximately 0.5-1.0% beyond the age of 40-45 years ^[132, 138, 139], with this rate shown to accelerate after the fifth decade of life ^[139]. Despite lean mass varying substantially on an individual level at any given age, most men aged greater than 70 years can expect to possess approximately 80% of the total body lean mass present when aged 20-30 years ^[132]. The decline in lean mass associated with ageing may not be uniform across differing muscles and regions, as an MRI-based study that examined 268 men (age range, 18-88 years) observed a more than two-fold decrement in lower limb lean mass when compared to that of the upper limb ^[139]. These results have been replicated in CT-based ^[140] and DXA-based ^[141] studies; thus, ageing likely influences lean mass distribution in men.

Fat mass and cross-sectional area

During the ageing process, total body fat mass and total body percent fat mass commonly increased in men until the seventh decade, after which it typically remained stable or decreased slightly throughout the remainder of life ^[142]. Similar age-related observations have been made in other total body measures of fat, including BMI and total body fat mass index (total body fat mass divided by height [m] squared) ^[139]. In a cohort of 929 older men (mean age, 74 years), total body fat mass measured via DXA increased approximately 0.5 kg over a three year follow-up; which equated to a 0.7%

increase per year ^[143]. Furthermore, these changes corresponded with an approximate 0.8% increase in total body percent fat mass ^[143]. Similarly, a sample of 53 older men (mean age, 61 years) followed for 9.4 years demonstrated a 0.7% yearly increase in total body fat mass and 0.6% yearly increase in total body percent fat mass ^[144]. Of note, this study may have been limited when compared to the former ^[143] due to the use of hydrodensitometry (rather than DXA) and smaller sample size, but is strengthened by the duration of follow-up. Interestingly, despite the difference in mean age of participants, similar changes in fat mass were observed. Collectively, these studies highlighted the increases in fat mass often reported in older men. However, these two specific measures should both be interpreted with caution whenever reported as they do not account for height, lean mass and potential age-related changes in lean mass. Furthermore, neither of these measures quantified the location of fat and its accumulation, which may play a role in quantification of risk.

To date, longitudinal age-related changes in the distribution of fat accumulation in men are limited. A recent DXA-based cross-sectional analysis of 1,133 men (age range, 20-87 years; mean age, 63 years) reported that when compared to men aged 20-30 years, men aged ≥ 80 years had a 23% greater gynoid fat mass index (gynoid fat mass divided by height [m] squared) ^[145]. Moreover, age-predicted central fat mass index (central fat mass divided by height [m] squared), android fat mass index (android fat mass divided by height [m] squared) and visceral fat mass by the age of 70 years were 83%, 82% and 181% greater, respectively, when compared to 20-30 year old men ^[145]. Subcutaneous fat mass index (subcutaneous fat mass divided by height [m] squared) was also shown to increase with age, with men aged 50 years and 85 years demonstrating greater values of 42% and 61%, respectively, when compared to men aged 20-30 years ^[145]. Breakpoint ages in the accumulation of fat mass were also observed for various regions, including central fat mass (70 years), android fat mass (73 years), subcutaneous fat mass (50 years) and visceral fat mass (68 years). Of note, the measures reported in this study were strengthened by height adjustment, a common confounding variable in studies that have examined body composition. In addition, a sample of 869 older men (mean age, 79 years) followed for five years were reported to decrease CT-derived abdominal visceral, abdominal subcutaneous and thigh fat by 0.5%, 1.4% and 0.3% per year respectively ^[146]. Thus supporting the notion that fat slightly decreases during the seventh decade of life and beyond ^[142]. In summary, these data suggest that fat accumulation occurs at multiple regions of the body as men age

up until approximately the seventh decade. Furthermore, there appears to be greater accumulation at centralised sites and the accumulation of subcutaneous fat notably plateaus earlier. However, given the novelty of these studies, further investigation is warranted before definitive conclusion may be drawn regarding the age-related distribution of fat accumulation in men.

The ageing process is also associated with increased intermuscular fat ^[40, 147], however, various methodological flaws in previous studies, such as small sample sizes and lack of control for known covariates, limit the ability to draw conclusions on the true rate of intermuscular fat accumulation and whether the ageing process alone plays a causative role. One cross-sectional analysis reported that age was associated with an approximately 0.2% yearly increase in intermuscular fat mass in 111 men (age range, 19-84 years) ^[148]. In addition to the cross-sectional nature of these observations, the age range and lack of control for known covariates, including diet, physical activity and health status, should be noted when interpreting these results. To date, the largest longitudinal study followed 869 men (mean age, 79 years) for five years and reported that mid-thigh intermuscular fat CSA increased 9.7% per year ^[146]. Of note, these results were strengthened by being controlled for known confounding variables such as age, race, sex, smoking status, alcohol consumption and physical activity. A similarly sized longitudinal trial, which also accounted for numerous covariates such as race, health status and physical activity levels, followed 813 men (mean age, 74 years) over a five-year period and observed an increase in mid-thigh intermuscular fat CSA of 9.7% per year ^[84]. Interestingly, despite the older age at baseline in both longitudinal samples, sizeable and consistent increases in intermuscular fat CSA were observed; thus contrasting the plateau/slight decrease in other measures of fat commonly observed in men beyond the seventh decade.

Muscle strength and power

As men age, various aspects of performance decline, beyond what can solely be attributed to losses in lean mass ^[132]. There is evidence that the rate of decline in muscle strength is at least two-fold greater than the decline in lean mass ^[39]. Therefore, other processes must be involved, such as increased intermuscular fat (see ‘Fat mass and cross-sectional area’ subheading within this section), mitochondrial dysfunction (e.g. age-related declines in mitochondrial mass, activity of tricarboxylic acid cycle enzymes, oxygen consumption and adenosine triphosphate synthesis ^[149]) and motor

neuron loss (e.g. age-related reduction in motor units^[150])^[53]. Reid et al.^[151] examined these processes and attempted to quantify the physiological mechanisms responsible for a similar three year decrement in lower-limb muscle performance between healthy older adults (-8.5%; n=26; mean age, 74 years) and mobility limited older adults (-8.8%; n=22; mean age, 77 years). In healthy older adults, losses in lower limb muscle power were associated with decreased neuromuscular activation, but no change in muscle strength and lean muscle CSA^[151]. Conversely, decrements in mobility limited older adults were associated with decreased muscle strength and lean muscle CSA, rather than changes in neuromuscular activation^[151]. Therefore, the assessment of performance is warranted when investigating age-related differences in lean mass to avoid the underestimation of risk that may occur when using muscle imaging outcomes alone.

Over a three year follow-up, a cohort of 929 older men (mean age, 74 years) were observed to lose 3.4% (Caucasian) to 4.1% (African-American) lower-limb muscle strength per year^[143]. Furthermore, these decrements were three times greater than the loss of lean mass observed during the study^[143]; which again demonstrated greater losses in muscle strength when compared to losses in lean mass in older adults. However, this study did not examine additional factors of muscle quality or neuromuscular activation, thus causality within this cohort remains elusive. Goodpaster et al.^[143] also observed that despite the ability of some older men to maintain or improve lean mass, muscle strength decrements were still apparent. Given these findings, interventions aimed at improving muscle strength and subsequent function in older adults should consider approaches beyond preserving or increasing lean mass alone. Similarly, handgrip strength, a measure of upper body muscle strength, in a cohort of 38 men (mean age, 75 years) was observed to decrease approximately 4.0% per year (3.8% when adjusting for fluctuation in weight)^[152]. These measures were accompanied by absolute (3.7% to 8.9%) and weight-adjusted (3.5% to 8.8%) decrements in muscle strength during elbow flexion, knee extension, trunk extension and trunk flexion in the same study^[152]. Whilst limited by a modest sample size, these declining trends were also shown in a larger study, albeit cross-sectional in nature^[153]. In a sample of 2,442 older men (mean age, 66 years), right-hand handgrip strength decreased 8.9% per decade from the sixth decade onwards; which equated to approximately 0.9% per year, and 0.7% to 1.0% per year when accounting for multiple comorbidities^[153]. Of note, there is some evidence that yearly

decrements in handgrip strength may remain consistent in older men ^[154]. Daly et al. ^[154] reported no difference in the magnitude of grip strength loss per year, with men aged 50-60 (n=41), 60-70 (n=49) and ≥ 70 (n=52) years demonstrating declines of 3.1%, 2.8% and 2.8% respectively. Beyond sample sizes alone, differences in the magnitude of change between these studies may be explained by various factors within study design, such as whether data was longitudinal or cross-sectional and the heterogeneity regarding participant demographics and health status. Regardless, evidence supports the notion that ageing is associated with a decline in muscle strength at various sites in men.

Functional capacity

Assessments of functional capacity may be more suitable for predicting risk in older men within the clinical and research setting, as these measurements are often easy to administer, require limited space and infrastructure and are less physically demanding than some assessments of muscle strength and power ^[24]. Given many tests of functional capacity incorporate aspects of gait (e.g. timed-up-and-go ^[133] and four-square step test ^[134]) and commonly aim to predict similar outcomes (e.g. falls risk), assessments of gait speed have received substantial attention in the research setting, particular in those potentially at greater risk of adverse events, such as older men. In a sample of 2,349 older adults (mean age, 76 years; 48% male) followed for three years, gait speed decreased 0.017 m/s (1.5%) per year ^[155]. Further follow-up (four years) and analysis of the same trial provided similar data and demonstrated declines of 0.015 m/s (1.3%) per year (n=2,306; mean age 75 years; 50% male) ^[156]. The authors also noted, albeit without supplying numerical data, declines were similar by sex, however, baseline gait speed of men was 0.10 m/s greater than that of women ^[156]. Whilst these follow-up results may have provided an underestimate of the true effect due to drop-out and potential survivorship bias, they supported the contention that gait speed continued to decline rather than reach a plateau. These decrements were corroborated in a similar two-year study that examined older men specifically (n=1,513; mean age, 72 years), in which gait speed decreased 0.019 m/s (1.7%) per year ^[157]. Furthermore, decrements in gait speed were observed to be larger as age increased, with reported decreases of 0.015 m/s (1.3%), 0.015 m/s (1.4%), 0.028 m/s (2.8%) and 0.038 m/s (3.9%) in men aged 65-69 (n=567), 70-74 (n=557), 75-79 (n=294) and ≥ 80 years (n=95), respectively ^[157]. Similar trends were detected in another study, in which gait speed decrements per year significantly differed between older men aged 50-60 (n=41;

+0.1%), 60-70 (n=49; -0.6%) and ≥ 70 (n=52; -1.7%) years ^[154]. Collectively, these studies demonstrated that gait speed declined with advancing age, with the magnitude of these decrements becoming larger as age increased.

Sarcopenia and sarcopenic obesity

The prevalence of sarcopenia varies by adopted definition and demographics in older men. A recent systematic review concluded that the overall estimated worldwide prevalence of sarcopenia in men was 10% (95%CI, 8.0-12%) ^[158]. When considering the EWGSOP definition ^[53], sarcopenia in cohorts of community-dwelling older men (mean age range, 67-86 years; sample size range, 66-568 older men) varies from 2.6% to 27% ^[95, 159-165]. Conversely, one study that applied this definition of sarcopenia to institution-dwelling older men (mean age, 84 years), albeit of limited sample size (n=31), reported a prevalence of 68%. Although conceivably justifiable due to the clinical characteristics that often predispose an individual to require institutional care (e.g. limited functional capacity or diminished cognitive function ^[166]), further research with larger samples is required to extrapolate whether this increased prevalence of sarcopenia is truly affecting institutional-dwelling older men. Several factors may be attributed for notable variation in prevalence, including lean mass measurement techniques, age, geographical location and sample size. Only two studies within community-dwelling older men utilised DXA for the assessment of lean mass (sarcopenia prevalence, 4.6-11% ^[160, 162]), whereas others relied on less reliable measures such as BIA (sarcopenia prevalence, 2.6-22%) and mid-upper arm circumference (sarcopenia prevalence, 26-27%) ^[95, 159, 161, 163-165]. Furthermore, the demographical heterogeneity amongst study cohorts may have contributed to the large range of prevalence. For example, when comparing a cohort of older men with a mean age of 67 years ^[162] to those with a mean age 74 years ^[160], DXA-based sarcopenia prevalence was 4.6% and 11%, respectively. Finally, a major limitation of these findings is the lack of a large-scale population-based trial in which many older men are assessed for sarcopenia with robust measures of muscle mass (e.g. DXA). Although financially burdensome, based on the limitations of research to date, these large-scale trials are warranted to assess the true prevalence of sarcopenia in older men. Therefore, the true prevalence of sarcopenia in community-dwelling older men is unknown, although based on the current literature utilising DXA-based measures, it is likely to be in the vicinity of 4.6-11%.

Similarly, the prevalence of sarcopenic obesity varies by definition and population group examined. The prevalence of sarcopenic obesity in older men based on a composite assessment of sarcopenia ^[53] and a total body percent fat mass ^[167] is unknown. However, studies utilising previously suggested definitions of sarcopenic obesity (although limited to a diagnosis of concurrent pre-sarcopenia and obesity as per definitions in this thesis; Table 2.1) have been conducted. Within a sample of 4,984 older adults (49% men; mean age, 70 years), there was a 19-fold range of variation (prevalence range, 4.4% to 84 %) between the eight definitions of sarcopenic obesity applied ^[105]. Of note, none of these definitions adopted measures of muscle strength or functional capacity, and thus may have underestimated or overestimated the prevalence of the sarcopenia component of the definition. Moreover, various other studies have reported the prevalence of sarcopenic obesity using multiple definitions in older men (age range, ≥ 50 years; sample size range, 269-3,169 older men) to be 4.0-19% ^[82, 98, 104, 107, 168]. Beyond the differences in definitions, variable population group demographics and sample sizes may have also impacted the prevalence of this syndrome. Until a standardised approach is available, the true prevalence of sarcopenic obesity in older men is unknown and its investigation is warranted due to the potential associated consequences beyond individual components, sarcopenia and obesity alone.

2.6.4 The clinical implications of age-related changes on muscle, fat and performance in men

Lean mass and muscle cross-sectional area

Muscle is the largest secretory organ in the body and decrements in muscle health that impair myokine responses and/or resistance to its effects may lead to numerous adverse effects ^[169]. When considering losses in lean mass alone, men with a total body percent lean mass $< 31\%$ (< 2 standard deviation below sex-specific young adults aged 18-39) within a sample of 14,528 healthy adults (mean age, 45 years) demonstrated greater insulin resistance (homeostatic model assessment of insulin resistance [HOMA-IR] ratio, 1.39-2.13) and pre-diabetes status (OR, 1.43-1.46), regardless of obesity status, when compared to a reference group of those without low lean mass or obesity ^[45]. However, it should be noted that this study used BIA rather than DXA, CT or MRI to quantify lean mass, which has its known limitations ^[112]. Regardless, the loss of lean mass, even during the early years of accelerated loss (mean age, 45 years), may predispose men to metabolic disorders such as diabetes, although further evidence is required using more robust analyses of body composition.

Additionally, in a sample of 796 older men (mean age, 65 years), Szulc et al. [48] observed that those within the lowest quartile of ALMI ($< 6.32 \text{ kg/m}^2$) had decreased areal bone mineral density (BMD; aBMD) at the femoral neck (-5.1%) and distal radius (-6.2%) when compared to those within the highest quartile of ALMI ($> 7.31 \text{ kg/m}^2$). Furthermore, men within the lowest quartile of ALMI also demonstrated lower external diameter (-4.2% to -6.7%), cortical thickness (-4.5% to -6.3%) and section modulus (-12.2% to -18.3%) of the femoral neck and distal radius when compared to those within the highest quartile of ALMI [48]; thus a loss of lean mass may be associated with increased fracture risk due to not only the loss of performance associated with decreased lean mass, but also the decreased size and bending strength of bone. A key limitation of this study however is the estimation of bone structure using DXA, an outcome not optimal via areal assessment and known to be more robustly assessed via volumetric CT-based methods [170]. Moreover, older men (mean age, 78 years) with lower ALMI ($< \text{two standard deviation below sex-specific population means, } < 7.26 \text{ kg/m}^2$) amongst a sample of 274 were shown to have greater self-reported mobility limitation across a range of ADLs (OR, 6.31) after adjusting for various confounding variables, such as age, smoking status and comorbidities, when compared to men with greater ALMI ($> 7.26 \text{ kg/m}^2$) [93]. Given the subjective nature of these data, future trials would benefit from the use of objective measures of functional capacity, such as short-distance gait speed, to assess these associations.

Collectively, the compromised metabolic risk, skeletal health and performance declines associated with decreased lean mass may in part explain the marked increase in mortality amongst these older men. For example, in a sample of 3,659 older adults (mean age, 69 years) followed for a median duration of 13 years, those in the lowest quartile of ALMI (men, $< 9.2 \text{ kg/m}^2$) had greater rates of mortality than those in the highest quartile of ALMI (men, $> 10.8 \text{ kg/m}^2$); 58% compared to 41%, respectively [46]. When adjusted for markers of cardiometabolic risk and demographical confounders, this relationship remained, as both the highest and second-highest (men, $> 10.0 \text{ kg/m}^2$) quartiles demonstrated reduced hazard ratios (HR) of 0.80 and 0.74 respectively, when compared to the lowest quartile. Thus, compromised lean mass is an independent risk factor of mortality in healthy older men.

Fat mass and cross-sectional area

Pending regional distribution, the accumulation of fat may pose differing health-related risk in older men. Obesity, commonly measured at the population level with BMI rather than specific imaging-based outcomes, is a recognised risk factor for cardiometabolic morbidity and mortality in older men ^[55, 171]. Furthermore, obesity has positive associations with a myriad of detrimental conditions in older men, such as hypogonadism ^[172, 173] and various cancers ^[174]. However, there is a continually documented paradox in which global obesity, albeit counterintuitive, appears to be favourable against mortality in older men when compared to those with normal weight ^[175]. Collectively, these measures of global fat mass and their ability to predict adverse outcomes may be limited in that distribution of fat is not considered and when using BMI specifically, muscle mass, and its potential protective effect, is not taken into account. Fat accumulation in subcutaneous depots, such as those in the gluteofemoral region, appear to be negatively associated with cardiometabolic risk, whereas the accumulation within depots of the abdominal cavity (android region) is positively associated with chronic inflammation, cardiometabolic risk and functional impairment ^[40]. For example, in a sample of 1,549 men (mean age, 49 years), CT-based measures of abdominal subcutaneous and visceral fat volume were shown to be positively correlated with hypertension (OR, 1.5-1.9), impaired glucose metabolism (OR, 1.5-1.8), diabetic status (OR, 1.6) and metabolic syndrome (OR, 2.5-4.2) ^[102]. Among these findings, the influence of visceral fat was shown to be greater than that of subcutaneous fat for all variables bar diabetic status (OR, both 1.6) ^[102]. Similar results were observed in 881 older men (mean age, 58 years), with increased abdominal subcutaneous and visceral fat volume shown to increase the risk of hypertension (OR, 1.45-1.55), diabetic status (OR, 1.69-1.78) and metabolic syndrome (OR, 3.46-3.57) ^[103]. Moreover, visceral fat was shown to have a greater association with hypertension when compared to that of subcutaneous fat; whereas subcutaneous fat had a greater association with diabetic status and metabolic syndrome when compared to visceral fat ^[103]. In contrast, in a cohort of 869 older men (mean age, 79 years) followed for 12 years, neither abdominal subcutaneous or visceral fat CSA assessed with CT was reported to be associated with mortality ^[146]. Similar results were observed in a cohort of 3,086 adults (51% men; mean age, 50 years) in which CT-derived subcutaneous and visceral fat volume did not increase the risk of all-cause mortality, despite visceral fat being independently associated with the increased risk of cardiovascular disease (HR, 1.44) and cancer (HR, 1.43) ^[176]. Regardless, android fat accumulation, and the

subsequently increased visceral fat, is of increased concern in older men but further investigation into the role of varying fat distribution profiles and ageing on overall mortality is warranted.

The age-related accumulation of fat within muscles may pose additional clinical implications. As increased intermuscular fat leads to decreased muscle density^[77] and therefore compromised muscle quality, the accumulation of this form of ectopic fat may impact the ability of a muscle to perform and in part explain the non-parallel decrements of lean mass and muscle strength/power associated with ageing^[40]. For example, in a cohort of 1,285 older men (mean age, 74 years), decreased mid-thigh muscle density was associated with decreased lower limb muscle strength ($r=-0.26$), independent of mid-thigh muscle CSA^[177]. Similarly, lower limb functional performance, as assessed via a composite score combining gait speed and the ability to repeatedly rise from a chair, was shown to decrease (regression coefficient, -0.244 to -0.292 Hounsfield units) per standard deviation (7 Hounsfield units) reduction in mid-thigh muscle density in a sample of 1,442 older men (mean age, 74 years)^[178]. This model was strengthened by accounting for known confounding variables, such as age, total body fat, education, physical activity, health status and muscle CSA^[178]. Although it is still unknown whether intermuscular fat is a marker or direct cause of impaired muscle performance, one potential mechanism to explain these relationships is decreased neural activation, with a previous study of 15 older adults (mean age, 71 years) observing an inverse relationship between intermuscular fat CSA accumulation and quadriceps activation ($r=-0.51$)^[179]. However, due to the small sample size and that this study only examined one muscle group, further investigation into whether this is a true relationship is required. Furthermore, investigation into other potential mechanisms is required before it can be determined whether direction causation exists between increased intermuscular fat and decreased muscle performance.

From a metabolic perspective, those in a sample of 1,447 older men aged 70-79 years who had impaired glucose tolerance ($n=235$; mid-thigh intermuscular fat CSA, 10.3 cm²) or type 2 diabetes ($n=397$; mid-thigh intermuscular fat CSA, 11.2 cm²) possessed greater amounts of mid-thigh intermuscular fat when compared to those with normal glucose tolerance ($n=815$; mid-thigh intermuscular fat CSA, 9.2 cm²)^[180]. Thus suggesting that increased mid-thigh intermuscular fat may also be associated with systemic decrements in blood glucose regulation. Again, whether mid-thigh

intermuscular fat is a marker or has a direct physiological effect is unknown, with the most commonly suggested causative hypotheses of this association stemming from the potentially increased proinflammatory cytokines ^[40]. Finally, for each standard deviation decrement in mid-calf muscle density amongst a sample of 1,063 older men (mean age, 77 years), there was an increased risk of all-cause mortality (HR, 1.18) and cardiovascular mortality (HR, 1.34) ^[181]. This analysis was strengthened as it accounted for numerous confounding variables, such as age, race, physical activity, health status and DXA-derived fat mass ^[181]. Collectively, although this ectopic depot is of concern for both morbidity and mortality in older men, the lack of quantification beyond sites of the lower limb and commonality of relying on one site in each analysis, suggests that these results should be interpreted with caution. However, it appears that intermuscular fat may be associated with numerous clinical implications in older men and further research is required to assess whether this type of fat is a marker or cause of these adverse outcomes.

Muscle strength and power

Muscle strength has been suggested to be a better independent predictor of functional impairment when compared to lean mass alone ^[44, 49, 182]. In a sample of 1,612 men aged > 70 years, handgrip strength provided more accurate multivariable-adjusted prevalence ratios when compared to ALMI for self-reported functional limitation (1.30 vs 1.19), performance-based functional limitation (1.80 vs 1.13) and physical disability (1.36 vs 1.15) ^[44]. Although unable to dismiss reverse causality (e.g. that functional impairment may have led to decreased muscle strength) due to the cross-sectional design, these findings support the use of this simple to administer assessment for the quantification of functional limitation within the clinical and research setting. Similarly, in a sample of 1,286 older men (age range, 70-79 years), knee extensor muscle strength was shown to be an independent determinant (HR, 1.66) of mobility limitations over a 2.5 year follow-up and was suggested to mediate the relationship between mid-thigh muscle CSA and mobilisation limitations ^[49]. These longitudinal findings further support the use of muscle strength assessments for quantifying the risk of functional limitation within the clinical and research setting; however, the use of non-handheld dynamometry, such as that used to quantify knee extensor muscle strength in this study, may pose feasibility limitations in the research setting. Among a sample of 5,995 older men (mean age, 74 years), those within the lowest quartile of handgrip strength (cut-off point not reported; referent) were associated with greater

falls risk over a 4.5 year follow-up when compared to those within the three highest quartiles (relative risk [RR], 0.74-0.84) ^[42]. The increased risk of falls is of specific concern within this susceptible population group given that a 5.3 year longitudinal study of 5,902 older men aged ≥ 65 years demonstrated that those in the lowest quartile of handgrip strength (< 36 kg) and those with the inability to complete an assessment of handgrip strength also had a hip fracture HR of 1.63 and 4.50, respectively, when compared those in the highest quartile ^[41]. These studies highlight that older men with compromised muscle strength are not only at risk of functional impairment, but also the additional consequences that commonly accompany these impairments, such as falls and fractures. In addition to these consequences, a recent meta-analysis of 14 studies examining handgrip strength in 53,476 community dwelling individuals of any age concluded that those in the lowest quartile of handgrip strength across all studies had an increased risk of mortality (HR, 1.67) when compared those in the highest quartile ^[43]. Furthermore, the authors reported that for each one kilogram decrease in handgrip strength all-cause mortality increased by 3.0% ^[43]. Thus there is evidence supporting the association between compromised muscle strength, particularly when assessed via handgrip dynamometry, and various forms of morbidity and mortality among older men.

Functional capacity

Measures of gait speed are often utilised to assess and quantify risk of incident disability, falls and fractures, hospitalisation and cognitive impairment ^[132]. In a sample of 5,995 healthy men (mean age, 74 years), those in the slowest quartile of narrow six metre usual pace gait speed were at greater risk of falling over a 4.5 year follow-up when compared to those in the two fastest quartiles (RR, 0.86-0.89) ^[42]. Although potentially limited by the self-reporting of falls, this study provided an additional functional capacity outcome that may be used within the research setting to quantify falls risk. A similar cohort of 5,902 healthy men aged ≥ 65 years, demonstrated those in the slowest quartile of narrow six metre usual pace gait speed (≥ 6.2 seconds) had a greater risk of hip fracture (HR, 3.70) when compared to those in the fastest quartile (< 4.5 seconds) ^[41]. Similarly, those unable to complete the assessment of gait speed also possessed a greater risk of hip fracture (HR, 3.53) when compared to the referent ^[41]. Thus, older men with compromised gait speed may be more likely to experience falls that result in injury, with this risk increased in those with severe mobility limitations. Furthermore, a recent meta-analysis that included

34,485 community-dwelling older adults (mean age, 74 years) across nine independent studies concluded that risk of mortality increased 12% for each 0.1 m/s decrease in walking speed ^[47]. Therefore, quantifying gait speed is an appropriate assessment tool for evaluating the risk of morbidity and mortality in older men.

Sarcopenia and sarcopenic obesity

Due to varying cut-off points and measures used to quantify sarcopenia, assessing accumulative risk may substantially differ among older adults depending on the definition adopted. For those including measures of lean mass only (defined as pre-sarcopenia in this thesis; Table 2.1) ^[81-83], the aforementioned clinical outcomes associated with these changes are probable. However, these definitions likely underestimate the range and severity of adverse outcomes, due to neglecting performance decrements commonly accompanying the age-related loss of lean mass. Composite definitions of sarcopenia, such as that proposed by EWGSOP ^[53], may predispose those diagnosed to not only the aforementioned adverse outcomes of low lean mass, but also the previously discussed complications associated with low muscle strength and/or functional capacity. Furthermore, when these markers of sarcopenia are concurrently compromised, they may synergistically predispose older men to greater risk and create a cycle that results in the continual exacerbation of clinical outcomes ^[183]. For example, those diagnosed with sarcopenia in a sample of 5,934 older men aged ≥ 65 years were at greater risk of recurrent falls (OR, 2.38), functional limitation (OR, 2.42) and mortality (OR, 1.83) over a 10-year follow-up period when compared to those not diagnosed with sarcopenia. Within the same study, the risk of these outcomes for those diagnosed with pre-sarcopenia via lean mass measures alone ^[81, 82], when compared to those not diagnosed with sarcopenia, was non-significant for recurrent falls, either non-significant or lower (OR, 1.30) for functional limitation and lower (OR, 1.22-1.25) for mortality. This provides rationale for the use of composite definitions of sarcopenia in older adults to avoid the underestimation of collective risk associated with this clinical syndrome state.

A similar relationship may be seen with sarcopenic obesity, where obesity and sarcopenia coexist and therefore potentially increases the risk of adverse outcomes, such as cardiovascular disease and mortality, beyond that of either diagnosis alone ^[55]. A key limitation with many of the previously conducted studies is that muscle strength and functional capacity were not considered when defining the sarcopenia component

of sarcopenic obesity (defined as concurrent pre-sarcopenia and obesity in this thesis; Table 2.1); hence, the specific risk of falls, fractures, functional limitation and mortality is unknown in older men diagnosed with this syndrome. Although uncommonly investigated, a recent study used a composite definition of sarcopenia^[53] and a total body percent fat mass of $\geq 30\%$ to define sarcopenic obesity^[101]. In this study 1,486 older men aged ≥ 70 years were followed for two years, and those diagnosed with sarcopenic obesity demonstrated a greater incidence rate ratio of falls (1.66) when compared to those without sarcopenia or obesity^[101]. Furthermore, incidence rate ratios tended to be larger, although not statistically significant, when compared to sarcopenic non-obese older men (1.58) and non-sarcopenic obese older men (1.30)^[101]. These findings support the notion that sarcopenic obesity, as defined by a composite definition of sarcopenia and total body percent fat mass definition of obesity, may predispose older men to a greater risk of falls when compared to either condition alone. However, further investigation is warranted to determine whether similar relationships exist for other known adverse outcomes, such as fractures, functional limitation and mortality.

2.6.5 The effects of prostate cancer on muscle, fat and performance in older men

As PCa is a disease of older men (mean age of diagnosis in Australia, 68 years^[63]), age-related declines outlined in Section 2.6.2 are common in those diagnosed. Although PCa itself has no known direct physiological influence on muscle, fat or performance outcomes, both the diagnosis of PCa and adverse effects associated with treatment may indirectly negatively alter these outcomes. The following section discusses the adverse effects of PCa diagnosis and non-hormonal active treatments; including radical prostatectomy (surgery), radiotherapy and chemotherapy^[64, 65].

Prostate cancer diagnosis

Following a diagnosis of PCa, a decrease in retrospective versus current self-reported physical activity was observed in a cohort of 59 older men (mean age, 65 years) by 72 minutes per week, which corresponded with decrements in all recorded intensity categories (low, moderate and strenuous)^[184]. Beyond potential self-report and recall bias, this association may be due to the psychological distress associated with the diagnosis of PCa; although when surveyed, only 31% of a similar cohort of 167 men admitted to experiencing significant levels of distress associated with their diagnosis^[185]. Furthermore, among another sample of 150 older men (mean age, 65 years), 19%,

8%, 17% and 7% reported clinically significant uncertainty of treatment decision, depression, general anxiety and PCa-specific anxiety, respectively ^[186]. Of note, these findings may be an underestimate due to the discomfort men often report when admitting to these types of concerns or problems due to social norms and expectations regarding masculinity ^[184]. These suggestions are supported by the increased rates of suicide among men diagnosed with PCa when compared to healthy population means (1.4 times greater in total; 1.9 times greater in first three months following diagnosis), which is commonly attributed in part to psychological distress ^[187]. Inadequate physical activity is associated with decreased cardiorespiratory fitness and therefore potentially increases the risk of all-cause mortality ^[188]; however, this relationship has yet to be examined in this population group. Regardless, low levels of physical activity may partially explain why men diagnosed with earlier stage PCa are more likely to die from cardiovascular disease than from PCa ^[187, 189]; although further long-term studies are required before definitive conclusions may be drawn from this relationship.

Non-hormonal active treatments

Commonly reported treatment-induced adverse effects following prostatectomy and/or radiotherapy include bladder neck contracture, haematuria, incontinence, urethral stricture, diarrhoea, rectal bleeding and impotence ^[74]. Additionally, these treatments have been reported to increased perceptions of fatigue, with men who have undergone radiotherapy reporting greater levels of fatigue when compared to prostatectomy (33% vs 22%) ^[190]. Moreover, prostatectomies may result in general surgical complications (e.g. blood loss during surgery, incontinence and impotence) ^[74]. Finally, men treated with various chemotherapy agents also report further adverse effects such as gastrointestinal complications, fluid retention and more severe fatigue ^[73]. Of note, due to increased survival rates following treatment ^[2, 63], these adverse effects may contribute to long term comorbidities in these men. Comorbidities associated with these treatment-induced adverse effects may directly or indirectly limit physical activity in men diagnosed with PCa ^[191]; thus potentially negatively impact muscle, fat and performance outcomes.

2.6.6 The clinical implications of prostate cancer-related changes on muscle, fat and performance in older men

Prostate cancer diagnosis

Given the unlikelihood of having a direct physiological influence on muscle, fat and performance outcomes, robust studies examining the difference between older men and older men diagnosed with PCa and not actively treated are limited. Additionally, given the number of potential confounding variables, isolating the effects of PCa diagnosis alone on these outcomes, of which are likely psychological in nature, would be challenging and any result would likely need to be interpreted with caution. As 51-77% of men diagnosed with PCa suitable for surgery and/or radiotherapy are likely to opt for immediate active treatment, quantifying treatment-induced adverse effects has received greater attention than that of diagnosis alone ^[2]. Regardless, the psychological burden of a PCa diagnosis should be considered in these men.

Non-hormonal active treatments

Despite the emphasis and attempt to quantify treatment-induced adverse effects, most studies have neglected to investigate changes to muscle, fat and performance outcomes ^[64, 74]. Furthermore, treatments such as chemotherapy are often used in conjunction with ADT, and thus adverse effects during therapy may be confounded by the hypogonadal state of these men. One study examining performance outcomes (six-minute walk test, grip strength and timed-up-and-go) in both healthy and non-hormonal treated men with PCa failed to report numerical outcomes regarding group descriptive statistics (e.g. mean and standard deviation) and results of between- or within-group statistical analyses ^[25]. Although the authors concluded that results did not reach minimum clinically important differences ^[25], it is unknown whether statistical differences were present between these two population groups.

There are several reasons potentially explaining the lack of studies examining differences in muscle, fat and performance between healthy men and those treated with non-hormonal therapies for PCa. First, the robust quantification of muscle and fat requires access to expensive devices and appropriately trained individuals, which may not always be feasible. Second, men diagnosed with PCa are more likely to be concerned with adverse effects of rapid onset and hindrance (e.g. urinary incontinence and sexual dysfunction) ^[192], and thus quantifying and attempting to ameliorate these issues has been preferential within the research setting. Finally, the risk of publication

bias associated with statistically non-significant findings may be applicable if there is no true difference between these population groups for muscle, fat and performance outcomes ^[193]. In spite of these reasons, there is a need to appropriately assess and report whether differences in muscle, fat and performance exist between these two populations in order to determine whether interventions are required and to assist in the design and logistics of future studies in which men treated with ADT are compared to control groups. Currently, it is unknown where men diagnosed with PCa, not treated with ADT lie on the continuum towards possessing muscle, fat and performance measures of clinical concern (Figure 2.5).

Figure 2.5. The potential range in which men diagnosed with prostate cancer, not treated with androgen deprivation therapy (ADT) lie on the continuum towards possessing muscle, fat and performance measures of clinical concern.

2.6.7 The effects of androgen deprivation therapy on muscle, fat and performance in older men with prostate cancer

Lean mass and muscle cross-sectional area

Primarily due to the onset of hypogonadism, lean mass losses of 2.0-3.6% have been reported after a year of continuous ADT of varying modalities ^[18-21] (Table 2.4). In addition, findings from a study of 25 older men (mean age, 68 years) who commenced ADT reported that lean mass decreased by 1.4% in the first 12 weeks of treatment ^[38]. Although many of these studies lacked a control group and were non-randomised in design, the decrements in lean mass exceed those commonly observed in the healthy older men (0.5-1.0% per year ^[132, 138, 139]). Moreover, limited observations following the first 12 weeks of ADT suggested that these decrements may occur rapidly following the onset of hypogonadism ^[38]. While mediating factors contributing to the loss of lean mass with ADT are multifaceted, duration of treatment and patient age appear to be important. For instance, men treated with ADT demonstrated the greatest losses in lean mass (2.6-3.2%) during the initial 6-9 months of treatment ^[12, 18, 21].

Specifically, one study observed a trend ($P=0.06$) in men treated with acute ADT ($\leq$ six months; $n=36$), in which they had a greater decline in total body lean mass (3.7% vs 2.0%) when compared to those treated with chronic ADT ($>$ six months; $n=132$) over a 36-month follow-up. This further strengthens the suggestion that these decrements rapidly follow the onset of hypogonadism. Furthermore, men aged ≥ 70 years ($n=127$) treated with ADT over a 36-month period were shown to lose approximately three times (2.8% vs 0.9%) the amount of lean mass when compared to similar men aged < 70 years ($n=41$)^[12]. Potential rationale for this observation include the aforementioned acceleration in age-related decreases in lean mass discussed in Section 2.6.2 (0.5-1.0% per year). Therefore, treatment duration and patient age should be considered as potential confounding variables when examining changes in lean mass within this clinical population group. Notably, after cessation of ADT and recovery of eugonadal testosterone levels, lean mass losses were not reversed over a two year follow-up in a cohort of 49 men (mean age, 73 years)^[194]. Thus suggesting that the associated complications of ADT may be prolonged after the cessation of treatment and continual intervention may be required to offset these decrements.

Table 2.4. Non-randomised controlled trials examining the effects of continual androgen deprivation therapy (ADT) in men with prostate cancer on lean mass and fat mass.

Authors	N	Average age (years)	Change in lean mass (total body)	Change in fat mass (total body or percent total body)
Gonadotropin-releasing hormone agonist only				
26 weeks				
Boxer et al. ^[22]	30	72	-2.1%	+9.5%
Hamilton et al. ^[21]	26	71	-3.2%	+12.0%
48 weeks				
Smith et al. ^[17]	32	66	-2.7%	+9.4%
52 weeks				
Lee et al. ^[19]	65	66	-2.0%	+6.6%
Hamilton et al. ^[21]	26	71	-3.6%	+14.1%
Combined androgen blockade				
12 weeks				
Smith et al. ^[38]	25	68	-1.4%	-
36 weeks				
Galvão et al. ^[23]	72	74	-2.4%	+13.8%
52 weeks				
Smith et al. ^[20]	26	65	-3.6%	+11.2%
Pharmacological (any modality)				
24 weeks				
Smith et al. ^[36]	22	67	-2.7%	-
48 weeks				
Smith et al. ^[37]	79	71	-3.8%	-
52 weeks				
Greenspan et al. ^[18]	80	69-71	Acute ADT: -3.5% Chronic ADT: NC	Acute ADT: +10.4% Chronic ADT: NC

N, number; NC, no change. Adapted from Owen et al. ^[195].

To date, only three studies using CT have assessed muscle CSA and/or density in men treated with ADT (Table 2.5) ^[15-17], with multiple noteworthy methodological limitations apparent in each. First, none of these studies had a control group. Second, known confounding variables, such as physical activity and diet, were not assessed or accounted for during analysis. Together, these limitations suggest that the findings within these studies should be interpreted with caution, and thus the true effect of ADT alone on muscle CSA and density likely remains elusive. Moreover, one study ^[15] used varying CT scanners, protocols and patient positioning throughout the study, which further confounded results. Finally, one study ^[16] was only published as a conference abstract, and thus extensive detail of the protocol is currently unknown. No further results or details of the protocol have been published. Among the currently available studies, muscle CSA has been shown to decrease within the first year of ADT at

numerous muscle sites, including lumbar paraspinal (3.2%), quadriceps (15%), rectus femoris (17%) and sartorius (22%) ^[15-17]. Additionally, paraspinal muscle CSA decreased 5.5% within the first six months of treatment with enzalutamide (a second generation anti-androgen commonly prescribed once first generation ADT becomes ineffective at limiting PCa activity ^[196]) in men who had previously undergone ADT for an average of 44 months ^[16]. These observations suggest that decrements in muscle CSA associated with ADT may continue to increase over time, rather than plateau, and/or that different ADT pathways may influence muscle CSA differently. However, these suggestions are only speculative, and until multiple robustly designed studies are performed, the true effects of ADT on muscle CSA are unknown. Due to this, comparing differences in muscle CSA between healthy men and those treated with ADT remains limited. Beyond study design, the varying rates of muscle CSA decline observed within men treated with ADT may be partially explained by the use of different muscle sites, which differ anatomically, physiologically and functionally ^[197]. For example, paraspinal muscles are continually recruited to support and move the spine, whereas muscles of the lower limb are predominantly required during ambulation ^[197] and therefore more prone to atrophy in those less likely to be physically active, such as men diagnosed with PCa ^[184]. Collectively, due to the lack of research and a range of limitations among current studies ^[15-17], drawing conclusions on the true effect of ADT on muscle CSA is difficult. Therefore, research is required to examine changes in muscle CSA via CT measures at various sites, whilst also accounting for confounding variables, such as age, disease status and treatment modality.

Table 2.5. Effects of androgen deprivation therapy (ADT) in men with prostate cancer on CT-derived muscle cross-sectional area (CSA).

Authors	N	Average age (years)	ADT details	Duration	Changes in muscle CSA	Notable limitations
Smith et al. ^[17]	32	66	Commencing GnRH agonist	48 weeks	CSA: -3.2% (paraspinal, fourth lumbar vertebrae)	No control group; not controlled for physical activity or diet
Chang et al. ^[15]	39	73	Commencing GnRH agonist	14.6-20 weeks	CSA: -15.4 (quadriceps), -16.6% (rectus femoris), -21.8% (sartorius)	No control group; different CT scanners, protocols and patient positioning between baseline and follow-up; not controlled for physical or diet
Ramalingam et al. ^[16] [Conference abstract]	39	74	Previous ADT, median duration 43.5 months; commencing enzalutamide	6 months	CSA: -5.5% (paraspinal, third lumbar vertebrae)	Limited detail of study protocol and outcomes; no control group; unknown if controlled for previous ADT use or other confounding variables

CT, computed tomography; GnRH, gonadotropin-releasing hormone.

Fat mass and cross-sectional area

Men treated with ADT were observed to experience a continuous increase in fat mass (Table 2.4), with the average annual gain exceeding 11% ^[198]. These annual gains contrast and exceed the plateau in fat mass accumulation commonly observed in older men ^[142]. Furthermore, following a two year period after cessation of ADT in a cohort of 72 men (mean age, 73 years), negative alterations to upper body, lower body and trunk fat mass remained ^[194]. Therefore, ADT-induced gains in fat mass may be of greater importance than those of ageing alone, given the prolonged nature of its presence and rate of accumulation. To date, limited studies have quantified if there are region-specific gains in fat mass during ADT ^[15, 17, 199], but of the limited research available, ADT has been associated with an 11-13% increase in abdominal subcutaneous fat mass ^[17, 199] and either an increase (22%) ^[199] or no change ^[17] in abdominal visceral fat mass after 48-52 weeks. Notable limitations of these studies include the small sample sizes (n=26-40 men) and lack of control groups ^[17, 199]. Furthermore, neither study controlled for confounding variables such as diet and physical activity. In addition, findings from a study of 39 men (median age, 73 years) commencing ADT reported increased fat infiltration of the rectus femoris, as assessed via CT-derived muscle density (-19%), after 15-20 weeks of treatment ^[15]. Similar to previous studies that have examined fat mass accumulation, this study also had a modest sample size (n=39) and lacked a control group. Moreover, variations in CT scanning protocol, including the use of multiple non-cross validated CT scanners suggests these results should be interpreted with caution. Given the lack of quantity and quality of research examining regional fat mass accumulation in men treated with ADT, there is a need for robustly designed longitudinal studies to determine the true effect of ADT on these outcomes.

Muscle strength and power

In addition to decrements in lean mass and muscle CSA, the potential subsequent loss of muscle performance, commonly assessed via measures of muscle strength and power, are of clinical importance in men treated with ADT. In line with definitions of sarcopenia, various studies have examined handgrip strength in men treated with ADT, with inconsistent findings demonstrated (Table 2.6) ^[25-30]. Cross-sectional analyses show that men treated with ADT possess either similar ^[26] or 29% less ^[27] handgrip strength when compared to age-matched healthy controls. Whereas 12-month longitudinal studies have reported decreases of 5.0% to 11% in men treated with ADT

when compared to PCa controls [25, 28, 29]. Whilst these decrements appear to be greater than that of healthy older men (approximately 4.0% per year), these studies had noteworthy methodological limitations and therefore these results should be interpreted with caution. Interestingly, the one longitudinal study that compared handgrip strength in men treated with ADT to healthy controls observed no difference, despite men treated with ADT having demonstrated significant decrements (5.0%) when compared to PCa controls. Common limitations among these studies include the lack of comparison to both healthy and PCa controls [26-30], with only one study to date including both within analyses [25]. Given the unknown degree in which men diagnosed and/or treated with non-hormonal therapies may experience indirect or direct decrements in handgrip strength (as discussed in Section 2.6.4; Figure 2.5), it is important that this population group is considered when attempting to quantify this outcome in men treated with ADT. The inclusion of both a healthy and PCa comparators would allow for the controlling of both age-related and PCa-related decreases; thus, increasing the likelihood of detecting the true effect of ADT on this outcome measure. Furthermore, each of these studies utilised a modest sample of men treated with ADT (n=20-87 men) and thus larger trials are warranted. Finally, inconsistent and poorly reported protocols regarding the collection of handgrip strength among these studies reduces the ability to compare observations. Hence, there is a need for future research to provide guidelines on standardising approaches when attempting to quantify handgrip strength in men treated with ADT [126].

Table 2.6. Effects of androgen deprivation therapy (ADT) in men with prostate cancer on handgrip dynamometer strength.

Authors	Study design	Duration (months)	N	Average age (years)	ADT details	Changes or difference in handgrip dynamometer strength	Notable limitations
Stone et al. [30]	Longitudinal	3	ADT=49	ADT=69	Commencing ADT	No change	Limited detail of protocol; no CON
Joly et al. [26]	Cross-sectional	0	ADT=57 HCON=51	ADT=73 HCON=72	Any form of ADT, median 1.8 years	No difference	No PCON
Soyupek et al. [27]	Cross-sectional	0	ADT=20 HCON=20	ADT=74 HCON=73	GnRH agonists > 12 months	-28.7%*	No PCON
Alibhai et al. [25]	Longitudinal	12	ADT=87 PCON=86 HCON=86	ADT=70 PCON=70 HCON=68	Commencing ADT	-5.0% [#]	Limited reporting of numerical results and statistical analyses
Gonzalez et al. [28]	Longitudinal	12	ADT=62 PCON=86	ADT=68 PCON=68	Commencing ADT	-5.3% [#]	40% of sample did not complete assessment due to comorbidities; No HCON
Cheung et al. [29]	Longitudinal	12	ADT=34 PCON=29	ADT=68 PCON=71	Commencing ADT	Dominant hand, -8.4% [#] Non-dominant hand, -10.5% [#]	No HCON

[#] P < 0.05 compared to PCON; * P < 0.05 compared to HCON. CON, controls; GnRH, gonadotropin-releasing hormone; HCON, healthy controls; PCON, prostate cancer controls.

Beyond this measure, the muscle strength and power of men treated with ADT has been assessed in various studies ^[28, 33]. Within a sample of 118 men, those treated with ADT (mean age, 70 years) demonstrated lower muscle strength (8.7-19%, as assessed via 1-RM chest press, seated row and leg extension) and power (13%, as assessed via a chair rise task) when compared to age-matched healthy controls ^[33]. Of note, this study was cross-sectional in design, rather than longitudinal, and also did not contain a PCa control in addition to the healthy control. Multiple confounding variables were left unaccounted for within this study despite the valid and reliable assessments used for quantifying muscle strength and power. In a sample of 62 men (mean age, 68 years) commencing ADT, no baseline differences were observed in muscle power, as assessed via a chair rise task, when compared to age-matched PCa controls. Conversely, after 6- and 12-month follow-up, men treated with ADT demonstrated decreased muscle power when compared to PCa controls (25% and 30% at each time-point, respectively) ^[28]. These findings suggest that decrements in muscle power may be largest in the first six months of ADT, similar to aforementioned observations in lean and fat mass. However, as almost 60% of men treated with ADT were precluded from one or more of these longitudinal assessments due to additional comorbidities, these results may have underestimated the true effect of ADT on muscle power over time. Given these issues and the likelihood of comorbidities among men treated with ADT, simplistic and easy to administer tests are required (e.g. handgrip strength).

Functional capacity

Limited studies have assessed short-distance gait speed in men treated with ADT, with measures commonly obtained as a component of the short physical performance battery (Table 2.7) ^[31-34]. Among cross-sectional analyses, differences have ranged from non-existent to 16% pending the duration of ADT (acute or chronic) and comparator group (PCa or healthy control). Most of these studies are limited in that they did not control for an extensive range of known confounding variables such as age, disease status, comorbidities, education and physical activity ^[200]. Moreover, only one longitudinal study has been conducted to date, in which men treated with acute ADT (< six months) at the commencement of the study decreased gait speed by 27% over a two year period when compared to healthy controls ^[34]. Conversely, men treated with chronic ADT ($\geq$ six months) maintained gait speed throughout this follow-up ^[34]. This suggests that similar to other ADT-related adverse effects, greater negative alterations occur closer to the onset of ADT-induced hypogonadism. However, this

study is not without limitation, a modest sample size (acute ADT, n=12; chronic ADT, n=23; healthy controls, n=13), age differences between groups and the exclusion of men with low BMD warrants caution when reviewing these results. Given these limitations it is possible that these men do not represent the wider ADT population group.

Table 2.7. Effects of androgen deprivation therapy (ADT) in older men with prostate cancer on gait speed.

Authors	Study design	Duration (years)	N	Average age (years)	ADT details	Change or difference in gait speed	Notable limitations
Clay et al. [32]	Cross-sectional	0	Acute ADT=13 Chronic ADT=42 PCON=25 HCON=13	Acute ADT=74*# Chronic ADT=73*# PCON=65 HCON=69	Acute ADT, mean duration 3.7 months; Chronic ADT, mean duration 30.7 months	Acute: no difference Chronic: -15.4%*	Non-age matched
Levy et al. [34]	Longitudinal	2	Acute ADT=12 Chronic ADT=23 HCON=13	Acute ADT=71* Chronic ADT=74* HCON=67	Acute ADT, mean duration 3.8 months; Chronic ADT, mean duration 24.6 months	Acute: -26.5%* Chronic: no change	Non-age matched; excluded men with limited function or low aBMD
Galvão et al. [33]	Cross-sectional	0	ADT=48 HCON=70	ADT=70 HCON=70	GnRH agonist only or CAB (> 2 months)	-6.3%*	No PCON
Bylow et al. [31]	Cross-sectional	0	ADT=63 PCON=71	ADT=72 PCON=71	ADT > 6 months, mean duration 41.7 months	No difference	No HCON

P < 0.05 compared to PCON; * P < 0.05 compared to HCON. aBMD, areal bone mineral density; acute, < 6 months; CAB, combined androgen blockade; Chronic, ≥ 6 months; GnRH, gonadotropin-releasing hormone; HCON, healthy controls; PCON, prostate cancer controls.

Sarcopenia and sarcopenic obesity

As discussed, individual components of composite definitions of sarcopenia (i.e. lean mass, handgrip strength and gait speed ^[51, 53]) have been reported in men treated with ADT in various cross-sectional and longitudinal studies (Table 2.4; Table 2.6; Table 2.7). However, no studies have examined all three components in the same cohort and thus conclusions on the prevalence and population-specific outcomes of composite definitions of sarcopenia are limited. Furthermore, studies that have examined losses in lean mass or differences in lean mass when compared to other cohorts (e.g. PCa and/or healthy controls) have not applied previously proposed criteria for pre-sarcopenia (low lean mass alone), therefore the prevalence of pre-sarcopenia is also limited. Individual components of sarcopenic obesity have also been reported in men treated with ADT, yet no studies have examined all components collectively (Table 2.4; Table 2.6; Table 2.7). Thus there is a need to apply established definitions to quantify the likelihood of men treated with ADT possessing or developing sarcopenic obesity.

2.6.8 The clinical implications of androgen deprivation therapy-related changes on muscle, fat and performance in older men with prostate cancer

To date, the vast majority of studies that examined the adverse effects of ADT on muscle, fat and performance focussed on quantifying these changes, rather than the morbidity and/or mortality associated with changes in these outcomes. However, ADT use in general has been associated with an increased risk of falls ^[201] and subsequent fractures ^[202-204]. Similarly, ADT has been associated with increased cardiometabolic risk via compromised blood lipid profiles, decreased insulin sensitivity and increased arterial stiffness ^[59, 205, 206]; however, this elevated risk appears to be associated with cardiometabolic morbidity ^[207], but not mortality within these men ^[208]. ADT is also associated with increased fatigue, depressive symptoms and sexual dysfunction may in part explain the lower health-related quality of life commonly reported in men treated with ADT ^[209], which is of further concern given the susceptibility to suicide among these men ^[187]. Whilst each of these clinical implications notably contributes to the burden of disease associated with the treatment of PCa with ADT, the following sections will focus on outcomes that may in part be explained by ADT-related changes in muscle and fat and subsequent decrements in functional performance.

Changes in lean mass and muscle CSA associated with ADT may adversely affect functional performance and the ability to complete ADLs, as well as predispose men treated with ADT to falls and subsequent fractures ^[60]. In a cohort of 50 men treated with ADT (median age, 78 years), 24% of men demonstrated impairment during basic ADLs, whereas 42% showed impairment during higher functioning ADLs ^[201]. Overall, 15% of this cohort reported worsening ability to complete either basic or higher functional ADLs after a three month follow-up ^[201]. Moreover, 22% reported a recent fall within the previous three months, and 56% of these reporters experienced a fall within the subsequent three month period ^[201]. Finally, 12% of men who did not initially report a fall experienced a fall during the three month follow-up ^[201]. Subsequently, 6.0-14% of men treated with ADT experienced a skeletal fracture at any site resulting from a fall after 21-47 months ^[210-213]. While the accelerated loss of BMD demonstrated in men treated with ADT likely explains the increased fracture rates following a fall in this population group, the high incidence of falls in these men are likely to be partially explained by decrements in lean mass and muscle CSA. These potential links are of additional concern given that men classified as possessing a higher risk of skeletal complications after PCa diagnosis were more likely to be treated with ADT ^[214].

Given the role of muscle as a secretory organ in the human body, changes in muscle mass or size may significantly influence myokine concentration and activity ^[169]. For example, compromised interleukin-6 concentration and activity is associated with reduced fat oxidation, increased inflammation and decreased insulin sensitivity ^[169]. Therefore, decrements in muscle mass and size during ADT may in part explain the increased prevalence of metabolic imbalances and subsequent disease in this population group. In men treated with ADT, insulin sensitivity assessed via an oral glucose tolerance test has been shown to decrease within the first 12 weeks of therapy ^[38, 215]. These studies also found that fasting plasma insulin increased 26-65% ^[38, 215]; thus further supporting the notion that glucose metabolism may be impaired in these men shortly after commencing treatment. Similarly, in a study of 26 men commencing ADT, HOMA-IR increased 12% after 52 weeks ^[199]; therefore there is some evidence that insulin resistance may remain elevated throughout therapy, however additional studies utilising this measure are required to confirm this observation and whether this is driven by changes in muscle mass and size.

Clinically, there are multiple consequences that may stem from ADT-related gains in total, regional and intramuscular fat mass ^[216]. For instance, potential increases in subcutaneous and visceral fat may contribute to the marked increase in cardiometabolic disorders in men treated with ADT ^[20, 56, 217]. These gains in fat mass and the subsequent increase in inflammatory cytokines may partially explain previously reported increments of 19-27% and 7.3% in serum triglycerides and low-density lipoprotein (LDL) cholesterol after 48-62 weeks of ADT, respectively ^[17, 20]. In addition, increased fat infiltration within muscle impairs muscular function in non-ADT treated older adults ^[40]; thus this phenomenon requires further investigation within this clinical population group.

Despite the aforementioned clinical implications potentially associated with compromised muscle, fat and performance, the lack of studies that have examined the prevalence of sarcopenia and sarcopenic obesity in men treated with ADT limits the ability to draw conclusions on the accumulative risk associated with concurrently possessing compromised muscle, fat and performance. For example, since obesity is associated with an up-regulation of inflammatory cytokines ^[218], and chronic low grade systemic inflammation has been shown to contribute to age-related muscle wasting ^[219], it is possible that ADT-induced increases in fat mass and size may further exacerbate the loss in muscle mass and size in men with PCa undergoing this treatment. Thus, possessing a number of ADT-induced adverse effects may predispose these men to a greater risk of various clinical implications and further research is required to progress this understanding.

2.7 Potential interventions to improve muscle, fat and performance in older men treated with androgen deprivation therapy for prostate cancer

Current guidelines for managing the myriad of ADT-induced adverse effects generally involve monitoring known risk factors, pharmacotherapy and/or lifestyle interventions; however guidelines appear to vary by country, organisation and expert opinion ^[14, 56-59]. Moreover, these guidelines tend to focus on addressing decrements in bone health, rather than the adverse effects associated with ADT on muscle, fat and performance. The limited number of guidelines that address changes in body composition associated with ADT tend to have placed greater emphasis on weight management, and do not specifically focus on monitoring fat or lean mass and size via robust measures, such as DXA or pQCT ^[56, 59]. Whilst guidelines for managing

metabolic health during ADT briefly discussed the link between lean mass and insulin resistance, they did not recommend any interventions specifically intended to preserve or improve lean mass or muscle CSA ^[14, 56, 57, 59]. However, regular exercise training and/or physical activity are recommended, but greater emphasis is placed on weight management as an outcome, rather than lean mass or muscle CSA ^[14, 56, 57, 59]. Although guidelines are evidence-based, it remains uncertain as to whether they are routinely implemented and followed over time and if they are effective in ameliorating or attenuating many of the adverse effects of ADT.

To date, only one set of guidelines ^[56], which focussed on bone and metabolic outcomes of ADT, has been implemented and evaluated ^[220]. In a two year prospective study, 236 men with PCa commencing ADT attended a clinic visit and received diet and lifestyle advice with overweight and obese men offered referral to a dietitian ^[220]. If required, men also received treatment for hypertension, hypercholesterolemia and osteoporosis as per standard management guidelines ^[56]. Men attending this clinic were assessed at 3-6 monthly intervals ^[220]. A summary of the assessment and management strategies used in this study are shown in Table 2.8. At the initial assessment, 87% of the men were overweight/obese, 61% had hypertension, 56% had hypercholesterolemia, 27% had prior cardiovascular disease, 11% had osteoporosis and 40% had osteopenia ^[220]. For the prospective study, 153 men had data available after 2-years of continuous ADT use ^[220]. The main findings from this study were a mean loss of 3.4% and 2.5% in lumbar spine (L1-4) and hip aBMD, respectively, over 2-years, unless the men were treated with antiresorptive therapy (n=14), in which case aBMD was maintained at both sites ^[220]. No measures of lean or fat mass or functional capacity were assessed in this study, however, an increase in waist circumference of 2.7 cm was indicative of an increase in abdominal fat mass ^[220]. In contrast, reductions were observed in blood pressure, total cholesterol and LDL-cholesterol with treatment ^[220]. While it is important to acknowledge that this was an observational study, which precludes inferences about causality, these findings provide some evidence that adhering to the current management guidelines for men with PCa treated with ADT may not mitigate some of the adverse effects associated with this treatment. Furthermore, the lack of thoroughly assessed muscle, fat and performance outcomes limits the ability to draw conclusions on whether or not guidelines can facilitate the management for ADT-induced adverse effects on these outcomes.

Table 2.8. Clinical assessment and management guidelines for androgen deprivation therapy (ADT)-associated cardiometabolic and skeletal adverse effects.

Cardiometabolic health

- Metabolic risk assessment prior to ADT commencement: body mass index, waist circumference, blood pressure, fasting blood glucose, oral glucose tolerance test (if fasting glucose between 5.5-6.9 mmol/L) and fasting lipid profile.
- Six-monthly to yearly metabolic assessment during the first 24 months of ADT.
- Lifestyle intervention and/or dietician to prevent weight gain and worsening of insulin resistance.
- Smoking cessation.
- Blood pressure < 130/80 mmHg.
- Lipid targets according to NCEP ATP III treatment guidelines
- In men with diabetes, intensification of management as necessary to main HbA1c target

Skeletal health

- At commencement of ADT: assessment for history of minimal trauma fractures and risk factors for osteoporosis, aBMD measurement by DXA and, in men with osteopenia, postero-anterior as well as lateral thoracolumbar spine X-rays.
- Yearly aBMD measurement during the first 24 months of ADT.
- Advice regarding regular physical exercise, smoking cessation and alcohol consumption of ≤ 2 standard drinks per day at each visit.
- Total daily calcium intake of 1,200–1,500 mg through diet, supplements, or both, unless there is a history of renal calculi.
- Vitamin D supplementation as necessary to achieve a target serum 25-hydroxyvitamin D level ≥ 75 nmol/L.
- Commencement of treatment with a bisphosphonate in men with a minimal trauma fracture, an aBMD T-score of ≤ -2.5 , or if 10-year absolute risk of a major osteoporotic fracture is $> 20\%$.

aBMD, areal bone mineral density; DXA, dual-energy x-ray absorptiometry; HbA1c, glycated haemoglobin; NCEP ATP III, national cholesterol education program adult treatment panel III. Adapted from Cheung et al. ^[220] on behalf of the Endocrine Society of Australia, the Australian and New Zealand Bone and Mineral Society and the Urological Society of Australia and New Zealand.

2.7.1 The role of exercise training on muscle, fat and performance in older men treated with androgen deprivation therapy for prostate cancer

In healthy older men, there is consistent and compelling evidence demonstrating that progressive resistance training (PRT) is safe and effective for improving lean mass and strength, with the greatest benefits typically observed with high-intensity training ^[24]. Exercise training has also been suggested to have an important role both pre- and post-diagnosis of cancer ^[221], with emerging evidence that increased physical activity levels

may improve treatment-related outcomes and prevent cancer recurrence through the reduction and maintenance of body fatness ^[222]. Exercise training has been implemented and reviewed across a range of treatments in men diagnosed with PCa ^[60, 223]. Safety concerns regarding injury and increased PSA (a marker of PCa disease activity) following exercise training have been dismissed in various trials ^[224-229]. Moreover, no long-term testosterone increases have been observed following exercise training in men treated with ADT ^[226-229]. There is also emerging evidence that exercise training is safe and well tolerated in men with bone metastases of prostatic origin, which are commonly observed in men treated with ADT ^[230]. The effects of exercise training in men diagnosed and/or treated for PCa are displayed in Figure 2.6.

Figure 2.6. The benefits of exercise training in men diagnosed and/or treated for prostate cancer (Owen et al. ^[231]).

In addition to the benefits in men diagnosed with PCa, the effects of various modalities of exercise training, including aerobic, resistance and impact exercises, on muscle health in men treated with ADT has been assessed in multiple RCTs ^[225, 227-229, 232-244] (Table 6) and reviewed ^[60, 245]. Although the optimal training load and exercise programming variables for eliciting improvements in muscle, fat and performance are unknown, it appears that aerobic training, PRT and the combination of both over periods of 12-52 weeks may improve outcomes, such as total body lean mass (0.7 kg ^[227, 246]) and ALM (0.5 kg ^[227, 238]), total body (-0.6 kg ^[234]) and trunk fat mass (-0.2 to -0.5 kg ^[234, 246]), upper (4.0-26% ^[227, 232, 234, 238, 243]) and lower body muscle strength (17-37% ^[227, 232, 234, 238, 243]), upper (47% ^[227]) and lower body muscle endurance (69% ^[227]) and gait speed (6.4% ^[227]), when compared to usual care (Table 2.9). Moreover, emerging evidence supports the use of impact exercises that aim to provide a loading stimulus to bone in these men ^[242-244], predominantly to address accelerated decrement in BMD, but whether this modality is of increased benefit to muscle, fat and

performance outcomes when compared to aerobic or PRT is unknown. Given the growing rationale that various forms of exercise training are beneficial in this clinical population group and the increased attention of syndromes such as sarcopenia and sarcopenic obesity, future trials should incorporate measures and cut-off points included in these definitions to assess whether these interventions can reduce the burden of disease associated with these syndromes.

Table 2.9. Randomised controlled trials that have examined the effect of aerobic and/or resistance exercise training compared to a non-exercise control on total body and regional lean and fat mass, muscle strength and endurance and gait speed in men treated with androgen deprivation therapy (ADT) for prostate cancer (PCa).

Authors	N	Age (years)	ADT (months)	Duration (weeks)	Exercise prescription	Results
Segal et al. [228]	INT, 82 CON, 73	INT, 68 CON, 68	INT, 12.5 CON, 13.4	12	Supervised, 3/week; PRT, 9ex, 2sets, 8-12reps, 60-70% 1RM	↑Upper and lower body muscle endurance
Segal et al. [229, 232]	INT(PRT), 23 INT(AT), 25 CON, 26	INT(PRT), 67 INT(AT), 66 CON, 65	INT(PRT), 3.0 INT(AT), 3.5 CON, 3.7	24	Supervised, 3/week; INT(PRT), 10ex, 2sets, 8-12reps, 70-80% 1RM; INT(AT), continuous, 15-45min, 50-75% VO ₂ peak	INT(PRT), ↑LM, ↓%FM, ↑Upper and lower body muscular strength INT(AT), ↔LM, ↔%FM, ↑Upper body muscle strength, ↔Lower body muscle strength
Culos-Reed et al. [225]	INT, 53 CON, 47	INT, 67 CON, 68	Not reported	16	Supervised, 1/week, 60min; AT, walking; PRT, light intensity; Unsupervised, 3-5/week, as supervised	↔Handgrip muscle strength
Galvão et al. [227, 233, 235, 236]	INT, 29 CON, 28	INT, 70 CON, 70	INT, 18.2 CON, 10.1	12	Supervised, 2/week; PRT, 10ex, 2-4sets, 6-12-RM; AT, 15-20min, 65-80% HRmax	↑LM, ↑ALM, ↔FM, ↔%FM, ↔TrunkFM, ↑Upper and lower body muscle strength, ↑Upper and lower body muscle endurance, ↑Short-distance gait speed
Winters-Stone et al. [242-244]	INT, 29 CON, 22	INT, 70 CON, 71	INT, 39.0 CON, 18.5	52	Supervised, 2/week; PRT, ex targeting hip and spine, 8-15RM or 0-15%BW, 1-2sets, 8-14reps; impact exercise (two-footed jump only), 10-50reps, 0-10%BW Unsupervised, 1/week; as supervised	↔LM, ↔FM, ↔%FM ↑Upper and lower body muscle strength, ↔Short-distance gait speed

Cormie et al. [234]	INT, 32 CON, 31	INT, 70 CON, 67	INT, 0.2 CON, 0.2	12	Supervised, 2/week; AT, 20-30min, various ex, 70-85%HRmax; PRT, 8ex, 1-4sets, 6-12RM Unsupervised, AT, 150min/week, moderate intensity	↔LM, ↑ALM, ↓FM, ↓%FM, ↓TrunkFM, ↑Upper and lower body muscle strength, ↔Short-distance gait speed
Nilsen et al. [238-240]	INT, 28 CON, 30	INT, 66 CON, 66	INT, 9.0 CON, 9.0	16	Supervised, 2/week; PRT, 9ex, 1-3sets, 6-10reps Unsupervised, 1/week; as supervised	↔LM, ↑ALM, ↔FM, ↔%FM, ↔TrunkFM, ↑Upper and lower body muscle strength
Sajid et al. [241]	INT(1), 8 INT(2), 6 CON, 5	INT(1), 78 INT(2), 76 CON, 72	INT(1), 67.4 INT(2), 58.7 CON, 60.0	6	Unsupervised, 5/week; INT(1); AT, 60-70%HRreserve, walking, 10,000 steps; PRT, resistance band, 1-4sets, 8-15reps; INT(2); as mode, intensity and duration of INT(1),Wii-Fit-based	INT(1), ↔LM, ↔Upper body muscle strength, ↔Handgrip muscle strength INT(2), ↔LM, ↔Upper body muscle strength, ↔Handgrip muscle strength
Wall et al. [246]*	INT, 50 CON, 47	INT, 69 CON, 69	INT, 2.0 CON, 2.0	26	Supervised, 2/week; PRT, 6ex, 6-12RM, 2-4sets, 1-2min rest; AT, various, 20-30min, 70-90%HRmax Unsupervised, AT, 150min/week	↑LM, ↓FM, ↓%FM, ↓TrunkFM

* secondary analysis, ↑ P < 0.05 compared to CON; ↓ P < 0.05 compared to CON; ↔ P > 0.05 compared to CON. %1RM, percentage of one-repetition maximum; %BW, percentage of body weight; %FM, total body percent fat mass; %HRmax, percentage of heart rate maximum; %HRreserve, percentage of heart rate reserve; %VO₂max, percentage of max oxygen uptake; %VO₂peak, percentage of peak oxygen uptake; ADT, androgen deprivation therapy; ALM, appendicular lean mass; AT, aerobic training; BW, body weight; CON, control; Ex, exercises; FM, total body fat mass; GRF, ground reaction force; INT, intervention; LM, total body lean mass; Min, minutes; Mo, month; PRT, progressive resistance training; Reps, repetitions; RM, repetition maximum.

2.7.2 The role of nutritional supplementation on muscle, fat and performance in older men treated with androgen deprivation therapy for prostate cancer

Given the range of treatment-induced adverse effects in men undergoing ADT, investigation of lifestyle interventions, such as nutritional supplementation of vitamin D, calcium and protein, is warranted ^[195]. Notably, the rationale for calcium supplementation, and in part vitamin D, predominantly stems from the need to address decreases in areal and volumetric BMD in men treated with ADT ^[195], and is beyond the scope of this thesis. The following sections will focus on the safety and potential efficacy of supplementation with vitamin D, calcium and protein in ADT-treated men.

In men treated with ADT, vitamin D supplementation, with variations from 400-2,000 IU, is suggested per day ^[247]. The Institute Of Medicine recommends that individuals should not exceed the tolerance upper intake limits of 2,000 mg calcium and 4,000 IU vitamin D per day ^[248]. However, The Endocrine Society contends that the tolerance upper limit for vitamin D in men greater than the age of 50 years at risk of deficiency, such as those diagnosed with PCa ^[249, 250], is 10,000 IU ^[251]. Regardless, supplementation under the care of medical professionals has been suggested to minimise the risk of adverse outcomes and medical complications associated with nutritional supplementation ^[248, 251]. Although debated, potential adverse outcomes associated with excess intake of calcium may include hypercalcemia, hypercalciuria, vascular and soft tissue calcification, nephrolithiasis, PCa, impaired iron and zinc metabolism and constipation ^[248]. Whereas, potential adverse outcomes associated with excess intake of vitamin D may include hypercalcemia, hypercalciuria, falls and fractures, PCa and all-cause mortality ^[248]. A recent systematic review and meta-analysis of prospective studies reported that although increased dairy or calcium intake was associated with an increased risk of PCa, no association was observed with supplemental or non-dairy calcium, which suggest that other components of dairy rather than fat and calcium may increase PCa risk ^[252]. In line with these mixed findings, supplementation at doses < 1,500 mg/d have been shown to either have no influence on PCa progression ^[253], reduce PCa risk ^[254] or decrease PSA velocity ^[255]. In addition, in men diagnosed with PCa, total milk/dairy intake after diagnosis was not associated with a greater risk of lethal PCa, with evidence of a decreased risk in those with a high intake of low fat dairy ^[256]. Moreover, previous studies that examined the effect of combined calcium and vitamin D supplementation in men treated with ADT (total n=1,175; 11 studies) ^[257-267] have reported adverse outcomes such as constipation

(n=99; 8.4%) and fragility bone fracture (n=1). Of note, due to the increased risk of fracture in this population group, it is unlikely this outcome was caused by supplementation of calcium and vitamin D. Additionally, in a cohort study of 1,476 men diagnosed with PCa, vitamin D supplementation was not associated with increased PCa mortality; although vitamin D deficiency was associated with increased all-cause mortality in this population group ^[268]. With regard to protein supplementation, although yet to be examined in men treated with ADT, increased protein intake is commonly shown to be well tolerated and accompanied by no serious adverse events in older population groups ^[269, 270]. Furthermore, a diet high in protein ($\geq 20\%$ of calories) was shown to reduce the risk of all-cause and cancer-related mortality in a cohort of 3,342 adults aged 66 years or greater ^[271].

No previous studies have examined the role of calcium or vitamin D supplementation compared to no supplement on muscle outcomes in men treated with ADT. In a study of 24 men supplemented with 500 mg calcium and 400 IU vitamin D for one year, lean mass declined 0.9% ^[259]; however a non-supplemented control was not provided. In healthy older population groups, there is some evidence to suggest calcium and vitamin D supplementation improved muscular function across a range of fitness assessments ^[272]. To date, no studies have examined the role of protein supplementation on muscular health in men treated with ADT. Although one study in healthy older adults reported that protein supplementation alone increased lean mass ^[273]. There is also evidence in older adults without PCa that higher protein intakes (> 1.2 g/kg) can enhance weight loss, offset muscle loss, improve lipid profiles and insulin sensitivity ^[274]. While this is not a universal finding, this could be explained by the modest level of protein intake achieved in some studies and/or the type (quality) of protein consumed. Of note, emerging evidence suggests that greater protein intake may be required in older adults, when compared to younger individuals, to potentially slow the rate of muscle loss ^[275-277]. This is thought to be due to the anabolic resistance of ageing muscle to stimuli such as amino acids and resistance exercise training ^[275, 277]. Given these findings in older adults, future studies are required to evaluate the potential role of nutritional supplementation interventions on muscle outcomes in men treated with ADT as there are currently no guidelines with regard to dietary or supplemental protein intake.

Although yet to be evaluated in men treated with ADT, research in older population groups has suggested that supplementation of calcium and vitamin D or vitamin D alone decreased falls and fracture risk ^[272, 278-280]. A meta-analysis evaluating the effectiveness of vitamin D supplementation in reducing fracture risk in older adults concluded that 400 IU per day was not sufficient to lower risk; at least 700-800 IU per day was required to potentially reduce fracture risk ^[278]. With regards to protein supplementation, whether the skeletal benefits observed in older adults influenced long-term fracture risk is unknown ^[281]. There is also some evidence that calcium and vitamin D deficiency is associated with impaired glucose metabolism and type 2 diabetes in general population groups ^[282]; thus nutritional supplementation may be a viable option to reduce type 2 diabetes incidence. It has also been suggested that protein supplementation in older population groups improved insulin sensitivity ^[273]. Future studies examining the role of nutritional supplementation in men treated with ADT should measure cardiometabolic risk factors known to be negatively altered by therapy.

A survey of current practice of clinicians in the diagnosis and management of osteoporosis indicated that 50% of Canadian urologists and radiation oncologists recommended calcium supplementation to men commencing ADT ^[283]. Similarly, 47% recommend vitamin D supplementation ^[283]. A similar survey has not been conducted within the Australian medical system. Therefore, despite various guidelines ^[247] and suggested benefits ^[56, 247, 253, 284-287], men treated with ADT are not commonly supplemented with calcium and vitamin D and deficiencies are highly prevalent ^[249, 250].

2.7.3 The role of combined exercise training and nutritional supplementation on muscle, fat and performance in older men treated with androgen deprivation therapy for prostate cancer

Given the efficacy of the previously mentioned exercise training and emerging evidence supporting the use of nutritional supplementation to potentially counteract the range of treatment-induced adverse effects in men undergoing ADT, it is therefore plausible that the combination of these interventions may optimise benefit in these men ^[195]. Notably, calcium and vitamin D supplementation likely play a beneficial role when considering exercise training that elicits bone-related adaptations, however, this section will focus on the potential benefits predominantly on muscle. To date, no

studies have examined the combination of exercise training and nutritional supplementation in these men; however, one study is currently being conducted ^[288]. The study is examining the role of a six month exercise training program combined with nutritional supplementation (1,000 mg calcium and 800 IU vitamin D per day) on various aspects of health influenced by ADT ^[288]. No results have been published from this trial.

Emerging evidence in older adults has provided rationale for the potential use of protein supplementation alongside PRT in clinical populations susceptible to decrements in muscle mass, size and performance, such as those treated with ADT ^[289]. Although yet to be examined within this population group, a recent meta-analysis of randomised controlled trials conducted in healthy older adults concluded that protein supplementation combined with PRT may elicit further gains in muscle mass and size than PRT alone ^[289]. However, the responses appeared to vary according to the type, amount, spread and/or change in protein intake, timing, pattern or distribution of intake and the potential influence of co-ingestion with other nutrients ^[290]. There is a growing body of evidence to suggest that high quality, rapidly digested, leucine rich protein sources (e.g. whey protein), when compared to other types of protein supplementation (e.g. casein and soy), can produce additive or synergistic benefits on post-exercise skeletal muscle protein synthesis and promote increases in muscle mass and size in older adults ^[291]. Similarly, recent findings suggests that 20-40 g of high quality protein may be required to elicit maximal gains in muscle mass and size in older adults ^[292]. Moreover, the timing of protein ingestion in relation to the exercise training session is also important with early (within 1-4 hours) post-PRT consumption of protein reported to be most effective for optimising muscle protein synthesis ^[292, 293]. Therefore, examining the efficacy of similar interventions is warranted in men treated with ADT to potentially augment the benefits from exercise training.

2.8 Summary

Worldwide, PCa is the most prevalent male cancers and in Australia accounts for the highest male cancer incidence and second highest male cancer-related mortality rate. ADT continues to be prescribed to men with both metastatic and non-metastatic PCa. Despite increased survival in selected patients, adverse effects of ADT include negative alterations to muscle, fat and performance, which commonly exceed that of the ageing process. However, methodological flaws in previous studies have limited

the ability to quantify the true effect of ADT on these outcomes, and there is a need to adequately control for known confounding variables (e.g. age, disease status, physical activity and diet). Once appropriately quantified, there is a need to consider how these decrements may be ameliorated. Interventions utilising exercise training have been shown to improve muscle, fat and performance outcomes in men treated with ADT. In addition, studies in non-ADT population groups that assessed nutritional supplementation interventions have shown benefits to these outcomes from increased calcium, vitamin D and protein intake. Thus, combining these two interventions may be more beneficial than either alone on these outcomes in this susceptible population group. To date, no studies have examined the role of a combined exercise training and nutritional supplementation intervention in men treated with ADT when compared to usual care. The following chapter will discuss the general methodology of the two studies presented within this thesis.

Chapter 3

General methods

3.1 Overview

This chapter details a cross-sectional study undertaken to assess the differences in muscle, fat and performance outcomes between men treated with androgen deprivation therapy (ADT) for prostate cancer (PCa), men diagnosed with PCa treated with non-hormonal approaches (PCa controls), and healthy controls (Chapter 4 and Chapter 5). This chapter also details the methodology of a 26-week randomised controlled trial (RCT) that examined the feasibility and efficacy of a multi-component exercise program combined with protein, calcium and vitamin D supplementation (Ex+ProCaD) compared to usual care (Chapter 6) in ADT-treated men. A published protocol emanating from the RCT in which the PhD candidate was the lead author is incorporated within this chapter (Appendix A).

The cross-sectional study presented in Chapter 4 aimed to compare total body lean and fat mass, regional lean mass and muscle cross-sectional area (CSA), muscle strength and functional capacity in men with PCa treated with ADT when compared to non-ADT treated PCa controls and healthy controls. Secondary aims were to compare the prevalence of pre-sarcopenia, sarcopenia, obesity and sarcopenic obesity across the three cohorts, and assess the influence of ADT use duration on all outcome measures.

The cross-sectional study presented in Chapter 5 aimed to compare total and regional fat mass, fat CSA and muscle density (as a measure of intermuscular fat) in men treated with ADT for PCa when compared to non-ADT treated PCa men and healthy controls. A secondary aim was to assess the influence of ADT use duration on these outcomes.

The RCT presented in Chapter 6 initially aimed to examine the efficacy of Ex+ProCaD compared to usual care in men treated with ADT for PCa. However, the continued delays in the recruitment of this clinical population group resulted in an extended study timeline beyond the scope of this thesis. Therefore, the RCT presented aimed to examine the feasibility of conducting the first 26-week period of the study with regard to recruitment, attrition, adherence, data collection and safety. A secondary aim was to examine descriptive data from the first 28 men who completed the interventional period.

3.2 Cross-sectional study

3.2.1 Study design

This was a nested cross-sectional analysis performed in parallel to the baseline of the RCT. A flow diagram of the study protocol is outlined in Figure 3.1. Three groups of men were compared in this analysis; A) men diagnosed with PCa and treated with ADT (referred to as ‘men treated with ADT’; participants in the RCT), B) men diagnosed with PCa and not treated with ADT (referred to as ‘PCa controls’), and C) men not diagnosed with PCa (referred to as ‘healthy controls’). The study was approved by the human research ethics committees at Deakin University (HREC 2013-184) and Alfred Health (Project No: 4515/15) and registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12614000317695). In accordance with ethics, all participants were provided with a plain language statement and consent form (Appendix D).

Figure 3.1. Flow diagram of the nested cross-sectional analysis that examined the differences between men treated with androgen deprivation therapy (ADT), prostate cancer (PCa) controls and healthy controls.

3.2.2 Participants

Eligible participants were men aged 50-85 years who met only one of the following criteria; A) currently treated with ADT for histologically diagnosed PCa (men treated with ADT), B) men diagnosed with PCa treated with non-hormonal therapy (PCa

controls), and C) men not diagnosed with PCa (healthy controls). Two age-matched control groups were used instead of one to account for both the potential role of PCa diagnosis/non-hormonal treatment and natural ageing. Participants were excluded if they did not have the ability to complete surveys in the English language, had any disorder known to affect bone, calcium or vitamin D metabolism (other than hypogonadism), were currently receiving pharmacological intervention known to affect bone metabolism (other than ADT), had supplemented with protein, calcium (> 600 mg/day) or vitamin D (> 1,000 IU/day) in the past three months, had undertaken progressive resistance training (PRT; > one session/week) or regular weight-bearing impact exercise (> 150 min/week) in the past three months, were current smokers, had a weight greater than 159 kg or had any absolute contraindications to exercise training (e.g. musculoskeletal, cardiovascular or neurological) according to the American College of Sports Medicine guidelines ^[24]. Specific to men treated with ADT, treatment must have been pharmacological (surgical orchiectomy excluded) and administered for greater than 12 weeks at enrolment. Additionally, ADT-treated men who had plans to travel for greater than six weeks continuously within the following 52 weeks were excluded. These exclusion criteria were chosen based on factors that may have influenced main outcomes of the RCT.

3.2.3 Recruitment and screening

Participants were recruited via PCa support groups and advertisements in state/local newspapers within Melbourne and surrounding areas in Victoria, Australia. PCa support groups were initially contacted via email with information regarding the study, with brief presentation provided to groups interested. Men treated with ADT were also recruited via direct referral from clinicians across various hospitals, private practices and health networks. The direct referral process included mass mail outs to potential participants and face-to-face discussions during regular consultations with physicians/specialists. All potential participants were screened initially via telephone when they made initial contact with a member of the research team to determine their eligibility based on the inclusion/exclusion criteria. All eligible participants were required to provide informed consent before participating in the study and men treated with ADT were required to obtain medical approval from their physician.

3.2.4 Blinding

Due to financial limitations, there was an inability to hire additional research staff to ensure that the researchers involved in the study were blinded to the group allocation. However, dual-energy x-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT) data were analysed blinded to group allocation.

3.2.5 Measurements

All measures were collected in each of the three groups examined. With the exception of blood samples, 24-hour food recalls and questionnaires, all data was collected at Deakin University. Blood samples were collected at an external commercial pathology clinic. The 24-hour food recalls were administered via telephone. Questionnaires were completed by participants at home prior to the testing sessions and checked by the research staff during these face-to-face testing sessions.

Body composition

Total and regional lean and fat mass (kg) and total body percent lean and fat mass (%) were assessed by DXA using software version 12.30.008 and enCore CoreScan software version 16 (Lunar iDXA, GE Lunar Corp., Madison WI, United States of America). Appendicular lean mass (ALM) was calculated as arm lean mass (kg) plus leg lean mass (kg) ^[77]. ALM index (ALMI) was calculated as ALM (kg) divided by height (m) squared ^[77]. ALM adjusted for body mass index (BMI; ALM_{BMI}) was calculated as ALM (kg) divided by BMI (kg/m^2) ^[294]. ALM adjusted for height and fat mass (ALM_{HFM}) was calculated using an established regression equation method ^[82] adapted to the current study sample ($ALM_{HFM} = -38.51 + 34.31 \times \text{height [m]} + 0.13 \times \text{total body fat mass [kg]}$). The short-term coefficient of variation (CV) for lean and fat mass repeated measures ranged from 1.0-1.7% within our laboratory.

Muscle and subcutaneous fat CSA and muscle density (as a measure of intermuscular fat) at the proximal (66%) radius and tibia were assessed using pQCT (XCT 3000, Stratec Medizintechnik GmbH, Pforzheim, Germany). Percent muscle and fat CSA was calculated as muscle or fat CSA (cm^2) divided by total limb CSA (cm^2). Thresholds of -40 to +40 mg/cm^3 hydroxyapatite density were used for estimating subcutaneous fat CSA. Muscle CSA was estimated by subtracting the total bone CSA and subcutaneous fat CSA from the total area of the 66% tibia or radius. The following CVs have been reported for muscle CSA (radius, 2.1-5.3%; tibia, 2.5-3.7%), muscle

density (radius, 1.4-3.2%; tibia 0.7-3.2%) and subcutaneous fat CSA (radius, 2.4-3.2%; tibia, 6.0-6.3%) for repeated measures in a sample of postmenopausal women [117].

Muscle strength

Muscle strength was obtained via chest press (Powerline Smith Machine PSM144X, Body-Solid Inc., Forest Park IL, United States of America), leg press (Omni Leg Press S-31-OPD, Synergy Fitness, Yatala, Australia) and seated row (Adjustable Tower Pulley System F3ATFS, Nautilus, Independence VA, United States of America) three-repetition maximum (3-RM) protocols [24]. The 3-RM protocols assessed the maximum weight that could be lifted for three repetitions whilst maintaining correct form and technique and were selected rather than one-repetition maximum protocols to reduce participant exertion. Prior to attempting these protocols, participants completed a five minute aerobic warm-up. Thereafter, each participant performed a warm-up set of eight to 10 repetitions with a light load. The participant then completed six to eight repetitions at a heavier weight. The load was increased incrementally until only three repetitions could be completed. A two to three minute recovery period was provided between each set. Muscle strength per kilogram body weight was calculated as muscle strength (kg) divided by weight (kg). The 3-RM protocol has been shown to have a test-retest intraclass correlation coefficient (ICC) of 0.97 in a sample of untrained men [295] and strongly correlates with 1-RM results [296].

Maximal muscle (grip) strength was assessed using a digital handheld dynamometer (Jamar Plus Digital, Lafayette Instrument Company, Lafayette IN, United States of America) [126]. The participant was seated with their forearm resting on the arm of chair whilst maintaining a 90° angle at the elbow. Participants were asked to squeeze the dynamometer maximally. Six trials were completed (three with each hand alternating) with the single highest score recorded. A CV of 6.3% was reported for grip strength repeated measures with the same device in a sample of advanced lung and gastrointestinal cancer patients [128].

Muscle power

Muscle power was assessed using the 30 second sit-to-stand test [130]. Participants began in a seated position with their arms folded across their chest on a chair without arms. Participants were instructed to stand fully upright and then return to a seated

position as many times as possible in 30 seconds. This test was performed in triplicate, with the best result recorded. This test was observed to have a test-retest ICC of 0.84 in a sample of community dwelling men aged 60 years and over ^[130].

Functional capacity

Functional capacity was assessed using the timed-up-and-go with cognitive task, four-square step test, Berg balance scale, four metre usual walk and 400 metre walk. The four-square step test and four metre usual walk were performed in triplicate, with the best result recorded. All other tests were performed once to avoid accumulative fatigue.

The timed-up-and-go with cognitive task measured dynamic balance and dual-tasking ^[297]. Participants were seated in a chair (height, 45 cm) that was placed at the end of a three metre walkway. Once instructed to begin, the participant was instructed to stand up, walk at a regular pace for three metres, turn, walk back to the chair and sit down. During this task, the participant was provided with a mental arithmetic task (e.g. counting backwards from 100 by 3's from a random number). A stopwatch was used to record the time taken (to the nearest millisecond) to complete this test. This test was observed to have an interrater ICC of 0.99 ^[133].

The four-square step test measured dynamic balance and stepping speed in four directions ^[134]. Participants were instructed to step forward, sideways, and backwards over four canes resting flat on the floor in a cross formation in a clockwise sequence and then back in an anticlockwise sequence. The participant was instructed to complete the test as fast as possible without touching the raised canes, and to face forward during the entire sequence. They were also instructed to ensure that both feet make contact with the floor in each square. The time (to the nearest millisecond) taken to complete the sequence was measured with a stopwatch. This test has been observed to have an interrater and test-retest ICC of 0.99 and 0.98 respectively in a sample of community dwelling adults aged 65 years and over ^[134].

The Berg balance scale measured overall balance with both dynamic and static components ^[136]. The test rated participants on 14 different tasks on an ordinal scale ranging from zero (unable to perform the task) to four (performs the task independently). Assessments included variations of sitting, standing, reaching,

leaning, turning and stepping. The scores of the 14 tasks were summed to produce a total score ranging from 0-56 points. Higher scores indicated better performance. This test was observed to have an interrater and test-retest ICC of 0.98 and 0.97 respectively in a sample of adults aged 65 years and over ^[136].

The four metre usual walk measured gait speed ^[137]. Participants were instructed to walk at a usual pace between two cones eight metres apart (two metre acceleration zone, four metre timed zone and two metre deceleration zone). Time was recorded when the participant's front foot entered the timed zone and stopped when their front foot exited the timed zone. The time (to the nearest millisecond) to complete the timed zone was recorded with a stopwatch. This method had an ICC of 0.96 within our laboratory.

The 400 metre walk test provided an estimate of mobility and cardiorespiratory fitness ^[298]. Participants were instructed to walk as fast as possible between two cones placed 20 metres apart (turning when they approach each cone). The time (to the nearest millisecond) taken to complete 10 laps (400 metres) was recorded. This test was observed to have a test-retest ICC of 0.95 in a sample of middle-aged women ^[299].

Pre-sarcopenia, sarcopenia, obesity and sarcopenic obesity

Pre-sarcopenia was defined as low ALM alone based on established criteria derived from previous studies (Table 3.1). Sarcopenia was defined as presenting with both low ALM and compromised muscle strength (handgrip strength) or functional capacity (gait speed) based on established definitions by the European Working Group on Sarcopenia in Older People (EWGSOP), Foundation for the National Institutes of Health (FNIH) and International Working Group on Sarcopenia (IWGS; Table 3.1). Severe sarcopenia was defined using the EWGSOP definition: low ALM, compromised muscle strength (handgrip strength) and functional capacity (gait speed), concurrently. Obesity was defined as $\text{BMI} \geq 30 \text{ kg/m}^2$ ^[99] or total body percent fat mass $\geq 30\%$ ^[100], with the latter commonly deemed a more appropriate indicator of obesity when compared to BMI ^[101]. There are no consensus definitions for sarcopenic obesity, thus sarcopenic obesity was defined as concurrent sarcopenia (EWGSOP) and obesity (total body percent fat mass $\geq 30\%$) and pre-sarcopenic obesity was defined as concurrent pre-sarcopenia ($\text{ALMI} \leq 7.26 \text{ kg/m}^2$ or $\text{ALMI} \leq 7.49 \text{ kg/m}^2$) and obesity (total body percent fat mass $\geq 30\%$). Measures of ALMI were chosen over ALM_{BMI} and ALM_{HFM} due to the latter measures already incorporating an adiposity component.

Table 3.1. Definitions of pre-sarcopenia and sarcopenia and relevant cut-points for each criteria proposed for men.

	Method	Lean mass	Muscle strength and Gait Speed
Pre-sarcopenia	IWGS ^[52]	$ALMI \leq 7.23 \text{ kg/m}^2$	-
	EWGSOP ^[53]	$ALMI \leq 7.26 \text{ kg/m}^2$	-
	IWGS/EWGSOP*	$ALMI \leq 7.49 \text{ kg/m}^2$	-
	Residual* ^[82]	$ALM_{HFM} \text{ residual} \leq -1.63$	-
	FNIH ^[51]	$ALM_{BMI} \leq 0.789 \text{ kg/kg/m}^2$	-
Sarcopenia	FNIH ^[51]	$ALM_{BMI} \leq 0.789 \text{ kg/kg/m}^2$	Handgrip strength < 26 kg
	EWGSOP ^[53]	$ALMI \leq 7.26 \text{ kg/m}^2$	Handgrip strength < 30 kg or gait speed < 0.8 m/s
	IWGS ^[52]	$ALMI \leq 7.23 \text{ kg/m}^2$	Gait speed < 1.0 m/s

* adapted for current study sample. ALM_{BMI} , Appendicular lean mass adjusted for body mass index; ALM_{HFM} , Appendicular lean mass adjusted for height and fat mass; ALMI, Appendicular lean mass index; EWGSOP, European Working Group on Sarcopenia in Older People; FNIH, Foundation for the National Institutes of Health; IWGS, International Working Group on Sarcopenia.

Anthropometry

Height and body mass were assessed using a portable stadiometer and scales respectively. BMI was calculated as weight (kg) divided by height (m) squared.

Habitual physical activity

The Community Healthy Activities Model Program for Seniors physical activity questionnaire was used to assess participation in a comprehensive list of low, moderate and vigorous physical activities ^[300]. Participants documented the frequency and duration of their participation in a ‘typical week’ of the preceding four weeks.

Diet

Diet was assessed using a 24-hour food recall performed during a one on one interview via telephone following the face-to-face testing session. Prior to the phone interview, the participant completed a 24-hour food diary with instructions that were discussed at the testing session. These instructions included how to use household measures (e.g. measuring cups, plates, bowls and glasses) to help estimate food portion sizes. In addition, a standard script was used during the phone interview to maximise the ability of participants to recall what was consumed. Dietary analysis was performed using Australia-specific dietary analysis software (FoodWorks, Xyris software, Highgate Hills, Australia).

Questionnaires

A demographic, clinical and lifestyle questionnaire was used to obtain background information from participants (e.g. age, ethnicity, non-hormonal PCa treatment and ADT use details). Past and current medical conditions and use of prescription medication (type and dose) was also included in the questionnaire (Appendix E).

3.2.6 Sample size calculation

Sample size calculations were based on the limited research examining differences in total body lean mass^[22, 237], handgrip strength^[27], gait speed^[32] and total body percent fat mass^[237] in men treated with ADT when compared to PCa or healthy controls. The mean (assumed standard deviation, based on pooled weighted average^[301]) differences in total body lean mass, handgrip strength, gait speed and total body percent fat mass were -4.0 kg (5.6 kg), -11.2 kg (5.9 kg), -0.18 m/s (0.60 m/s) and +5.4% (6.4%), respectively. To detect differences of these magnitudes in total body lean mass, handgrip strength, gait speed and total body percent fat mass, 35, 6, 25 and 23 men in each group provided 80% power ($P < 0.05$, two-tailed), respectively.

3.2.7 Statistical analysis

All analyses were performed using SPSS 24.0 (IBM Corp, Chicago IL, United States of America). Initially, all data were screened for outliers and descriptive statistics were computed to compare the three groups on known confounding variables of the primary outcomes. Equality of variances of all data were assessed using Levene's test. Normality of distribution of all data were assessed using Shapiro-Wilk's test. Data in violation of equality of variance or normal distribution underwent natural log (arm lean mass, ALM_{BMI} , four-square step test, arm fat mass, leg fat mass, forearm fat CSA, forearm percent fat CSA, lower leg fat CSA, lower leg percent fat CSA, forearm muscle density and lower leg muscle density) or square root (total body fat mass, android fat mass, gynoid fat mass and abdominal visceral fat mass) transformation prior to all analyses, but all data presented were derived from raw values. Between-group comparisons were assessed by analyses of covariance (ANCOVA), with age (years) and physical activity (energy expenditure; kilojoules/day) as covariates. The Kruskal-Wallis test was used for data that remained non-parametric following transformation (chest muscle strength relative to weight, back muscle strength relative to weight, timed-up-and-go, 30-second sit-to-stand, gait speed, abdominal

subcutaneous fat mass). Post-hoc analyses applied the Bonferroni correction, with the addition of Mann-Whitney tests following non-parametric analyses. In the men treated with ADT only, the strength and direction of associations between duration of ADT use and all outcomes were assessed by Spearman rank-order correlation coefficient. Continuous data were reported as mean $\pm$ standard deviation, whereas categorical variables were reported as frequency and percentage, unless stated otherwise. A significance level of $P < 0.05$ was adopted for all statistical tests.

3.3 Randomised controlled trial [IMPACT study]

3.3.1 Study design

The study presented within this thesis examined the effects of a 26-week single-blinded, two-arm RCT consisting of a supervised and structured multi-component exercise program in combination with a daily nutritional supplement on muscle, fat and performance outcomes (Figure 3.2). Notably, this study was part of a larger 52-week RCT, however, ongoing recruitment issues and the subsequent extensions of study duration to ensure statistical power was attained for main outcomes (DXA and pQCT assessed bone health; see Appendix A) resulted in recruitment being extended until the intended sample size is achieved; thus, final data collection is beyond the timeframe of candidature. Additionally, within- and between-group statistics were not presented as: 1) trial results may change with follow-up of the complete cohort of participants; 2) the reporting of preliminary results may introduce biases that jeopardise the eventual outcomes; and 3) the lack of adequate statistical power may increase the probability of a type II error ^[302]. Men with PCa treated with ADT were randomised to either Ex+ProCaD or a usual care control group (who also received vitamin D). Men allocated to usual care did not receive a placebo drink as typical ingredients used to develop a placebo drink (e.g. maltodextrin as a food additive) have the potential to alter blood glucose levels and muscle mass. A factorial 2x2 trial was not conducted for several reasons: 1) the large sample size that would be required to detect an interaction, and 2) findings from previous research in older adults which indicates that the benefits of exercise training on musculoskeletal health require adequate nutrition (e.g. dietary calcium > 1000 mg/day) ^[303]. This study did not evaluate whether the combination of protein, calcium and vitamin D with exercise training was more effective than either of these treatments alone, but determined if combining the two approaches was effective for improving multiple health outcomes. This trial was undertaken within the Institute for Physical Activity and Nutrition at

Deakin University. The study was approved by the human research ethic committees at Deakin University (HREC 2013-184) and Alfred Health (Project No: 455/15) and was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12614000317695). In accordance with ethics, all participants were provided with a plain language statement and consent form (Appendix D).

Figure 3.2. Prospective Consolidated Standards of Reporting Trials (CONSORT) diagram of the 26-week RCT presented within this thesis (adapted from Owen et al. [304], Appendix A).

3.3.2 Participants

Eligible participants were men treated with ADT, as outlined in Section 3.2.2.

3.3.3 Recruitment and screening

Eligible participants were recruited and screened as outlined in Section 3.2.3.

3.3.4 Randomisation and blinding

Randomisation was at the level of the individual participant following baseline testing, stratified by age (< 65 or ≥ 65 years) and BMI (< 30 or ≥ 30 kg/m²), using a computer-generated random number sequence by an independent researcher not affiliated with the study. Furthermore, sealed opaque envelopes were utilised to ensure allocation concealment. Due to the nature of the intervention (i.e. exercise training and nutritional supplementation) and the inability to hire additional research staff due to financial limitations, neither the participants nor researchers involved in the study were blinded to the group allocation, with the exception of the DXA and pQCT scans which were assessed independently.

3.3.5 Intervention group

Multi-component exercise program

The 26-week exercise program consisted of two gym-based sessions and one home-based session per week. The two gym-based sessions were supervised by an Accredited Exercise Physiologist (tertiary trained exercise professional) in a community-based health and fitness facility. All intervention group participants were provided with a yearly membership at a community-based health and fitness centre and had the opportunity to complete their home-based sessions in this setting at their own discretion.

The exercise training program was a multi-component program that followed key training principles of specificity and progressive overload and was individually tailored to the participant's health and functional status. The program followed similar exercise prescription guidelines in terms of the structure, type and dose (frequency, sets, repetitions, intensity) of training to the previous 'Osteo-cise: Strong Bones for Life' community-based osteoporosis prevention exercise program in healthy older adults in which significant improvements were observed in musculoskeletal health and function (Table 3.2) ^[305-307]. To ensure progressive overload and promote a sense of achievement for the men, the 52-week program was divided into five mesocycles (training phases). The first mesocycle (four weeks; adoption phase) focussed on orientation to the exercise program, with an emphasis on correct technique. The four subsequent 12-weekly mesocycles focussed on progression through three 4-weekly microcycles (preparatory phase, challenge phase and consolidation phase). Each gym-based session (approximately 60 minutes) consisted of a warm-up and cool-down and

a combination of aerobic training, PRT, weight-bearing impact activities and challenging balance/functional exercises. More specific details about each training component are provided below. Notably, the 26-week interventional period ended towards the end of the third mesocycle during the consolidation period.

Table 3.2. Structure of the exercise program and training doses for the 52-week randomised controlled trial.

Phase			Aerobic training		Progressive resistance training					Weight-bearing impact training			Functional and core stabilisation training	
Microcycle	Week	Mesocycle	Duration	%HR _{MAX}	Sets	Reps	RPE ¹	Speed ²	Rest	Sets	Reps	Intensity ³	Sets	Duration/reps
#1	1-4	Orientation	15-25 min	55-75%	2	12-15	3-4	Slow	1-2 min	3	10-20	Low	2	Balance exercises, 30-
#2	5-8	Preparatory	15-25 min	60-75%	2	10-15	3-4	Slow	1-2 min	3	10-20	Low to moderate	2	60 seconds or until
	9-12	Challenge	15-25 min	60-75%	2	8-12	5-8	Rapid	2 min	3	10-20		2	fatigue; Core
	13-16	Consolidation	15-25 min	60-75%	2	8-12	5-8	Rapid	2 min	3	10-20		2	stabilisation exercises,
#3	17-20	Preparatory	15-25 min	60-75%	2	10-15	3-4	Slow	1-2 min	3	10-20	Moderate	2	10-15 reps or up to 50
	21-24	Challenge	15-25 min	60-75%	2	8-12	5-8	Rapid	2 min	3	10-20		2	for abdominal based
	25-26	Consolidation	15-25 min	60-75%	2	8-12	5-8	Rapid	2 min	3	10-20		2	exercises

Initially adapted from Gianoudis et al. ^[305]. ¹ RPE: Rating of perceived exertion (1-10); ² Speed: slow (2-3 sec concentric and 2-3 sec eccentric contractions), rapid (rapid concentric and 2-3 sec eccentric contractions); ³ Intensity: low (ground reaction force [GRF] ~ 1-3 x body weight), moderate (GRF ~ 3-6 x body weight), high (GRF ~ 6-9 x body weight) (adapted from Owen et al. ^[304]; Appendix A)

Aerobic training

For the aerobic exercise, participants were prescribed 15-25 minutes of continuous aerobic training at 55-75% of predicted heart rate maximum via modalities such as stationary cycling, treadmill walking or rowing. The type of aerobic exercise prescribed were based on each participant's preference and functional capabilities.

Progressive resistance training

For PRT, participants were prescribed 5-6 targeted hip, spine and forearm resistance exercises using machine and free weights (two sets of 12–15 reps at moderate intensity [3-4 on the 10-point rating of perceived exertion (RPE) scale] for each exercise for the first 4-8 weeks, progressing to two sets of 8–12 reps at moderate to hard intensity [4-6 on the RPE scale] thereafter; resistance was increased as tolerated to maintain intensity and ensure progressive overload). During the first mesocycle, five resistance exercises were available to choose from for each training session (leg press, bench press, one hip targeted, one spine targeted and one upper body exercise). New resistance exercises were introduced at the start of each subsequent mesocycle (three hip targeted, three spine targeted and one upper body targeted). Varying combination of the nine resistance exercises in each of these mesocycles were prescribed each session. After the initial eight weeks of training, participants were progressively taught to perform the concentric (lifting) phase of all lower body exercises at high velocity. This was designed to improve movement speed and muscle power. When possible, participants performed resistance exercises standing with the aim to also improve balance and physical function.

Weight-bearing impact exercise

For the weight-bearing impact-loading exercises, participants were prescribed three exercises (interspersed amongst the PRT exercises) consisting of three sets of 10-20 repetitions that utilised body weight as the primary load. The program focused on lower limb exercises designed to load the hips. The exercises prescribed were based on a battery that was previously shown to be safe and effective for improving femoral neck and lumbar spine areal bone mineral density in older men ^[305]. This battery included a range of exercises from low to high intensity (magnitude of peak ground reaction forces) and difficulty (easy, moderate, hard) and is divided into three broad categories: stationary movements (e.g. marching on spot, mini-tuck jumps), forward/backwards movements (e.g. forward bench step-ups, drop jumps) and lateral

movements (e.g. side-to-side jumping). Training intensity was increased progressively by increasing the height of jumps, by adding additional weight, increasing the rate of impact loading or multi-directional movement patterns (e.g. diagonal loads).

Challenging balance/functional exercise

Challenging balance and functional exercises included a range of static and dynamic exercises, including fit ball exercises (e.g. sitting on fit-ball with knee extension), standing balance activities (e.g. single leg standing) and dynamic functional tasks (e.g. heel-to-toe walking). Participants were prescribed two exercises per session and asked to complete two sets of 30-60 seconds or for a given number of repetitions. To ensure progression, participants were prescribed a new exercise or advanced to a more challenging level (e.g. closing eyes, reducing base of support, confounding visual fixation, changing centre of mass or adding a second manual or cognitive task) once they have mastered the previous exercise (e.g. it is no longer challenging).

Core stabilisation exercise

Key muscle groups known to help maintain good posture, improve pelvic floor function and trunk stability (e.g. rotator cuff, scapular stabilisers, transverse abdominis, pelvic floor muscles) were targeted with these exercises, which are important for balance and muscular performance^[308]. Participants were prescribed two exercises per session with light to moderate resistance in two sets of 10-15 repetitions. Of note, abdominal-based exercises were prescribed in two sets of up to 50 repetitions.

Home-based exercise program

The home-based exercise program consisted of similar types of exercise to the gym-based sessions, but body weight and resistive tubing (provided to participants) were used for resistance exercises. This provided participants with knowledge and experience of ways to exercise relatively inexpensively in a home-based setting following the completion of the study. The home-based program was explained and demonstrated to the participants during the initial gym-based sessions and instructions were provided. Three resistance exercises, three weight-bearing impact-loading exercises and three functional exercises following the same training principles as gym-based sessions were prescribed for each home-based session. The home-based program was progressed and new exercises were introduced once the previous exercises were no longer challenging for the participant.

Nutritional supplement

The nutritional supplement consisted of a daily whey-protein, calcium and vitamin D enriched drink (powder) combined with a single vitamin D tablet. Participants were provided with a 26-week supply of powder in single use sachets and tablets. Each sachet was mixed with 150 ml of water and shaken vigorously in a ‘shake-and-take’ container (provided to participant). Each sachet of powder contained approximately 25 g of whey protein concentrate 80% (WPC80; containing approximately 2.4 g of leucine), 1,200 mg calcium carbonate (approximately 480 mg elemental calcium) and 1,000 IU vitamin D (Omniblend, Campbellfield, Australia). The vitamin D tablet contained 1,000 IU (Ostelin, Macquarie Park, Australia). On the non-training days, participants were asked to take one sachet every morning before breakfast. This was designed to try and ensure a more even protein intake throughout the day which has been reported to optimise muscle protein balance ^[309]. On exercise training days, participants were encouraged to consume the sachet within 1-2 hours of completing their exercise session as early post-exercise consumption of protein has been shown to promote an increase in muscle protein synthesis and muscle hypertrophy in older adults ^[293, 310].

3.3.6 Usual care control group

Participants allocated to usual care received ongoing care from their physician/specialist but did not receive additional education or access to exercise training or the protein, calcium and vitamin D enriched nutritional supplement powder sachet. Due to current practice guidelines ^[247] and a pilot study conducted in 31 men undergoing ADT for PCa in which 65% reported taking vitamin D supplementation (90% at least 1,000 IU/day), all men randomised to usual care received 1,000 IU vitamin D per day.

3.3.7 Measurements

All measures were collected at baseline and 26 weeks. All participants underwent all measures except those specific to treatment allocation (i.e. compliance to the intervention). A summary of the outcome measures are shown in Table 3.3 and outlined in Section 3.2.5. Additional measurements specific to the RCT included prostate specific antigen, compliance and adverse events.

Table 3.3. Summary of data collection.

Variable	Data collection method	Data collection points	
		Baseline	26 weeks
Outcome measures			
Body composition	DXA total body and regional lean and fat mass	x	x
	pQCT 66% radius and tibia subcutaneous fat and muscle cross-sectional area and muscle density	x	x
Muscle strength	One-repetition maximum chest press, leg press and seated row	x	x
	Handgrip strength	x	x
Muscle power	30 second sit-to-stand	x	x
Functional capacity	Timed-up-and-go with cognitive task	x	x
	Four-square step test	x	x
	Berg balance scale	x	x
	Four metre usual walk	x	x
	400 metre walk	x	x
Blood	Overnight, fasted prostate specific antigen	x	x
Additional measures			
Anthropometry	Height, weight, body mass index	x	x
Habitual physical activity	Community Healthy Activities Model Program for Seniors physical activity questionnaire	x	x
Diet	24-hour food recalls	x	x
Questionnaires	Demographic questionnaire	x	-
	Clinical, medical and lifestyle questionnaire	x	x
Exercise program adherence	Calculated from monthly calendars	Collected every 4 weeks	
Supplement compliance	Calculated from supplement returned	-	x
Adverse events	Calculated from monthly calendars	Collected every 4 weeks	

DXA, dual-energy x-ray absorptiometry; pQCT, peripheral quantitative computed tomography.

Prostate specific antigen

Fasted, resting morning blood samples were collected at a commercial pathology clinic and sent to a central laboratory accredited by the National Association of Testing Authorities Royal College of Pathologists Australasia. Total prostate specific antigen (free and complexed) was assessed via immunoassay (Roche Diagnostics, Mannheim, Germany).

Compliance

Compliance with the exercise training program (i.e. attendance at each training session) and nutritional supplement (i.e. consumption) was assessed via attendance record and self-reported diaries, respectively. Diaries were monitored weekly and calendars were monitored monthly by the participant's Accredited Exercise Physiologist and researchers. In addition to the calendars, compliance with the sachets and vitamin D tablets were checked by counting all returned at the 26 week testing session.

Adverse events

Any adverse events potentially associated or confirmed to be associated with the exercise program or protein, calcium and vitamin D supplementation was recorded by the exercise trainers at each exercise training sessions for the intervention group participants and monthly phone calls by the research staff to the control group participants. For this trial, an adverse event consisted of any health-related unfavourable or unintended medical occurrence (e.g. sign, symptom, syndrome or illness) that developed or worsens during the trial. All adverse events were assessed for seriousness, causality and expected outcome by the researchers and followed during the trial. Although there was no formal data monitoring committee, all data was reviewed at regular intervals throughout the study and researchers involved in recruitment, testing and implementing the trial updated the research team monthly about the study progress.

Feasibility

Feasibility outcomes are presented in Table 3.4.

Table 3.4. Feasibility outcomes examined in the randomised controlled trial.

Outcome	Measures
Recruitment	Enrolled participants compared to total screened potential participants Reasons for ineligibility or declined participation Enrolment timeline Efficacy of recruitment pathways
Attrition	Participants available for follow-up Reasons for loss to follow-up
Adherence	Supervised, home-based and total exercise training sessions completed Sachet supplement consumed Vitamin D tablet supplement consumed (both groups)
Data collection	Collected data compared to missing data
Safety	Number, severity and relatedness to the study of adverse events Prostate specific antigen

3.3.8 Sample size calculation

The larger 52-week RCT was statistically powered to observe changes in the primary outcomes (DXA and pQCT-derived measures of bone health), as well as various other outcomes known to be negatively influenced by ADT and potentially ameliorated by exercise training and nutritional supplementation interventions (Appendix A). Overall, it was estimated that a sample size of 51 men per group (102 in total) would be required, which accounted for a conservative 30% attrition rate.

3.3.9 Statistical analysis

All data were collated using STATA statistical software (STATA, College Station TX, United States of America). After data were screened for outliers, descriptive statistics were computed. Where possible, endpoint measures were obtained from any participant lost to follow-up and all randomised subjects that had completed 26-week follow-up by the time of data analysis for this chapter were included in descriptive statistics. Baseline measures and changes in outcome variables were computed as means $\pm$ standard deviation or 95% confidence intervals. Net differences were calculated by subtracting within-group changes for the control group from within-group changes for the intervention group.

3.4 Summary

The studies presented in this thesis include a cross-sectional analysis between men treated with ADT, PCa controls and healthy controls and a 26-week RCT that examined the feasibility and efficacy of Ex+ProCaD compared to usual care in men treated with ADT for PCa. Notable strengths of these studies included the use of valid

and reliable measurement tools (e.g. DXA and Jamar handheld dynamometer), accounting for a range of potential confounding variables (e.g. physical activity, diet, ageing and PCa diagnosis) and the assessment of novel outcomes within this clinical population group (e.g. forearm and lower leg muscle and fat CSA via pQCT). The following chapters will present the results of the cross-sectional study (Chapter 4 and Chapter 5) and 26-week RCT (Chapter 6).

Chapter 4

The effects of androgen deprivation therapy in men with prostate cancer on sarcopenia and its determinants and sarcopenic obesity: results from a cross-sectional study

4.1 Declaration statement

Under the guidance of supervisors, the candidate developed the study concept and initiated the project, provided significant input into the development of the protocol, implemented the protocol and oversaw the collection of the data, analysed and interpreted all data presented.

4.2 Overview

This chapter presents the results from a cross-sectional study. The study examined whether there were any differences in total body lean and fat mass, regional lean mass and muscle cross-sectional area (CSA), muscle strength and functional capacity in men treated with androgen deprivation therapy (ADT) when compared to prostate cancer (PCa) and healthy controls. Moreover, this chapter presents between-group comparisons of the prevalence of pre-sarcopenia, sarcopenia, obesity and sarcopenic obesity, as well as within-group correlations between ADT use duration and muscle, fat and performance outcomes in men treated with ADT.

4.3 Introduction

PCa is one of the most commonly diagnosed male cancers both worldwide and in Australia ^[1, 2]. Besides the notable contribution to male cancer-related deaths ^[1], the diagnosis and treatment of PCa may predispose men to a range of adverse health outcomes. One specific treatment, ADT, is often accompanied by prospective decrements in lean mass and muscle CSA ^[15-21], increased fat mass ^[17-23] and reduced muscle strength and functional capacity ^[25-34]. While rates of compromise vary between trials, in part due to factors such as ADT duration and patient age, men treated with ADT tend to lose 2.0-3.6% lean mass and gain 11% fat mass per year ^[195]. Moreover, measures of muscle strength, such as via handgrip dynamometry, may decrease 5.0-11% per year in these men ^[25, 28, 29]. However, the true extent to which these outcomes may be compromised in these men in comparison to non-ADT treated individuals is unclear due largely to methodological inconsistencies in previous studies, including a lack of appropriate control group(s), differences in the measurements used to quantify muscle, fat and performance and the inability to account for different potential confounding variables such as diet and physical activity ^[15-23, 25-34, 36-38]. Similarly, region-specific alterations to lean mass and muscle CSA are poorly understood ^[17-23]; thus limiting the ability to quantify the risk of further complications associated with these changes (e.g. falls risk). Furthermore, since these

outcomes may be affected by other factors present in men treated with ADT, including increased age ^[63] and the diagnosis and non-hormonal treatment of PCa ^[74, 186], it is important to consider these known covariates by including appropriate control comparison groups when attempting to quantify the effects of ADT on body composition and performance. Once these individual factors are appropriately quantified, the application of known syndromes, such as sarcopenia, may allow for enhanced risk assessment in this susceptible population group.

Sarcopenia was initially measured as the loss of muscle (lean) mass associated with ageing ^[80], but now includes measures of muscle strength and functional capacity, most commonly assessed via handgrip strength and gait speed, respectively ^[51, 53]. Subsequently, low muscle (lean) mass alone is now considered pre-sarcopenia. Worldwide, the prevalence of sarcopenia assessed using dual-energy x-ray absorptiometry (DXA) is approximately 8.0% in older men ^[158]. However, there is currently debate surrounding the clinical cut-offs for diagnosing sarcopenia, and thus there is no consensus definition. Notable definitions include those proposed by the European Working Group on Sarcopenia in Older People (EWGSOP; low appendicular lean mass [ALM] adjusted for height [ALMI] and low handgrip strength or slow gait speed) ^[53], Foundation for the National Institutes of Health (FNIH; low ALM adjusted for body mass index [BMI; ALM_{BMI}] and low handgrip strength) ^[51] and International Working Group on Sarcopenia (IWGS; low ALMI and slow gait speed) ^[52]. Moreover, these conditions may be concurrent with obesity, thus deeming an individual to have sarcopenic obesity ^[54, 55]. While the definition of this syndrome remains in its infancy, its application may assist in quantifying the accumulative risks of ADT in this susceptible population group given the aforementioned concurrent effects on muscle and fat. To date, men diagnosed with these syndromes have been shown to be at greater risk of falls ^[81, 88, 89], fractures ^[48, 88, 90], functional impairment ^[88, 91-94] and mortality ^[88, 91, 95, 96]. Although, no studies have investigated the prevalence of sarcopenia or sarcopenic obesity in men with PCa treated with ADT.

The aim of this study was to compare total body lean and fat mass, regional lean mass and muscle CSA, muscle strength and functional capacity in men with PCa treated with ADT when compared to non-ADT treated PCa controls and healthy controls. Secondary aims were to compare the prevalence of pre-sarcopenia, sarcopenia, obesity

and sarcopenic obesity across the three cohorts, and assess the influence of ADT use duration on all outcome measures.

4.4 Methods

Details on the methodology of this study are discussed in Chapter 3. Briefly, this was a cross-sectional study in which comparisons were made between 42 men treated with ADT for PCa, 54 men treated with non-hormonal therapies (men currently treated with active surveillance were eligible for inclusion in this group) for PCa (PCa controls) and 70 men not diagnosed with PCa (healthy controls). Men treated with ADT were recruited via clinician referral from Alfred Health (Melbourne, Australia) and six private practices (all within Victoria, Australia), as well as from 32 PCa support groups and advertisements in state/local newspapers. PCa and healthy controls were recruited from PCa support groups and advertisements in state/local newspapers.

Height and weight were assessed using standard techniques. BMI was calculated as weight (kg) divided by height (m) squared. Habitual physical activity and diet were assessed by self-reported questionnaire and 24-hour food recall, respectively. Demographical, clinical and lifestyle information was assessed by questionnaire.

Total body and regional lean mass and total body fat mass and percentage fat mass were assessed by DXA. ALM was calculated as arm lean mass (kg) plus leg lean mass (kg) ^[77]. ALMI was calculated as ALM (kg) divided by height (m) squared ^[77]. ALM adjusted for height and fat mass (ALM_{HFM}) was calculated using an established regression equation method ^[82] adapted to the current study sample (ALM_{HFM} = -38.51 + 34.31 x height [m] + 0.13 x total body fat mass [kg]). ALM_{BMI} was calculated as ALM (kg) divided by BMI (kg/m²) ^[294]. Muscle and limb CSA of the forearm (66% radius) and lower leg (66% tibia) was assessed by peripheral quantitative computed tomography (pQCT) ^[311, 312]. Percent muscle CSA was calculated as muscle CSA (cm²) divided by total limb CSA (cm²). Muscle strength was assessed by various three-repetition maximum (3-RM) protocols and handgrip dynamometry. Muscle strength per kilogram body weight was calculated as muscle strength (kg) divided by weight (kg). Functional capacity was assessed by a battery of common valid and reliable tests: 30-second sit-to-stand (a measure of lower limb muscle performance), timed-up-and-go with a secondary cognitive task (a measure of dual-task gait speed), four-square step test (a measure of dynamic mobility), Berg balance scale (a measure of static and

dynamic balance), four metre usual walk (a measure of gait speed) and 400 metre walk (a measure of mobility limitations). Missing data among the three groups is presented in Table 4.1.

Table 4.1. Missing data in the three groups.

Measure	Added after study began			Unable to define ROI			Movement artefact *			Pre-existing comorbidities			Total		
	ADT	PC	HC	ADT	PC	HC	ADT	PC	HC	ADT	PC	HC	ADT	PC	HC
Dietary intake	8	0	0	-	-	-	-	-	-	-	-	-	8	0	0
DXA total body scan	-	-	-	1	0	0	-	-	-	-	-	-	1	0	0
pQCT forearm	-	-	-	1	0	0	5	6	8	-	-	-	6	6	8
pQCT lower leg	-	-	-	0	0	0	2	4	2	-	-	-	2	4	2
Handgrip muscle strength	6	0	0	-	-	-	-	-	-	1	0	0	7	0	0
Chest muscle strength	-	-	-	-	-	-	-	-	-	9	15	18	9	15	18
Leg muscle strength	-	-	-	-	-	-	-	-	-	6	13	14	6	13	14
Back muscle strength	6	0	0	-	-	-	-	-	-	7	14	15	13	14	15
30-second sit-to-stand	-	-	-	-	-	-	-	-	-	0	0	1	0	0	1
Gait speed	6	0	0	-	-	-	-	-	-	0	0	0	6	0	0
400 metre walk	-	-	-	-	-	-	-	-	-	1	1	1	1	1	1
Berg balance scale	-	-	-	-	-	-	-	-	-	1	0	0	1	0	0

Data are: number of participants with missing data. ADT, men treated with androgen deprivation for prostate cancer; DXA, dual energy x-ray absorptiometry; HC, healthy control; PC, prostate cancer control; pQCT, peripheral quantitative computed tomography; ROI, region of interest. * Excluded based on scores of four or five on the visual inspection rating scale of participant movement proposed by Blew et al. ^[311].

Pre-sarcopenia was defined as low ALM alone based on established criteria derived from previous studies (Table 4.2). Sarcopenia was defined as presenting with both low ALM and compromised muscle strength (handgrip strength) or functional capacity (gait speed) based on established definitions by EWGSOP, FNIH and IWGS (Table 4.2). Severe sarcopenia was defined using the EWGSOP definition: low ALM, compromised muscle strength (handgrip strength) and functional capacity (gait speed), concurrently. Obesity was defined as BMI ≥ 30 kg/m² [99] or total body percent fat mass $\geq 30\%$ [100], with the latter commonly deemed a more appropriate indicator of obesity when compared to BMI [101]. There are no consensus definitions for sarcopenic obesity, thus sarcopenic obesity was defined as concurrent sarcopenia (EWGSOP) and obesity (total body percent fat mass $\geq 30\%$) and pre-sarcopenic obesity was defined as concurrent pre-sarcopenia (ALMI ≤ 7.26 kg/m² or ALMI ≤ 7.49 kg/m²) and obesity (total body percent fat mass $\geq 30\%$). Measures of ALMI were chosen over ALM_{BMI} and ALM_{HFM} due to the latter measures already incorporating an adiposity component.

Table 4.2. Definitions of pre-sarcopenia and sarcopenia and relevant cut-points for each criteria proposed for men in the study.

	Method	Lean mass	Muscle strength and Gait Speed
Pre-sarcopenia	IWGS [52]	ALMI ≤ 7.23 kg/m ²	-
	EWGSOP [53]	ALMI ≤ 7.26 kg/m ²	-
	IWGS/EWGSOP*	ALMI ≤ 7.49 kg/m ²	-
	Residual* [82]	ALM _{HFM} residual ≤ -1.63	-
	FNIH [51]	ALM _{BMI} ≤ 0.789 kg/kg/m ²	-
Sarcopenia	FNIH [51]	ALM _{BMI} ≤ 0.789 kg/kg/m ²	Handgrip strength < 26 kg
	EWGSOP [53]	ALMI ≤ 7.26 kg/m ²	Handgrip strength < 30 kg or gait speed < 0.8 m/s
	IWGS [52]	ALMI ≤ 7.23 kg/m ²	Gait speed < 1.0 m/s

* adapted for current study sample. ALM_{BMI}, Appendicular lean mass adjusted for body mass index; ALM_{HFM}, Appendicular lean mass adjusted for height and fat mass; ALMI, Appendicular lean mass index; EWGSOP, European Working Group on Sarcopenia in Older People; FNIH, Foundation for the National Institutes of Health; IWGS, International Working Group on Sarcopenia.

Based on previous research, this study was powered ($\geq 80\%$, $P < 0.05$, two-tailed) to detect the following between-group differences between men treated with ADT and healthy controls (hypothesised to demonstrate the largest differences between groups): total body lean mass (mean $\pm$ standard deviation; -4.0 kg $\pm$ 5.6 kg) [237], total body percent fat mass ($5.4\% \pm 6.4\%$) [237], handgrip strength (-11.2 kg $\pm$ 5.9 kg) [27] and gait speed (-0.18 m/s $\pm$ 0.60 m/s) [32].

All analyses were performed using SPSS 24.0 (IBM Corp, Chicago IL, United States of America). Initially, all data were screened for outliers and descriptive statistics were computed to compare the three groups on known confounding variables of the primary outcomes. Equality of variances of all data were assessed using Levene's test. Normality of distribution of all data were assessed using Shapiro-Wilk's test. Data in violation of equality of variance or normal distribution underwent natural log (arm lean mass, ALMBMI, four-square step test) or square root (total body fat mass) transformation prior to all analyses, but all data presented were derived from raw values. Between-group comparisons were assessed by analyses of covariance (ANCOVA), with age (years) and physical activity (energy expenditure; kilojoules/day) as covariates. The Kruskal-Wallis test was used for data that remained non-parametric following transformation (chest muscle strength relative to weight, back muscle strength relative to weight, timed-up-and-go, 30-second sit-to-stand, gait speed). Post-hoc analyses applied the Bonferroni correction, with the addition of Mann-Whitney tests following non-parametric analyses. In the men treated with ADT only, the strength and direction of associations between duration of ADT use and all outcomes were assessed by Spearman rank-order correlation coefficient. Continuous data were reported as mean $\pm$ standard deviation, whereas categorical variables were reported as frequency and percentage, unless stated otherwise. A significance level of $P < 0.05$ was adopted for all statistical tests.

4.5 Results

4.5.1 Participant characteristics

Participant characteristics of the three groups are shown in Table 4.3. On average, men treated with ADT were approximately four years older than PCa and healthy controls ($P=0.002$). Men treated with ADT taking additional prescription medication were on average prescribed one more form of medication than PCa and healthy controls ($P=0.024$), despite no significant difference in the presence or total number of comorbidities. When compared to PCa controls only, men treated with ADT were more likely to have had advanced PCa and previously undergone radiotherapy or chemotherapy, but not prostatectomy. No other significant differences were observed between the groups, but men treated with ADT reported a 30% and 23% lower level of habitual physical activity (energy expenditure) compared to PCa and healthy controls, respectively ($P=0.054$).

Table 4.3. Participant characteristics of men with prostate cancer (PCa) treated with androgen deprivation therapy (ADT), PCa controls and healthy controls.

	Men treated with ADT	PCa controls	Healthy controls	P-value
n	42	54	70	-
Age (years)	73 ± 6	69 ± 7	69 ± 7	0.002
Height (cm)	174.2 ± 6.7	176.3 ± 7.1	175.7 ± 6.5	0.324
Weight (kg)	86.5 ± 18.0	82.8 ± 13.4	85.5 ± 12.6	0.413
Body mass index (BMI; kg/m ²)	28.4 ± 5.0	26.6 ± 3.9	27.6 ± 3.3	0.094
Highest level of education, n (%)				
Primary or some high school	4 (9.5)	3 (5.6)	8 (11.4)	0.146
Completed high school	8 (19.0)	3 (5.6)	7 (10.0)	
Technical/trade certificate	7 (16.7)	17 (31.5)	12 (17.1)	
University or tertiary level	23 (54.8)	31 (57.4)	43 (61.4)	
Current work status, n (%)				
Full-time	3 (7.1)	10 (18.5)	10 (14.3)	0.426
Part-time	5 (11.9)	9 (16.7)	13 (18.6)	
Retired	34 (81.0)	35 (64.8)	47 (67.1)	
Ethnicity, n (%)				
Caucasian	40 (95.2)	53 (98.1)	65 (92.9)	0.238
Asian	1 (2.4)	1 (1.9)	5 (7.1)	
African	1 (2.4)	0 (0.0)	0 (0.0)	
Comorbidities*, n (%)	39 (92.9)	43 (79.6)	61 (87.1)	0.168
If yes, total (n)	3 ± 1	2 ± 1	2 ± 1	0.334
Prescription medication, n (%)	33 (78.6)	36 (66.7)	45 (64.3)	0.267
If yes, total (n)	4 ± 2	3 ± 2	3 ± 2	0.024
Energy expenditure (kJ/d)	2400 ±1481	3245 ± 1940	3016 ± 1678	0.054
Time since PCa diagnosis (months)	91 ± 81	72 ± 58	-	0.177 ^a
Stage of PCa, n (%)				
Localised/removed	15 (35.7)	46 (85.2)	-	< 0.001 ^a
Advanced	24 (57.1)	6 (11.1)	-	
Unknown	3 (7.1)	2 (3.7)	-	
Duration of ADT (months)	34 ± 45	-	-	-
Previous prostatectomy	20 (47.6)	37 (68.5)	-	0.039 ^a
Previous radiotherapy	30 (71.4)	12 (22.2)	-	< 0.001 ^a
Previous chemotherapy	6 (14.3)	0 (0.0)	-	0.004 ^a
Current active surveillance	-	8 (14.8)	-	-

Data are: mean ± standard deviation unless stated otherwise. * comorbidities included asthma/respiratory problems, chronic bronchitis, muscle/ligament problems, back pain, angina/stroke/heart condition, diabetes, hypertension and hypercholesterolaemia; ^a men treated with ADT versus PCa controls only.

4.5.2 Dietary intake

Dietary intakes for the three groups are reported in Table 4.4. No significant differences were observed between groups for any outcomes. Using current consensus criteria in terms of the recommended dietary protein intake for older adults [313], the proportion of men with a protein intake ≤ 1.2 g/kg/d was similar between men treated with ADT (48%), PCa controls (48%) and healthy controls (60%). Similarly, when a protein intake of ≤ 1.0 g/kg/d was considered, there were no differences between the groups (men treated with ADT, 31%; PCa controls, 33%; healthy controls, 27%).

Table 4.4. Mean daily dietary intakes of men with prostate cancer (PCa) treated with androgen deprivation therapy (ADT), PCa controls and healthy controls.

	Men treated with ADT	PCa controls	Healthy controls	P-value
n	34	54	70	-
Energy (kJ/d)	8661 $\pm$ 1779	8211 $\pm$ 2196	8571 $\pm$ 2354	0.563
Protein (g/d)	96 $\pm$ 26	102 $\pm$ 34	99 $\pm$ 31	0.750
Protein (g/kg/d)	1.12 $\pm$ 0.31	1.26 $\pm$ 0.44	1.18 $\pm$ 0.38	0.256
Protein (% of energy/d)	19 $\pm$ 5	21 $\pm$ 6	20 $\pm$ 4	0.069
Carbohydrate (g/d)	227 $\pm$ 70	201 $\pm$ 68	218 $\pm$ 66	0.170
Carbohydrate (% of energy/d)	43 $\pm$ 10	40 $\pm$ 10	42 $\pm$ 9	0.352
Fat (g/d)	74 $\pm$ 32	75 $\pm$ 32	73 $\pm$ 29	0.881
Fat (% of energy/d)	31 $\pm$ 10	33 $\pm$ 11	31 $\pm$ 7	0.250
Saturated fat (g/d)	28 $\pm$ 12	26 $\pm$ 12	29 $\pm$ 13	0.388
Saturated fat (% of energy/d)	12 $\pm$ 5	11 $\pm$ 4	12 $\pm$ 4	0.397
Calcium (mg/d)	846 $\pm$ 324	757 $\pm$ 361	879 $\pm$ 340	0.146

Data are: mean $\pm$ standard deviation.

4.5.3 Body composition

Lean mass and muscle cross-sectional area

There were no significant differences between the groups for total body or regional lean mass, ALMI, forearm or lower leg muscle CSA or lower leg percent muscle CSA (Table 4.5). In contrast, there was significant between-group differences for total body percent lean mass, ALM_{BMI} and forearm percent muscle CSA (Table 4.5). Post-hoc analyses showed that men treated with ADT had 12% and 10% lower ALM_{BMI} when compared to PCa ($P=0.008$) and healthy controls ($P=0.018$), respectively (Figure 4.1). Similarly, forearm percent muscle CSA was 6.4% and 5.6% lower in men treated with ADT compared to PCa ($P < 0.001$) and healthy controls ($P < 0.001$), respectively. Total

body percent lean mass was also 4.6% lower than PCa controls ($P=0.006$), but not healthy controls ($P=0.099$).

Figure 4.1. Unadjusted mean percentage differences for appendicular lean mass (ALM) and ALM adjusted for body mass index (ALM_{BMI}) between men with prostate cancer (PCa) treated with androgen deprivation therapy (ADT), PCa controls (PCON) and healthy controls (HCON); *, $P < 0.05$; #, $P < 0.01$.

Table 4.5. Mean total body and regional lean mass, muscle cross-sectional area and total body fat mass in men with prostate cancer (PCa) treated with androgen deprivation therapy (ADT), PCa controls and healthy controls, and the mean difference between the three groups.

	Unadjusted mean ± standard derivation			P-value	Adjusted mean difference (95% CI)		
	Men treated with ADT	PCa controls	Healthy controls		Men treated with ADT vs PCa controls	Men treated with ADT vs healthy controls	PCa controls vs healthy controls
Lean mass							
Total body (kg)	52.5 ± 6.9	54.9 ± 6.2	55.5 ± 6.4	0.532	-0.3 (-3.5, 2.9)	-1.2 (-4.2, 1.8)	-1.0 (-3.6, 1.7)
Total body (%)	62.4 ± 7.4	67.0 ± 6.0	65.5 ± 5.5	0.008	-4.2 (-7.4, -1.0) [#]	-2.7 (-5.7, 0.3)	1.5 (-1.2, 4.2)
Arm (kg) ^a	6.0 ± 1.1	6.7 ± 0.9	6.8 ± 1.0	0.060	-0.2 (-0.7, 0.3)	-0.3 (-0.8, 0.2)	-0.2 (-0.6, 0.3)
Leg (kg)	17.8 ± 2.7	18.7 ± 2.7	19.1 ± 2.6	0.365	0.0 (-1.3, 1.3)	-0.6 (-1.8, 0.7)	-0.6 (-1.7, 0.5)
Appendicular (kg)	23.9 ± 3.8	25.3 ± 3.5	25.9 ± 3.5	0.276	-0.3 (-2.0, 1.5)	-1.0 (-2.6, 0.7)	-0.7 (-2.2, 0.7)
ALMI (kg/m ²)	7.86 ± 0.96	8.14 ± 0.84	8.36 ± 0.78	0.105	-0.02 (-0.45, 0.40)	-0.29 (-0.68, 0.11)	-0.26 (-0.61, 0.09)
ALM _{BMI} ^a	0.859 ± 0.127	0.966 ± 0.131	0.948 ± 0.118	0.006	-0.077 (-0.140, -0.014) [#]	-0.063 (-0.124, -0.003) *	0.014 (-0.039, 0.067)
Muscle cross-sectional area							
Forearm (cm ²)	38.4 ± 5.8	41.4 ± 5.2	42.2 ± 6.0	0.073	-1.6 (-4.5, 1.4)	-2.7 (-5.5, -0.1)	-1.1 (-3.6, 1.4)
Forearm (%)	67.1 ± 7.1	73.4 ± 4.5	72.7 ± 4.8	< 0.001	-6.1 (-9.1, -3.1) [#]	-5.4 (-8.2, -2.5) [#]	0.8 (-1.7, 3.2)
Lower leg (cm ²)	72.7 ± 12.7	73.5 ± 9.4	76.4 ± 12.1	0.180	3.1 (-2.6, 8.9)	-0.5 (-5.8, 4.9)	-3.6 (-8.4, 1.2)
Lower leg (%)	73.5 ± 8.0	76.1 ±7.0	77.2 ± 6.3	0.097	-2.0 (-5.8, 1.8)	-3.2 (-6.7, 0.3)	-1.2 (-4.4, 2.0)
Fat mass							
Total body (kg) ^b	29.4 ± 10.7	24.4 ± 8.5	26.1 ± 7.5	0.019	5.8 (1.1, 10.4) *	3.9 (-0.4, 8.2)	-1.9 (-5.7, 2.0)
Total body (%)	34.8 ± 7.8	30.0 ± 6.4	31.5 ± 5.4	0.006	4.5 (1.1, 7.9) [#]	3.1 (-0.1, 6.3)	-1.4 (-4.2, 1.4)

Data are: unadjusted raw mean $\pm$ standard deviation and age- and physical activity-adjusted raw mean difference (95% confidence interval). * P < 0.05; # P < 0.01; ^a analysis used natural log transformed data; ^b analysis used square root transformed data. ALM, appendicular lean mass; ALM_{BMI}, appendicular lean mass adjusted for body mass index; ALM_{HFM}, residual of appendicular lean mass adjusted for height and fat mass; ALMI, appendicular lean mass index.

Fat mass

There was a significant between-group difference for total body fat mass and total body percent fat mass (Table 4.5). Subsequent analyses revealed that men treated with ADT had 5.0 kg greater total body fat mass when compared to PCa controls ($P=0.015$), but not healthy controls ($P=0.190$), and 4.8% greater total body percent fat mass when compared to PCa controls ($P=0.005$), but not healthy controls ($P=0.061$).

4.5.4 Muscle strength

A between-group difference was observed for absolute leg (leg press) and back (seated row) muscle strength, but not chest (chest press) or handgrip (handheld dynamometer) muscle strength (Table 4.6). Further analyses revealed that men treated with ADT did not differ from either control group in leg or back muscle strength, but PCa controls had 7.6% less back muscle strength when compared to healthy controls ($P=0.040$; Figure 4.2). When muscle strength was expressed per kilogram body weight, all four measures of muscle strength differed between groups ($P < 0.05$, all). Compared to PCa controls, men treated with ADT had 15% and 13% lower weight-adjusted back ($P=0.001$) and chest muscle strength ($P=0.006$), respectively (Figure 4.2). Similarly, men treated with ADT had 21%, 18% and 13% lower weight-adjusted leg ($P=0.046$), back ($P < 0.001$) and chest muscle strength ($P=0.003$), respectively, when compared to healthy controls (Figure 4.2). Trends were also observed for weight-adjusted handgrip strength when men treated with ADT were compared to PCa ($P=0.054$) and healthy controls ($P=0.051$). Moreover, when muscle strength was expressed per kilogram lean mass, a between group difference was observed for back muscle strength only ($P=0.003$). Men treated with ADT had 12% lower muscle-adjusted back muscle strength compared to healthy controls ($P=0.001$), but not PCa controls ($P=0.065$). No other significant differences were observed between groups for muscle strength outcomes.

Table 4.6. Mean muscle strength and functional capacity outcomes in men with prostate cancer (PCa) treated with androgen deprivation therapy (ADT), PCa controls and healthy controls, and the mean differences between the three groups.

	Unadjusted mean ± standard derivation			P-value	Adjusted mean difference (95% CI)		
	Men treated with ADT	PCa controls	Healthy controls		Men treated with ADT vs PCa controls	Men treated with ADT vs healthy controls	PCa controls vs healthy controls
Muscle strength							
Handgrip (kg)	38.0 ± 7.3	41.9 ± 6.6	43.3 ± 8.0	0.058	-1.8 (-5.6, 2.0)	-3.5 (-7.1, 0.1)	-1.7 (-4.7, 1.4)
Handgrip/weight (kg/kg)	0.45 ± 0.12	0.52 ± 0.10	0.51 ± 0.09	0.034	-0.06 (-0.11, 0.00)	-0.05 (-0.11, 0.00)	0.00 (-0.04, 0.05)
Chest (kg)	38.0 ± 10.0	40.3 ± 6.6	42.6 ± 11.2	0.172	1.6 (--3.7, 6.9)	-1.9 (-6.7, 3.0)	-3.5 (-8.0, 1.0)
Chest/weight (kg/kg) ^b	0.45 ± 0.10	0.51 ± 0.11	0.51 ± 0.12	0.005	-0.05 (-0.11, 0.02) [#]	-0.05 (-0.11, 0.01) [#]	0.00 (-0.06, 0.06)
Leg (kg)	131.4 ± 49.9	143.5 ± 41.5	160.2 ± 49.5	0.045	5.6 (-19.9, 31.1)	-15.7 (-39.1, 7.6)	-21.3 (-43.1, 0.4)
Leg/weight (kg/kg)	1.53 ± 0.51	1.80 ± 0.48	1.88 ± 0.51	0.050	-0.15 (-0.43, 0.14)	-0.27 (-0.53, 0.00) *	-0.12 (-0.36, 0.12)
Back (kg)	48.6 ± 12.5	52.1 ± 9.4	56.2 ± 11.2	0.027	0.8 (-5.3, 7.0)	-4.4 (-10.1, 1.3)	-5.2 (-10.2, -0.2) *
Back/weight (kg/kg) ^b	0.56 ± 0.11	0.65 ± 0.10	0.67 ± 0.10	< 0.001	-0.07 (-0.13, 0.00) [#]	-0.09 (-0.15, -0.03) [#]	-0.02 (-0.07, 0.03)
Functional capacity							
Timed-up-and-go (sec) ^b	11.02 ± 4.02	11.61 ± 4.52	11.49 ± 4.97	0.517	-1.68 (-3.98, 0.62)	-1.45 (-3.62, 0.71)	0.23 (-1.70, 2.15)
Four-square step test (sec) ^a	10.05 ± 2.21	9.04 ± 1.84	9.03 ± 2.05	0.281	0.53 (-0.47, 1.53)	0.58 (-0.36, 1.51)	0.05 (-0.79, 0.88)
30-second sit-to-stand (n) ^b	13 ± 5	15 ± 4	15 ± 4	0.017	0 (-2, 2)	-1 (-3, 1) [#]	-1 (-3, 1)
Gait speed (m/s) ^b	1.40 ± 0.18	1.48 ± 0.19	1.50 ± 0.22	0.039	-0.05 (-0.15, 0.06) *	-0.07 (-0.17, 0.03) *	-0.02 (-0.11, 0.06)
400 metre walk (sec)	286 ± 38	275 ± 32	265 ± 42	0.142	0 (-19, 19)	11 (-6, 29)	11 (-4, 27)
Berg balance scale (n)	55 ± 2	55 ± 2	55 ± 1	0.460	0 (-1, 1)	0 (-1, 0)	0 (0, 1)

Data are: unadjusted raw mean $\pm$ standard deviation and age- and physical activity-adjusted raw mean difference (95% confidence interval). * P < 0.05; [#] P < 0.01; ^a analysis used natural log transformed data; ^b Kruskal-Wallis test used for non-parametric data. 3-RM, three-repetition maximum.

Figure 4.2. Unadjusted mean percentage differences for handgrip, chest, leg and back muscle strength (black) and weight-adjusted handgrip, chest, leg and back muscle strength (white) between men with prostate cancer (PCa) treated with androgen deprivation therapy (ADT), PCa controls (PCON) and healthy controls (HCON); * $P < 0.05$; # $P < 0.01$.

4.4.5 Functional capacity

Gait speed and 30-second sit-to-stand were found to differ between groups (Table 4.6). Men treated with ADT had 14% lower 30-second sit-to-stand performance when compared to healthy controls ($P=0.006$), but not PCa controls ($P=0.054$), and 5.6% and 6.9% slower gait speed when compared to PCa ($P=0.023$) and healthy controls ($P=0.021$), respectively. No further significant between-group differences were observed for functional capacity outcomes.

4.5.5 Sarcopenia and obesity

Pre-sarcopenia

The prevalence of pre-sarcopenia differed between groups when assessed by ALM_{HFM} residual (≤ -1.63) and ALM_{BMI} (Table 4.7; Figure 4.3). Further statistical analysis showed that men treated with ADT had a greater prevalence of pre-sarcopenia as per FNIH (27-34%) and residual (7.2-10%) methods when compared to PCa and healthy controls. No other significant differences were observed for pre-sarcopenia prevalence between groups.

Figure 4.3. Prevalence (percentage) of pre-sarcopenia (black) and non-sarcopenia (white) according to the different definitions in men with prostate cancer (PCa) treated with androgen deprivation therapy (ADT), PCa controls and healthy controls; * $P < 0.05$ when compared to PCa controls; # $P < 0.05$ when compared to healthy controls; EWGSOP, European Working Group on Sarcopenia in Older People; FM%, total body percent fat mass; FNIH, Foundation for the National Institutes of Health; IWGS, International Working Group on Sarcopenia.

Table 4.7. Group prevalence and between-group differences in pre-sarcopenia, sarcopenia and obesity in men with prostate cancer (PCa) treated with androgen deprivation therapy (ADT), PCa controls and healthy controls.

					P-values		
	Men treated with ADT	PCa controls	Healthy controls	P-value	Men treated with ADT vs PCa controls	Men treated with ADT vs healthy controls	PCa controls vs healthy controls
Pre-sarcopenia, n (%)							
ALMI, ≤ 7.26 kg/m ² (EWGSOP)	8 (19.5)	6 (11.1)	6 (8.6)	0.225	0.253	0.094	0.635
ALMI, ≤ 7.23 kg/m ² (IWGS)	8 (19.5)	6 (11.1)	6 (8.6)	0.225	0.253	0.094	0.635
ALMI, ≤ 7.49 kg/m ² (IWGS/EWGSOP*)	12 (29.3)	12 (22.2)	10 (14.3)	0.159	0.434	0.056	0.251
ALM _{BMI} , < 0.789 (FNIH)	17 (41.5)	8 (14.8)	5 (7.1)	< 0.001	0.003	< 0.001	0.167
ALM _{HFM} , ≤ -1.63 (residual*)	15 (36.6)	9 (26.5)	10 (29.4)	0.013	0.027	0.007	0.715
Sarcopenia, n (%)							
EWGSOP	2 (5.9)	1 (1.9)	1 (1.4)	0.369	0.310	0.203	0.853
Handgrip strength < 30 kg	6 (17.1)	2 (3.7)	2 (2.9)	0.011	0.030	0.009	0.791
Gait speed < 0.8 m/s	1 (2.8)	0 (0.0)	0 (0.0)	0.177	0.218	0.161	-
IWGS	0 (0.0)	0 (0.0)	0 (0.0)	-	-	-	-
Gait speed < 1.0 m/s	1 (2.8)	0 (0.0)	0 (0.0)	0.177	0.218	0.161	-
FNIH	2 (5.7)	0 (0.0)	0 (0.0)	0.028	0.076	0.043	-
Handgrip strength < 26 kg	2 (5.7)	0 (0.0)	1 (1.4)	0.143	0.076	0.214	0.378
Obesity, n (%)							
BMI, ≥ 30 kg/m ²	11 (26.2)	9 (16.7)	15 (21.4)	0.523	0.254	0.563	0.506
FM%, $\geq 30\%$	30 (73.2)	26 (48.1)	46 (65.7)	0.031	0.014	0.414	0.049

Pre-sarcopenia and obesity, n (%)							
ALMI, $\leq 7.26 \text{ kg/m}^2$ and FM%, $\geq 30\%$	6 (14.6)	1 (1.9)	3 (4.3)	0.025	0.018	0.054	0.447
ALMI, $\leq 7.49 \text{ kg/m}^2$ and FM%, $\geq 30\%$	7 (17.1)	5 (9.3)	7 (10.0)	0.434	0.256	0.279	0.890

Data are: number of cases (percentage). * adapted for current study sample. ALM_{BMI} , appendicular lean mass adjusted for body mass index; ALM_{HFM} , residual of appendicular lean mass adjusted for height and fat mass; ALMI, appendicular lean mass index; BMI, body mass index; EWGSOP, European Working Group on Sarcopenia in Older People; FM%, total body percent fat mass; FNIH, Foundation for the National Institutes of Health; IWGS, International Working Group on Sarcopenia.

Muscle weakness and functional impairment

The prevalence of muscle weakness, as defined by handgrip strength < 30 kg, differed between groups and specifically between men treated with ADT and PCa controls (17% vs 3.7%) and healthy controls (17% vs 2.9%). No significant differences were noted for muscle weakness defined as < 26 kg; with only three cases observed overall ($n=2$, men treated with ADT; $n=1$, healthy controls). Functional impairment prevalence, as defined by gait speed < 1.0 m/s or < 0.8 m/s, did not differ between groups ($P=0.177$, both), and was only detected for one participant overall regardless of the cut-off applied ($n=1$, men treated with ADT).

Sarcopenia

Overall two participants were classified having sarcopenia according to the FNIH definition, both of which were men treated with ADT (Table 4.7). When using the EWGSOP definition, two men treated with ADT, one PCa control and one healthy control were classified as having sarcopenia. When the IWGS definition of sarcopenia was applied, no cases were observed. Similarly, there were no cases of severe sarcopenia as per the EWGSOP definition.

Obesity

A between-group difference was observed for obesity as defined by total body percent fat mass $\geq 30\%$ (Table 4.7), with a higher prevalence observed in men treated with ADT (73%) compared to PCa controls (48%), but not healthy controls (66%). Healthy controls also had a higher prevalence of obesity when compared to PCa controls. No significant between group differences were observed for obesity as defined by BMI.

Sarcopenic obesity

No men were classified as having sarcopenic obesity. However, concurrent pre-sarcopenia ($ALMI, \leq 7.26$ kg/m²) and obesity (total body percent fat mass, $\geq 30\%$) differed among groups. Subsequent analyses showed that men treated with ADT had a higher prevalence of concurrent pre-sarcopenic and obesity (14%) when compared to PCa controls (1.9%), but not healthy controls (4.3%). These differences were not observed when using the ALMI cut-off of ≤ 7.49 kg/m² to define pre-sarcopenia.

4.5.6 Duration of androgen deprivation therapy use

On average, men treated with ADT had undergone hormonal treatment for 34 months (standard deviation, 45 months). Duration of ADT use negatively correlated with forearm ($r_s=-0.43$) and lower leg ($r_s=-0.38$) percent muscle CSA (Table 4.8). On average, there were losses of approximately 0.1% of total limb muscle CSA per month of ADT use at both sites (Figure 4.4). No other variables were found to correlate significantly with duration of ADT use.

Figure 4.4. Scatterplot of the relationship between duration of androgen deprivation therapy (ADT) and lower leg and forearm percent muscle cross-sectional area (CSA) in men treated with ADT.

Table 4.8. Spearman's rho correlations (and P-values) between androgen deprivation therapy (ADT) use duration and body composition, muscle strength and functional capacity outcomes in men with prostate cancer treated with ADT.

Measure	ADT duration (month), Spearman's rho correlations	
Lean mass		
Total body (kg)	0.11	P=0.506
Total body (%)	-0.24	P=0.138
Arm (kg)	0.06	P=0.728
Leg (kg)	0.11	P=0.499
Appendicular (kg)	0.10	P=0.536
ALMI (kg/m ²)	0.20	P=0.208
ALM _{BMI} (kg/kg/m ²)	-0.23	P=0.144
Muscle cross-sectional area		
Forearm (cm ²)	-0.08	P=0.654
Forearm (%)	-0.43	P=0.005
Lower leg (cm ²)	-0.02	P=0.914
Lower leg (%)	-0.38	P=0.022
Fat mass		
Total body (kg)	0.23	P=0.151
Total body (%)	0.23	P=0.147
Muscle strength		
Handgrip (kg)	-0.01	P=0.947
Handgrip/weight (kg/kg)	-0.14	P=0.389
Chest (kg)	0.24	P=0.172
Chest/weight (kg/kg)	0.28	P=0.875
Leg (kg)	0.03	P=0.849
Leg/weight (kg/kg)	-0.02	P=0.892
Back (kg)	0.14	P=0.464
Back/weight (kg/kg)	0.04	P=0.845
Functional capacity		
Timed-up-and-go (sec)	-0.24	P=0.132
Four-square step test (sec)	-0.27	P=0.087
30-second sit-to-stand (n)	0.09	P=0.550
Gait speed (m/s)	0.12	P=0.467
400 metre walk (sec)	-0.01	P=0.925
Berg balance scale (n)	-0.05	P=0.760

ALM_{BMI}, appendicular lean mass adjusted for body mass index; ALMI, appendicular lean mass index.

4.6 Discussion

To our knowledge, this is the first study to evaluate the effects of ADT on the prevalence of sarcopenia or sarcopenic obesity and its components simultaneously within a sample of older men treated with ADT for PCa in comparison to men with PCa not receiving ADT and healthy controls. The main findings from this study were that absolute total body and regional lean mass and muscle CSA were no different between the three groups, but after adjusting for differences in adiposity, men treated with ADT had 10-12% lower ALM and 5.6-6.4% lower forearm muscle CSA compared to PCa and healthy controls. Similarly, absolute leg, back and chest muscle strength were comparable between the groups, but when expressed relative to body weight, men treated with ADT had 13-21% lower muscle strength relative to PCa and healthy controls. Gait speed was also impaired in men treated with ADT when the three groups were compared. Subsequently, there was a greater prevalence of pre-sarcopenia and sarcopenia in men treated with ADT compared to both controls when definitions that consider adiposity-adjusted ALM were applied (i.e. ALM_{BMI} and ALM_{HFM}), but not those that adjust ALM for height alone (i.e. $ALMI$). Collectively, these findings suggest that it is important to account for adiposity when comparing muscle-based outcomes in men treated ADT to PCa controls and healthy controls.

Effects of androgen deprivation therapy on total body and regional lean mass

To our knowledge, only two previous studies have quantified differences in absolute total body lean mass between men treated with ADT and both healthy and PCa controls concurrently ^[314, 315]. Basaria et al. ^[314] observed no significant difference in absolute total body lean mass in 20 men (mean age, 70 years) treated with ADT when compared to age-matched healthy (n=18) and PCa controls (n=20). In contrast, absolute total body lean mass was 3.7 kg and 3.8 kg lower in 67 men treated with chronic ADT (> six months; mean age, 71 years) when compared to healthy (mean age, 63 years) and PCa controls (mean age, 67), respectively ^[315]. However, these findings should be interpreted with caution given the 4-8 year discrepancy in age between groups and the lack of control for this confounding variable in the analyses ^[315]. In our study, we observed that absolute total body lean mass was 2.4-3.0 kg lower in men treated with ADT compared to both controls, but these differences were not significant. Nevertheless, given that lower amounts of lean mass are associated with a myriad of adverse outcomes, including compromised cardiometabolic risk, an increased risk for osteoporosis and related fractures, mobility limitations and mortality ^[45, 46, 48, 93], these

differences are likely to be clinically meaningful. Indeed, losses of lean mass that classify patients as pre-sarcopenic or sarcopenic (using various established cut-offs) have been associated with poorer outcomes in cancer patients, such as those associated with mortality, disease progression, treatment-related complications and patient-reported outcomes ^[316].

A unique component of our study was that we investigated the effects of ADT on absolute regional lean mass (arm, leg and appendicular) in men treated with ADT and both PCa and healthy controls. Consistent with the findings for absolute total body lean mass, we found no significant differences in absolute arm, leg or ALM, although the latter was 1.4-2.0 kg lower in men treated with ADT when compared to both controls. These findings are partially supported by the only other known cross-sectional study that examined differences in absolute regional lean mass between 48 men treated with ADT (mean age, 70 years) and 70 age-matched healthy controls ^[33]. In this study, there were no differences between groups for either arm, leg or ALM, although ADT-treated men had a 0.8 kg lower ALM. ^[33] Of note, this study did not include a PCa control group, hence the diagnosis and/or non-hormonal treatment of PCa in these men may have influenced these findings. Moreover, robust measures of diet and physical activity were not controlled for in the analyses. Thus, it is possible that the approximate two-fold greater differences in absolute ALM we observed were more likely to reflect the true effects of ADT in these men when compared to controls. The lack of any significant differences between the three groups in our study may relate in part to the marked heterogeneity in terms of the duration of ADT use (3-169 months) among treated men, with 31% of our sample treated for less than nine months. Previous research has indicated that duration of ADT appears to be important when considering lean mass, with losses of up to 2.6-3.2% of total body lean mass occurring within the initial 6-9 months of treatment ^[195]. Given that around one-third of men in our study had not received ADT for this duration when assessed for this study, it is possible that we may have underestimated the true effects of chronic ADT ($\geq$ six months) on total body and regional lean mass. However, it is worth noting that we observed no association between ADT duration and total body or regional lean mass in our study. This association has received limited attention when considering ADT duration as a continuous variable, however, when dichotomised, men treated with acute ($<$ six months) ADT trended towards greater losses in lean mass (3.7% vs 2.0%) when compared to men undergoing chronic ($\geq$ six months) ADT over a three year

period ^[12]. Additionally, a 52-week prospective study of 80 men observed that men treated with acute ADT (mean age, 69 years) demonstrated a loss of 3.5% total body lean mass, whereas men treated with chronic ADT (mean age, 71 years) showed no change ^[18]. Collectively these findings suggest that while the loss of absolute lean mass may be greater after the initial onset of hypogonadism, these losses may eventually decelerate or plateau. Identifying the time-point in which these decelerations or plateaus may occur could lead to advancements in clinical decision making with regard to the long term management of PCa with ADT.

The accumulation of total body adiposity during ADT, compared to that of normal ageing, is well established in men with PCa ^[195]. For instance, previous cross-sectional studies have shown that total body fat mass is greater in men treated with ADT when compared to non-treated PCa men (mean difference, 3.9 kg ^[315]) and healthy controls (mean difference, 5.7-5.8 kg ^[315, 317]). Similarly, total body percent fat mass has been reported as 3.9-6.0% ^[32, 314, 315, 318] and 2.9-9.8% ^[32, 33, 314, 315, 317, 318] greater in ADT-treated men when compared to PCa and healthy controls, respectively. In line with these findings, we found that men treated with ADT had greater total body fat mass compared to PCa control (5.0 kg and 4.8%) and tended to have greater fat mass than healthy controls (3.3 kg and 3.3%). Interestingly, in a sample of 1,129 healthy older men (mean age, 74 years), Koster et al. ^[319] observed that leg lean mass was 1.3 kg greater per standard deviation increment (7.0 kg) of total body fat mass, suggesting that men with greater adiposity have increased lean mass ^[319]. Consistent with these findings, there is evidence from one cross-sectional study that showed obese older men (mean BMI, 31.9 kg/m²; mean age, 66 years) have 18%, 26% and 14% higher absolute lean mass in the trunk, android and gynoid regions, respectively, than age-matched healthy weight men (mean BMI, 23.4 kg/m²) ^[320]. It has been suggested that the greater lean mass often observed in overweight/obese individuals may be explained by additional muscle contractile work required during normal locomotion and activities of daily living associated with carrying around the excessive fat ^[320]. In light of these findings, and the observation of greater amounts of fat mass in the ADT-treated men in our study compared to controls, there is a need to adjust muscle outcomes for adiposity and/or body size in this cohort of men to gain a greater understanding of the effects.

To date, there have been a number of methods proposed to adjust lean mass for adiposity and/or body size, including the FNIH method that adjusts ALM for BMI (ALM_{BMI}) and the EWGSOP approach adjusting ALM for height alone (ALMI) ^[51, 53]. When ALM was adjusted for BMI in our study, we found that men treated with ADT had 10-12% lower ALM_{BMI} than both controls. In contrast, no difference was observed between groups when adjusting ALM for height (ALMI). To our knowledge, only one other study in men treated with ADT adjusted ALM for height (ALMI) and observed that 30 ADT-treated men (mean age, 72 years) and 25 age-matched non-ADT hypogonadal controls had similar ALMI (mean, both 7.5 kg/m²). These findings in hypogonadal men (regardless of whether induced by ADT or not) were of a similar magnitude to the mean ALMI in our study (mean, 7.86 kg/m²). However, to our knowledge adiposity-based adjustments are yet to be applied in men treated with ADT when compared to controls, but some studies have considered adjustment for body size (e.g. total body percent lean mass). Clay et al. ^[32] reported that 42 men treated with chronic ADT (> six months; mean age, 73 years) had 4.4% and 4.5% lower total body percent lean mass compared to PCa and healthy controls, respectively. Similarly, a cohort of 29 chronic ADT-treated men (> six months; mean age, 73) were shown to have 3.9% and 5.4% less total body percent lean mass when compared to PCa and healthy controls, respectively ^[318]. When we expressed total body lean mass as a percentage of total body weight, we found that men treated with ADT had 4.6% less total body percent lean mass when compared to PCa controls, but not healthy controls. While adjustment for body size when expressed as total body percent lean mass tends to detect compromised muscle in men treated with ADT when compared to controls, our findings that ALM_{BMI} in ADT-treated men differed to both groups, whereas total body percent lean mass only differed in comparison to PCa controls, supports the use of adiposity-based adjustments when considering these men and their susceptibility to treatment-induced increases in adiposity.

Effects of androgen deprivation therapy on appendicular muscle cross-sectional area

Another novel aspect of this cross sectional study was the assessment of forearm and lower leg muscle CSA assessed via pQCT, which is important as this technique can provide an accurate measure of muscle size ^[77]. However, consistent with the DXA absolute arm, leg and ALM findings, there were no significant differences between the three groups for absolute muscle CSA at either site. While no previous studies appear to have assessed the effects of ADT on pQCT-derived muscle CSA at these sites,

several prospective studies examining absolute muscle CSA at different sites (i.e. paraspinal, quadriceps, rectus femoris and sartorius) observed decrements of 3.2-5.5% in paraspinal muscles and 15-22% in muscles of the upper leg over 15-48 weeks of therapy [15-17]. Unfortunately these studies did not include control groups and neglected to account for known confounding variables, such as physical activity and diet [15-17]. While the lack of any significant differences in absolute muscle CSA (and lean mass) between ADT-treated men and controls in our study conflicts with our initial hypotheses, an interesting observation in our study was the forearm muscle CSA expressed as a percentage of total arm area was 6.1% and 5.4% smaller in the ADT men compared to PCa and healthy controls, respectively. This suggests that relative to body size, men treated with ADT have smaller forearm muscle size. However, lower limb muscle size does not appear to be compromised, which could be due to the fact that this is a weight-bearing (loaded) site [320], suggesting that ADT may have regional effects leading to greater losses at non weight-bearing sites. Moreover, regardless of the lack of difference between the three groups, we found that ADT duration was negatively correlated with both forearm and lower leg percent muscle CSA. Whilst these findings are difficult to explain given that we did not observe similar correlations for body size- and adiposity-adjusted lean mass outcomes, this may potentially be explained by the increased accuracy of quantifying muscle via pQCT when compared to DXA [77].

Effects of androgen deprivation therapy on muscle strength

With regard to muscle strength, previous research has shown that age-related losses in healthy older men are two-to-four fold greater than the losses in muscle mass [39], and that low muscle strength is a stronger predictor than muscle mass for poor physical performance, functional limitations and physical disability [182]. This suggests that muscle strength may be a clinically more relevant measure to assess than muscle mass. In our study, we found that absolute handgrip strength and muscle strength of the legs, back and chest was lowest in the ADT men, but there were no significant differences between the three groups. Previous studies in men treated with ADT have reported mixed results in terms of muscle strength when compared to both PCa and healthy controls [198]. Consistent with our findings, Joly et al. [26] reported no difference in handgrip strength between 57 men treated with ADT (mean age, 73 years) and 51 healthy age-matched controls. In contrast, another study in 20 men treated with ADT (mean age, 74 years) found that handgrip strength was 29% lower compared to 20 age-

matched healthy controls ^[27]. Notably, ADT-treated also demonstrated 67% poorer hand dexterity and were more likely to self-report compromised hand function when compared to healthy controls ^[27]. As ADT has not been previously associated with compromised hand dexterity and function, these differences may indicate that men treated with ADT in this previous study had poorer health than ADT-treated men in the current study; thus potentially explaining why these men had approximately 10 kg lower handgrip strength than those in our study. Galvão et al. ^[33] showed that 48 men treated with ADT (mean age, 70 years) had 15% and 9.1% less chest (chest press 1-RM) and back (seated row 1-RM) muscle strength, respectively, but similar leg muscle strength (leg press 1-RM) when compared to 70 age-matched healthy controls. Similarly, another cross-sectional study of 20 men treated with ADT (mean age, 70 years) demonstrated that they had approximately half the chest muscle strength (bench press 1-RM) of 18 age-matched PCa controls, yet no difference in leg muscle strength (leg press 1-RM) ^[314]. Collectively, these results suggest that similar to muscle size, non-load bearing sites (e.g. muscles of the upper body) are more likely to be compromised by ADT when compared to appropriately selected controls.

As with muscle mass, there is some evidence that increased body size and/or adiposity has been associated with greater muscle strength in healthy older men ^[319], and thus muscle strength is often normalised to body weight (e.g. expressed as strength per kilogram of body weight). In our study, when measures of muscle strength were expressed relative to weight, we found that men treated with ADT had 13% lower chest and 15-18% lower back muscle strength compared to both controls. Moreover, ADT-treated men had 21% lower leg muscle strength per kilogram of body weight compared to healthy controls, but not PCa controls. However, no significant differences were observed in weight-adjusted handgrip strength between the three groups. These findings suggest that treatment with ADT may have systemic effects on muscle strength when normalised to body weight. While our study is the first to report muscle strength per kilogram of body weight in men treated with ADT, similar adjustments were applied in a sample of 1,129 men aged 70-79 years after it was observed that for every standard deviation increase in fat mass (approximately 7.1 kg), leg muscle strength was 3.0-4.7 Nm greater ^[319]. Additionally, leg muscle strength per kilogram of body weight was 0.6-0.9 Nm/kg lower per standard deviation increase in fat mass ^[319]. This suggests that despite having greater absolute leg muscle strength, relative to body weight, men with greater body size were weaker. Potential reasons for

these observations may include the accumulation of fat around and/or within muscle tissue (termed intermuscular or intramuscular fat; see Chapter 5) or potential neurological changes associated with ADT-induced hypogonadism. Indeed, in healthy older men there is evidence that an increase in skeletal muscle fat infiltration is associated with lower muscle strength ^[177]. The influence of ADT on skeletal muscle fat infiltration will be discussed in Chapter 5. It has also been reported that age-related losses in muscle strength were only weakly associated with changes in muscle CSA ^[84]. This may be related to various age-related neurological changes, including a decrease in the number of functional motor units and the rate in which these can be maximally discharged, as well as a reduction in spinal excitability ^[321]. In our study, when muscle strength was expressed per kilogram of lean mass, we found that back muscle strength was significantly lower in ADT-treated men compared to controls. Whilst there were no between-group differences observed for the other measures of muscle strength per kilogram of lean mass, the findings from our study provide some evidence to support the notion that ADT induced impairments in muscle strength may be independent of changes in lean mass. Previous research has reported that androgens, such as testosterone, can enhance neural excitability ^[322, 323]; thus, hypogonadism may impair neural function in men treated with ADT which may influence muscle strength. Therefore, despite men with ADT having similar absolute muscle strength values compared to PCa and healthy controls, men treated with ADT appear to possess compromised muscle strength relative to body size/composition, with these deleterious effects likely extending beyond a loss of lean mass and/or muscle CSA alone.

Effects of androgen deprivation therapy on gait speed

In addition to muscle mass and strength, functional performance has been identified as a key factor associated with an increased risk for incident disability, falls and fractures, hospitalisation, cognitive impairment and dementia ^[132]. In our study, we found that men treated with ADT had 5.6-6.9% slower gait speed (0.08-0.10 m/sec) compared to both controls. A pooled analysis of seven studies involving 27,220 community-dwelling older adults aged 65 years or greater reported a 25-32% risk reduction for incident disability for every 0.1 m/sec increment in gait speed ^[324]. Similarly, there is evidence that for every 0.1 m/sec increase in gait speed, the risk of mortality is reduced by 12% ^[47]. However, it is important to note that the mean gait speed of the men treated with ADT in our study was 1.40 m/sec, which is well above the 0.8-1.0 m/sec threshold that has been reported to be associated with incident disability, falls and fractures,

hospitalisation and mortality ^[51, 53]. Thus, despite a significant difference in our study between men treated with ADT relative to PCa and healthy controls, the absolute values remain within the healthy range, which suggests that such a difference may not be clinically relevant. Consistent with our findings, a previous study found that although 48 men treated with ADT (mean age, 70 years) had 6.3% slower gait speed when compared to 70 age-matched healthy controls, group mean values were 1.25 m/sec and 1.33 m/sec, respectively ^[33], which are both also above clinically relevant cut-offs. In contrast, no difference was observed between 63 ADT-treated men (mean age, 72 years) and 71 age-matched PCa controls, however, similar to our study, both groups had a gait speed within the healthy range (both > 1.20 m/sec) ^[31]. While men treated with ADT tend to have compromised gait speed relative to controls, these values are likely not of clinical significance, given the lack of adverse outcomes associated with speeds greater than 1.00 m/sec. Therefore, exploration of other measures of functional capacity are warranted in men treated with ADT to potentially detect those at greater risk of long term adverse effects on functional outcomes.

Effects of androgen deprivation therapy on muscle power

Measures of lower limb muscle power, which represented the ability to produce force rapidly, have been suggested to be a better predictor than muscle strength with regard to predicting mobility and ambulation impairments, as well as falls, in older adults ^[151, 325, 326]. In our study, we examined functional muscle power via the 30-second sit-to-stand test ^[130], that has shown good correlation ($r=0.6$) with the Nottingham power rig ^[131], which is generally considered the gold standard for quantifying muscle power in older adults ^[129]. We found that men treated with ADT had 14% lower 30-second sit-to-stand performance compared to healthy controls, but not PCa controls. Notably, on average men treated with ADT completing two less repetitions during the 30-second test when compared to both controls (13 vs 15 repetitions). In a sample of 2,140 adults aged 60 years or greater, 13 repetitions was associated with self-reported physical independence in men aged 70-74 years (mean age of ADT group in our study, 73 years) ^[327]; thus, differences observed in our study between men treated with ADT and controls may not be of clinical relevance. However, within the same study, men aged 70-74 years who scored less than 15 repetitions were associated with not having the ability to retain physical independence ^[327]. Therefore our findings suggest that when compared to PCa and healthy controls, men treated with ADT were likely to currently be physically independent, but may be at risk of losing physical independence in the

long-term; hence, investigating approaches to preserve this independence is warranted in this susceptible population group. These results are in part supported by the only other cross-sectional analysis that compared sit-to-stand performance, albeit a time to complete five repetitions protocol, in ADT-treated men and both PCa and healthy controls [32]. Clay et al. [32] observed that 42 men treated with chronic ADT (mean duration, 30.7 months; mean age, 73 years) had 10% (15.2 seconds vs 13.7 seconds) poorer functional muscle power when compared to PCa controls (n=25), but not healthy controls (n=20), when adjusted for age, comorbidities, BMI and total body percent fat mass. Moreover, 13 men treated with acute ADT (mean duration, 3.7 months; mean age, 74 years) within the same study on average completed the test in 13.2 seconds and showed no differences compared to either control [32]. Although the sample size in this study was small, these findings suggest that the duration of ADT may be an important factor when evaluating the effects of ADT on muscle power. However, in our study we found no association between duration of ADT use and 30-second sit-to-stand performance. While it is difficult to directly compare the findings across studies due to the dissimilar sit-to-stand protocols used and the variables accounted for in the analyses, collectively the findings suggest that ADT may impair functional muscle power and suggest that these men are at risk of losing independence and/or recurrent falls. However, further studies using more robust measures are needed to understand the true effects on ADT on muscle power.

Effects of androgen deprivation therapy on balance and mobility

It is well established that impairments in static and/or dynamic balance are associated with increased falls risk in community-dwelling older adults [328]. Additionally, assessments of mobility, particular those of distances/duration capable of inducing cardiorespiratory and/or muscular fatigue (e.g. 400 metres), have been shown to independently predict mortality in older adults [329]. Within our study, we observed no differences in assessments of balance or mobility (timed-up-and-go, four-square step test, Berg balance scale and 400 metre walk) between the three groups. Men treated with ADT in our study demonstrated mean values of 11.02 seconds, 10.05 seconds, 55 points and 286 seconds (approximately 4.75 minutes) for timed-up-and-go, four-square step test, Berg balance scale and 400 metre walk, respectively. These results are within healthy ranges based on the previously proposed cut-offs for predicting falls risk in community-dwelling older adults for timed-up-and-go (≥ 15 seconds [133]), four-square step test (≥ 15 seconds [134]) and Berg balance scale (45 points [330]). Moreover,

evidence from 948 adults aged 65 years or greater showed that the ability to complete the 400 metre walk was associated with three-fold lower risk of mortality when compared to those unable to complete the test ^[329]. Therefore, men treated with ADT in our study likely did not possess increased falls and mortality risk associated with balance and mobility. Our findings are supported by observations that timed-up-and-go performance did not differ between 57 men treated with ADT (mean age, 73 years) and 51 age-matched healthy controls, with ADT-treated men similarly having had mean results (6 seconds) below previously proposed cut-offs for falls risk ^[26]. Of note, the lower time to complete the test in comparison to men treated with ADT in our study may stem from our study having used a dual-task version of the timed-up-and-go, as opposed to the traditional single-task protocol, which has been shown to take less time to complete ^[133]. In contrast to our findings, in the only other known cross-sectional study that investigated differences in 400 metre walk performance between 48 ADT-treated men (mean age, 70 years) and 70 age-matched healthy controls, those treated with ADT were found to have 6.8% poorer performance ^[33]. However, this difference may be of limited clinical relevance given that the ADT-treated men in this study completed the test in approximately 4.5 minutes ^[33], which would classify them in the fastest quartile of community-dwelling older adults ^[329]. Collectively, it appears that men treated with ADT do not have compromised balance and mobility when compared to appropriately selected controls and are therefore not at increased risk of falls and mortality commonly associated with poorer outcomes in these tests.

Effects of androgen deprivation therapy on (pre)sarcopenia, obesity and sarcopenic obesity

Globally sarcopenia is now recognised as a clinical condition characterised by varying combinations of slow gait speed, impaired muscle strength and low ALM ^[51-53]. Although there remains a lack of consensus internationally with regard to the precise clinical cut-points for each of these measures, based on the most widely adopted criteria we found that the prevalence of sarcopenia in our cohort of ADT men and controls was 0.0% using the IWGS definition and ranged from 1.4% to 5.9% for the EWGSOP and 0.0% to 5.7% for the FNIH definitions, respectively. To our knowledge, this study is the first to evaluate the prevalence of sarcopenia using these methods in men treated with ADT compared to appropriately selected controls. Although significant differences were observed when ADT-treated men were compared to both controls using the FNIH definition which adjusted ALM for adiposity (BMI), these

findings must be interpreted with caution given that only two men treated with ADT were found to be sarcopenic (and no controls). Overall, the low prevalence of sarcopenia can be largely related to the fact that there was little evidence of impaired gait speed (<0.8 or < 1.0 m/s) in any of the groups, with only one participant treated with ADT having met this criteria. This limitation, as well as the low prevalence of sarcopenia specifically in men treated with ADT, may be partially attributed to the recruitment strategies utilised for this cross-sectional analysis. ADT-treated men were recruited on the basis of involvement in an ongoing exercise training RCT, thus the influence of recruitment bias, both from potential participants (e.g. healthier men may have been more likely to seek involvement) and selection criteria (e.g. exclusion of men with absolute contraindications to exercise), cannot be discounted and the applicability of these findings to the broader ADT patient population group should be interpreted with caution. Nevertheless, given the role of adiposity observed in our study on various muscle outcomes, these findings further support the concept that for men treated with ADT it is important to account for adiposity when evaluating the effects of this therapy on muscle.

Given the low prevalence of sarcopenia in men treated with ADT compared to controls in our study, we also examined established cut-offs for pre-sarcopenia (low lean mass alone) to assess the ability of these definitions to distinguish risk in this group. We found that when adjusted for adiposity (ALM_{BMI} and ALM_{HFM}), rather than height ($ALMI$), 7.2-34% more men treated with ADT were pre-sarcopenic when compared to either controls. Similar discrepancies between definitions were shown in a cohort of 1,435 older men (mean age, 74 years), whereby 8.9% of overweight (BMI, 25-29 kg/m^2) and 0.0% of obese (BMI, ≥ 30 kg/m^2) men were diagnosed with sarcopenia using the $ALMI$ definition (< 7.23 kg/m^2), compared to 15% and 12% of overweight and obese men, respectively, when the residual method of ALM_{HFM} was applied^[82]. This further highlights the need to account for adiposity in populations with increased adiposity, such as men treated with ADT for PCa. While yet to be examined in men treated with ADT specifically, adiposity-adjusted cut-offs (e.g. $ALM_{BMI} < 0.789$) have been associated with an increased risk of all-cause mortality (OR, 1.47) in a cohort of 4,449 older adults (age, ≥ 50 years)^[331]. Therefore, the adiposity-adjusted definitions and cut-offs (i.e. ALM_{BMI} and ALM_{HFM}) for pre-sarcopenia appears to have increased sensitivity to detect potentially clinically relevant differences when comparing ALM in men treated with ADT compared to appropriately selected controls.

Although in their infancy, definitions of sarcopenic obesity may provide unique insights into the risk profile of ADT-treated men given the significance of considering adiposity when comparing muscle outcomes to appropriately selected controls. Sarcopenic obesity has been shown to be associated with a myriad of health issues in older men, such as increased cardiometabolic risk and subsequent mortality, beyond that of sarcopenia or obesity alone ^[55]. In our study we observed no cases of sarcopenic obesity, but 13% more men treated with ADT presented with pre-sarcopenia and obesity concurrently when compared to PCa controls, but similar differences were not apparent when compared to healthy controls. Furthermore, differences were only detected when using the ALMI cut-off of $\leq 7.26 \text{ kg/m}^2$ (EWGSOP ^[53]) as opposed to $\leq 7.49 \text{ kg/m}^2$ (EWGSOP/IWGS ^[52, 53] adapted for our study sample). This further strengthens the notion that the development of ADT population-specific cut-offs for ALM may improve the ability to detect risk in these men when compared to their non-ADT counterparts and healthy controls. Collectively, these findings should also be interpreted with caution given the current lack of a consensus definition of sarcopenic obesity and the limited number of cases observed in our study. Nevertheless, our findings regarding muscle outcomes relative to adiposity highlight the potential for more robust future definitions of sarcopenic obesity to act as a risk assessment tool in this susceptible population group.

4.7 Strengths and limitations

This study has many strengths, inclusion of both PCa and healthy controls allowed for the effects of ADT to be quantified independent of PCa diagnosis, non-hormonal PCa treatment and ageing. Additionally, the assessment of each component of the most widely used composite definitions of sarcopenia ^[51-53] allowed for the novel application of sarcopenia within this group, which permitted an assessment of risk beyond that of individual outcomes alone. Furthermore, a range of potential confounding variables were accounted for via a strict list of inclusion/exclusion criteria for both PCa and healthy controls, validated assessments of confounders such as physical activity (energy expenditure) and diet (energy intake). Moreover, this study used robust measures of lean and fat mass via DXA and muscle CSA via pQCT; of which the latter provided the first known measurements of the forearm and lower leg in men treated with ADT compared to both PCa and healthy controls. Finally, this study was adequately powered to detect significant differences between groups for

multiple key outcomes, including total body lean mass, total body percent fat mass, handgrip strength and gait speed.

However, several limitations also need to be considered when interpreting results. First, volunteer bias may have yielded results which were not representative of the broader population. As mentioned in the discussion, men treated with ADT in this analysis were involved in a larger RCT in which all agreed to be potentially allocated to a 52-week exercise training and nutritional supplementation intervention, which may have limited the study sample to only those capable and willing to complete such an intervention; therefore these men may have been healthier than the average man treated with ADT. Conversely, PCa and healthy controls were recruited for a single visit promoted as a ‘free health assessment’, thus potentially increasing the likelihood that those with pre-existing medical conditions or concerns would volunteer; hence these individuals may have had compromised health when compared to the general population. Second, for some measures there was missing data, such as the 3-RM protocols, in which 20-25% of the total sample did not complete tests due to an unexpectedly high prevalence of relative contraindications (e.g. current musculoskeletal injury, hypertension or cardiometabolic disease) for exercise testing as defined by the American College of Sports Medicine ^[24]; thus, further supporting that our control groups may have had poorer overall health when compared to the broader population. Third, while less crucial in cross-sectional studies when compared to those prospectively designed, the majority of outcomes were not obtained by a researcher blinded to group allocation; however, DXA and pQCT outcomes were assessed blinded to group allocation. Fourth, the potential that reverse casualty was observed cannot be excluded (e.g. increased fat mass may have led to PCa progression and thus the need for ADT ^[332]). Fifth, due to the cross-sectional design of this study, causality could not be assessed for outcomes of interest. Finally, although applied in previous studies to account for the confounding role of adiposity, there are limited long-term prospective studies that have established the ability of adiposity- and body size-adjusted muscle mass, size and strength outcomes to predict risk in older men, let alone in men treated with ADT, and thus the inference of risk associated with these outcomes should be made with caution.

4.8 Summary and Conclusion

In summary, our study demonstrated that men treated with ADT did not have compromised absolute total body and regional muscle mass and muscle CSA when compared to PCa and healthy controls, however ADT-treated men had greater total body fat mass. When accounting for these differences via body size- or adiposity-based adjustments, men treated with ADT were shown to have lower regional lean mass and muscle CSA compared to controls. Similar findings were observed when muscle strength outcomes were adjusted for weight. Men treated with ADT were also shown to differ in some, but not all, measures of functional capacity when compared to controls. Subsequently, men treated with ADT were more likely than both controls to present with pre-sarcopenia, sarcopenia, obesity and pre-sarcopenia/obesity concurrently.

In conclusion, the absolute differences in total body and regional lean mass between men treated with ADT and controls were likely of clinical relevance in terms of risk stratification and more noticeably occurred in non-load bearing sites (i.e. upper body), suggesting that these sites may be more suitable for monitoring the long-term risk associated with ADT. Moreover, considering these differences relative to body composition (i.e. ALM_{BMI} and ALM_{HFM}), due to greater amounts of total body fat mass associated with ADT, would likely increase the ability to detect those at risk in this susceptible population group. Muscle strength outcomes warrant similar considerations (i.e. body composition adjustments and monitoring non-load bearing sites) if these tests are to be used for risk stratification and/or clinical decision making. Based on our observations, assessments of balance and mobility are less likely than assessments of functional muscle power to identify men at risk of long-term adverse outcomes, such as recurrent falls or losing independence. Collectively, risk stratification of ADT-treated men may benefit from the use of body composition-adjusted cut-offs of pre-sarcopenia (i.e. ALM_{BMI} and ALM_{HFM}), but limited evidence was found to support the use of known sarcopenia and/or sarcopenic obesity cut-offs. Thus, the development and evaluation of ADT-specific cut-offs for sarcopenia and sarcopenic obesity may aid risk stratification in this clinical population group. In the following chapter, differences in regional fat, including a novel marker of intermuscular fat (pQCT-derived muscle density), will be examined between men treated with ADT and controls.

Chapter 5

The effects of androgen deprivation therapy in men with prostate cancer on regional depots of fat: results from a cross-sectional study

5.1 Declaration statement

Under the guidance of supervisors, the candidate developed the study concept and initiated the project, provided significant input into the development of the protocol, implemented the protocol and oversaw the collection of the data, analysed and interpreted all data presented.

5.2 Overview

This chapter presents the results from a cross-sectional study. The study examined whether there were any differences in regional fat mass and cross-sectional area (CSA) and muscle density (as a marker of intermuscular fat) in men treated with androgen deprivation therapy (ADT) when compared to prostate cancer (PCa) and healthy controls. Additionally, this chapter presents within-group correlations between ADT use duration and outcomes discussed in men treated with ADT.

5.3 Introduction

In developed countries, PCa has been commonly shown to contribute to male cancer-related morbidity and mortality ^[1, 2]. Appropriately selected men with PCa have benefited from ADT in terms of disease progression and survival ^[5-9], however, the hypogonadism induced by the treatment is often associated with a marked increase in total body percent fat mass (6.6-14%) ^[17-23]. The accumulation of fat mass may in part explain why men treated with ADT have been shown to have a 11-20% and 16-44% increased risk of cardiovascular disease and type 2 diabetes, respectively, when compared to men not treated with this therapy ^[207, 333, 334]. This is of importance given that the most common cause of non-cancer-related mortality in men diagnosed with PCa is cardiovascular disease ^[189, 335]. However, given that the accumulation of fat in varying depots may have differing effects in terms of the risk of morbidity and mortality in older men ^[40], the investigation of regional fat depots is warranted.

Currently, the gold standard for the acquisition of regional fat mass and CSA with high accuracy is magnetic resonance imaging (MRI) and computed tomography (CT) ^[40, 111]. These tools have the advantage of providing a three-dimensional assessment of fat CSA or volume ^[111]. However, the high cost of CT and MRI scan acquisition and data processing, complications with claustrophobic and severely obese individuals (body mass index [BMI] ≥ 40 kg/m²), and in the case of CT, high exposure to ionising radiation ^[76, 111], may in part explain why these techniques are less commonly used in

the research setting. Advancements in the precision and availability of dual-energy x-ray absorptiometry (DXA) ^[118, 119] and peripheral quantitative CT (pQCT) ^[117] for quantifying regional fat mass and CSA have led to suggestions that these measures may have the potential to be of clinical importance with regard to risk stratification and clinical decision making in men treated with ADT ^[216].

Previous research has shown that fat accumulation in subcutaneous depots, such as those in the gynoid (hips) region, appear to be negatively associated with cardiometabolic risk in healthy older men, whereas the accumulation of fat within depots of the abdominal cavity (android region) have been shown to be positively associated with this risk ^[40]. Moreover, differences within these specific regions may be of clinical relevance, with findings in healthy men demonstrating that abdominal visceral fat, when compared to abdominal subcutaneous fat, tends to be associated with an increased risk for hypertension (odds ratio [OR], 1.9 vs 1.5), impaired glucose metabolism (OR, 1.8 vs 1.5), diabetes (OR, both 1.6) and metabolic syndrome (OR, 4.2 vs 2.5) ^[102]. Similarly, the accumulation and infiltration of fat within muscle, leading to decreased muscle density ^[77], has been associated with many of the above cardiometabolic risk factors as well as decreased lower limb muscle strength and functional capacity, independent of muscle CSA ^[177, 178].

To date, the accumulation of fat within regional depots has received limited attention in men treated with ADT compared to appropriately selected controls. To our knowledge, only one study has compared DXA-derived arm, leg and trunk fat mass in ADT men compared to healthy controls ^[33]. This study found that only leg fat mass was greater (17%; 1.1 kg) in ADT-treated men compared to controls ^[33]. Only one study has also examined muscle density (as a marker of intermuscular fat) in ADT-treated men (n=39) and showed that 15-20 weeks of therapy resulted in a 19% decrease in rectus femoris muscle density ^[15]. However, this study did not include an appropriately selected control group and utilised varying CT scanners due to the multi-centre design ^[15]. Two prospective studies have examined regional fat outcomes in men treated with ADT, and found that ADT-treated men had an 11-13% increase in abdominal subcutaneous fat mass and either a 22% increase or no change in abdominal visceral fat mass ^[17, 199]. However, a limitation of these studies is that they included small sample sizes (total n=26-32) and no control group. Therefore, the primary aims of this study were to compare total and regional fat mass, fat CSA and muscle density

(as a measure of intermuscular fat) in men treated with ADT for PCa when compared to non-ADT treated PCa men and healthy controls. A secondary aim was to assess the influence of ADT use duration on these outcomes.

5.4 Methods

Details on the methodology of this study are discussed in Chapter 3. Briefly, this was a cross-sectional study in which comparisons were made between 42 men treated with ADT for PCa, 54 men treated with non-hormonal therapies (men currently treated with active surveillance were eligible for inclusion in this group) for PCa (PCa controls) and 70 men not diagnosed with PCa (healthy controls). Men treated with ADT were recruited via clinician referral across various hospitals, private practices and health networks, as well as from PCa support groups and advertisements in state/local newspapers. PCa and healthy controls were recruited from PCa support groups and advertisements in state/local newspapers.

Total and regional fat mass (arm, legs, android, gynoid, abdominal visceral and abdominal subcutaneous) was assessed by DXA. Forearm (66% radius) and lower leg (66% tibia) fat CSA and muscle density (as a marker of intermuscular fat) were assessed by pQCT ^[312]. Habitual physical activity and diet were assessed by self-reported questionnaire and 24-hour food recall, respectively. Demographical, clinical and lifestyle information was assessed by questionnaire. Missing data among the three groups is presented in Table 5.1.

Table 5.1. Missing data in the three groups.

Measure	Added after study began			Unable to define ROI			Movement artefact *			Pre-existing comorbidities			Total		
	ADT	PC	HC	ADT	PC	HC	ADT	PC	HC	ADT	PC	HC	ADT	PC	HC
DXA total body scan	-	-	-	1	0	0	-	-	-	-	-	-	1	0	0
pQCT forearm	-	-	-	1	0	0	5	6	8	-	-	-	6	6	8
pQCT lower leg	-	-	-	0	0	0	2	4	2	-	-	-	2	4	2

Data are: number of participants with missing data. ADT, men treated with androgen deprivation for prostate cancer; DXA, dual energy x-ray absorptiometry; HC, healthy control; PC, prostate cancer control; pQCT, peripheral quantitative computed tomography; ROI, region of interest. * Excluded based on scores of four or five on the visual inspection rating scale of participant movement proposed by Blew et al. ^[311].

All analyses were performed using SPSS 24.0 (IBM Corp, Chicago IL, United States of America). Initially, all data were screened for outliers and descriptive statistics were computed to compare the three groups on known confounding variables of the primary outcomes. Equality of variances of all data were assessed using Levene's test. Normality of distribution of all data were assessed using Shapiro-Wilk's test. Data in violation of equality of variance or normal distribution underwent natural log (arm fat mass, leg fat mass, forearm fat CSA, forearm percent fat CSA, lower leg fat CSA, lower leg percent fat CSA, forearm muscle density and lower leg muscle density) or square root (total body fat mass, android fat mass, gynoid fat mass and abdominal visceral fat mass) transformation prior to all analyses, but all data presented were derived from raw values. Between-group comparisons were assessed by analyses of covariance (ANCOVA), with age (years) and physical activity (energy expenditure; kilojoules/day) as covariates. The Kruskal-Wallis test was used for data that remained non-parametric following transformation (abdominal subcutaneous fat mass). Post-hoc analyses applied the Bonferroni correction, with the addition of Mann-Whitney tests following non-parametric analyses. In the men treated with ADT only, the strength and direction of associations between duration of ADT use and all outcomes were assessed by Spearman rank-order correlation coefficient. Continuous data were reported as mean $\pm$ standard deviation, whereas categorical variables were reported as frequency and percentage, unless stated otherwise. A significance level of $P < 0.05$ was adopted for all statistical tests.

5.5 Results

5.5.1 Participant characteristics

Participant characteristics of the three groups were reported in Chapter 4. In brief, men treated with ADT were approximately four years older, more likely to take one additional prescription medication and tended to have a 23-30% lower level of habitual physical activity (energy expenditure) when compared to both control groups. No differences were observed between groups for diet.

5.5.2 Total and regional fat mass and cross-sectional area

A significant between-group difference was observed for total body fat mass and percent fat mass, but not weight (Table 5.2). Men treated with ADT had 5.0 kg ($P=0.015$) and 4.8% ($P=0.005$) greater total body fat mass and percent fat mass, respectively, when compared to PCa controls, but not healthy controls (both $P >$

0.061). With regard to regional fat mass, there were no significant differences between the groups for android or abdominal visceral fat mass. A between-group difference was observed for arm, leg and gynoid fat mass and forearm fat CSA and percent fat CSA. Post-hoc analyses revealed that when compared to PCa and healthy controls, men treated with ADT had 19% greater arm fat mass ($P=0.003$ and $P=0.006$, respectively), 20-21% greater leg fat mass ($P=0.007$ and $P=0.016$, respectively), 15-18% greater gynoid fat mass ($P=0.012$ and $P=0.032$, respectively), 29-36% greater forearm fat CSA ($P=0.002$ and $P=0.023$, respectively) and 4.8-5.8% greater forearm percent fat CSA ($P=0.001$ and $P=0.004$, respectively). Men treated with ADT also tended to have greater abdominal subcutaneous fat mass (0.2 kg; $P=0.067$) and lower limb fat CSA (18-22%; $P=0.070$) when compared to controls.

Table 5.2. Mean weight, total body and regional fat mass and fat cross-sectional area, and the mean adjusted between-group differences in men treated with androgen deprivation therapy (ADT), prostate cancer (PCa) controls and healthy controls.

	Unadjusted mean ± standard derivation			P-value	Adjusted mean difference (95% CI)		
	Men treated with ADT	PCa controls	Healthy controls		Men treated with ADT vs PCa controls	Men treated with ADT vs healthy controls	PCa controls vs healthy controls
Total body							
Weight (kg)	86.5 ± 18.0	82.8 ± 13.4	85.5 ± 12.6	0.092	6.7 (-0.7, 14.1)	3.6 (-3.4, 10.5)	-3.1 (-9.3, 3.0)
Fat mass (kg) ^b	29.4 ± 10.7	24.4 ± 8.5	26.1 ± 7.5	0.019	5.8 (1.1, 10.4) *	3.9 (-0.4, 8.2)	-1.9 (-5.7, 2.0)
Fat mass (%)	34.8 ± 7.8	30.0 ± 6.4	31.5 ± 5.4	0.006	4.5 (1.1, 7.9) #	3.1 (-0.1, 6.3)	-1.4 (-4.2, 1.4)
Regional fat mass							
Arm (kg) ^a	2.9 ± 1.0	2.4 ± 0.7	2.4 ± 0.7	0.002	0.7 (0.2, 1.1) #	0.6 (0.2, 1.0) #	0.0 (-0.4, 0.3)
Leg (kg) ^a	8.4 ± 3.3	6.8 ± 2.3	6.9 ± 2.1	0.005	1.8 (0.5, 3.1) #	1.7 (0.4, 2.9) *	-0.1 (-1.2, 1.0)
Android (kg) ^b	3.2 ± 1.5	2.6 ± 1.3	2.9 ± 1.1	0.106	0.6 (0.0, 1.3)	0.3 (-0.4, 0.9)	-0.3 (-0.9, 0.2)
Gynoid (kg) ^b	4.2 ± 1.4	3.5 ± 1.3	3.6 ± 1.1	0.010	0.8 (0.1, 1.4) *	0.7 (0.1, 1.3) *	-0.1 (-0.6, 0.4)
Abdominal visceral (kg) ^b	2.0 ± 1.3	1.6 ± 1.0	1.9 ± 0.9	0.122	0.4 (-0.2, 0.9)	0.1 (-0.4, 0.6)	-0.3 (-0.8, 0.2)
Abdominal subcutaneous (kg) ^c	1.2 ± 0.5	1.0 ± 0.5	1.0 ± 0.4	0.067	0.2 (0.0, 0.5)	0.2 (0.0, 0.4)	0.0 (-0.2, 0.2)
Fat cross-sectional area							
Forearm (cm ²) ^a	12.0 ± 6.5	8.3 ± 3.4	9.0 ± 3.6	0.003	4.0 (1.5, 6.5) #	3.2 (0.9, 5.5) *	-0.8 (-2.9, 1.3)
Forearm (%) ^a	20.1 ± 7.9	14.3 ± 4.9	15.3 ± 5.1	0.001	5.7 (2.4, 8.9) #	4.7 (1.6, 7.8) #	-0.9 (-3.7, 2.4)
Lower leg (cm ²) ^a	21.4 ± 12.5	17.8 ± 8.8	17.2 ± 8.1	0.070	4.0 (-1.2, 9.2)	4.5 (-0.3, 9.4)	0.5 (-3.8, 4.9)
Lower leg (%) ^a	20.6 ± 8.3	17.8 ± 7.0	17.0 ± 6.5	0.067	2.4 (-1.5, 6.3)	3.3 (-0.3, 6.9)	0.9 (-2.3, 4.2)
Muscle density							
Forearm (mg/cm ³) ^a	77.3 ± 2.3	78.2 ± 1.9	77.7 ± 1.7	0.171	-0.6 (-1.7, 0.4)	-0.2 (-1.2, 0.8)	0.5 (-0.4, 1.3)
Lower leg (mg/cm ³) ^a	73.5 ± 3.4	74.8 ± 3.3	74.7 ± 3.1	0.069	-0.7 (-2.4, 0.9)	-0.6 (-2.2, 0.9)	0.1 (-1.3, 1.5)

Data are: unadjusted mean $\pm$ standard deviation and adjusted mean difference (95% confidence interval). * P < 0.05; # P < 0.01; ^a analysis used natural log transformed data; ^b analysis used square root transformed data; ^c Kruskal-Wallis test used for non-parametric data.

5.5.3 Muscle density

Muscle density averages and between-group differences are shown in Table 5.2. No significant differences were observed between groups, although men treated with ADT trended ($P=0.069$) towards having poorer lower leg muscle density (indicative of increased intermuscular fat) when compared to controls.

5.5.4 Duration of androgen deprivation therapy use

The sample of men treated with ADT had undergone an average treatment duration of 34 months (standard deviation, 45 months). Duration of ADT was shown to correlate positively with arm (Spearman's rho [r_s]=0.36), leg ($r_s=0.39$), gynoid ($r_s=0.34$) and abdominal subcutaneous fat mass ($r_s=0.37$), and forearm ($r_s=0.34$) and lower leg fat CSA ($r_s=0.44$; Table 5.3). Duration of ADT was also negatively correlated with forearm muscle density ($r_s=-0.34$). On average, each month of ADT tended to be associated with a 0.1-0.2 cm² greater fat CSA and 0.04 mg/cm³ lower muscle density at both the forearm and lower leg (Figure 5.1).

Table 5.3. Correlations between androgen deprivation therapy (ADT) use duration and fat mass, fat cross-sectional area and muscle density outcomes in men with prostate cancer treated with ADT.

Measure	ADT duration (month), Spearman's rho correlations	
Fat mass		
Arm (kg)	0.36	P=0.020
Leg (kg)	0.39	P=0.012
Android (kg)	0.13	P=0.433
Gynoid (kg)	0.34	P=0.028
Abdominal visceral (kg)	0.05	P=0.761
Abdominal subcutaneous (kg)	0.37	P=0.021
Fat cross-sectional area		
Forearm (cm ²)	0.34	P=0.044
Lower leg (cm ²)	0.44	P=0.005
Muscle density		
Forearm (mg/cm ³)	-0.34	P=0.046
Lower leg (mg/cm ³)	-0.31	P=0.054

Data are: Spearman's rho.

Figure 5.1. Scatterplot of the relationship between duration of androgen deprivation therapy (ADT) and lower leg and forearm fat cross-sectional area (CSA) and muscle density in men treated with ADT; Spearman's rho, r_s .

5.6 Discussion

To our knowledge, this was the first study to compare regional fat depots in men treated with ADT and both PCa and healthy controls simultaneously. The main findings were that subcutaneous fat depots, specifically within the arms, legs and gynoid region, were 15-36% greater in men treated with ADT when compared to both control groups. However, these men did not possess greater abdominal visceral fat and only trended towards increased abdominal subcutaneous fat. Similarly, when compared to either control, men treated with ADT demonstrated no significant differences in appendicular muscle density (as a marker of intermuscular fat), although a trend was observed for men on ADT to exhibit an increase in leg intermuscular fat. Moreover, all subcutaneous fat depots, with the exception of android region, were shown to be positively correlated with ADT duration. Additionally, forearm muscle

density was shown to negatively correlate with ADT duration, which indicated the presence of greater amounts of intermuscular fat. Collectively, the findings of this study suggest that ADT-induced gains in adiposity more commonly affect subcutaneous fat depots with fat gains tending to occur throughout treatment with ADT.

Effects of androgen deprivation therapy on android and gynoid fat mass

Total body adiposity is a known risk factor for cardiometabolic morbidity and mortality [55, 171], however, pending regional distribution, the accumulation of fat in varying depots may pose differing disease risks [40]. For example, increased abdominal (android region) fat mass has been commonly associated with chronic inflammation, impaired glucose tolerance, increased blood lipids and decreased mobility [40]. Accumulation within subcutaneous depots, such as those within the gluteofemoral region, are less often associated with these adverse outcomes [40, 336]. In our study, we found that men treated with ADT had greater gynoid fat mass (0.6-0.7 kg; 15-18%), but not android fat mass, when compared to either PCa or healthy controls. The only known cross-sectional analysis that examined regional fat mass differences between 48 men treated with ADT (mean age, 70 years) and 70 age-matched healthy controls did not measure android or gynoid fat mass, however, trunk fat mass was observed to be similar between the two groups [33]. Although a different region of interest, android fat mass is encapsulated within the trunk region and thus these observations support our findings that men treated with ADT may not have greater abdominal fat mass when compared to appropriately selected controls. The clinical significance of an increase in gynoid fat mass remains uncertain given the conflicting findings reported in the literature. For instance, in a cohort of 175 healthy men (mean age, 45 years), each increment of 0.5 kg DXA-derived gynoid fat mass was associated with approximately double the risk of impaired glucose metabolism, increased serum triglycerides or hypertension [337]. In contrast, in a larger population-based study of 3,818 men (mean age, 49 years), each 7.6 cm increase in hip circumference (as a marker of gynoid region fat mass), was associated with a decreased risk of impaired glucose metabolism (OR, 0.55), increased serum triglycerides (OR, 0.58) and hypertension (OR, 0.80) [338]. While the latter study relied on a less robust assessment of gynoid fat mass, these observations should not be dismissed given similar associations have been reported in several other studies examining various measures of gluteofemoral fat depots [40, 336]. However, many of these studies have utilised gluteofemoral region outcomes less

comparable to DXA-derived gynoid fat mass, such as hip circumference and thigh fat CSA ^[336], therefore limiting comparisons between measures. Moreover, these studies tended to neglect the likely increased muscle mass and size associated with increased adiposity ^[319]; thus these negative associations should be interpreted with caution. Despite the uncertainty with regard to the risk associated with fat accumulation within these depots, our findings suggest that fat accumulation during ADT may more commonly occur within subcutaneous depots, such as those in the gynoid region.

Effects of androgen deprivation therapy on abdominal visceral and subcutaneous fat mass

As discussed already, fat mass within the abdominal cavity (android region) may pose differing cardiometabolic risk pending on whether it is stored within subcutaneous or visceral depots ^[40, 336]. When compared to subcutaneous depots within this region, visceral fat mass tends to be a better predictor of hypertension, impaired glucose metabolism, diabetic status and metabolic syndrome in older men ^[102, 103]. We found that men treated with ADT had similar abdominal visceral fat mass compared to both controls, but tended to have 0.2 kg greater abdominal subcutaneous fat mass. There is evidence to suggest that a 0.8 kg increment in abdominal subcutaneous fat mass is associated with an increased risk of hypertension (OR, 1.45), diabetes (OR, 1.78) and metabolic syndrome (OR, 3.57), in a sample of 881 men (mean age, 58 years) ^[103]. Given the absolute difference in abdominal subcutaneous fat mass between ADT-treated men and controls was four-fold smaller than that of what has been previously shown to be associated with adverse health outcomes, this trend is likely not of clinical relevance. To date, studies that have examined abdominal subcutaneous and visceral fat mass in men treated with ADT have been prospective in nature and shown an 11-13% increase in subcutaneous fat, yet mixed findings for visceral fat (22% increase or no change) ^[17, 199]. Notably, these studies did not include control groups or account for known confounding variables, such as physical activity and diet, thus limiting comparisons to our findings. Collectively, our findings indicate that ADT use does not appear to have any marked effect on abdominal visceral or subcutaneous fat mass. Although, these results must be interpreted with caution given the use of DXA, which despite being shown to highly correlate ($r=0.83$) with CT-derived visceral fat CSA in overweight older men (mean age, 66 years; mean BMI, 29.7 kg/m²) ^[120], only provided an estimate of visceral and subcutaneous fat mass within this region of interest.

Effects of androgen deprivation therapy on arm and leg fat mass and cross-sectional area

There is limited evidence that the accumulation of fat within subcutaneous depots of the arms and legs is associated with adverse health outcomes ^[336, 339]. Our study found that men treated with ADT had greater arm (19%; 1.5-1.6 kg) and leg (20-21%; 0.5 kg) fat mass when compared to both PCa and healthy controls. These findings were in part supported by the observation that leg fat mass was 17% (1.1 kg) greater in 48 men treated with ADT (mean age, 70 years) compared to 70 age-matched healthy controls, whereas no between-group difference in arm fat mass were shown, although ADT-treated men had values 8.7% (0.2 kg) greater ^[33]. Although likely limited with regard to predicting risk of adverse outcomes, our findings suggest that the accumulation of fat during ADT more commonly occurs in subcutaneous depots within the arms and legs.

DXA-derived total body and regional fat mass has been shown to be highly correlated with that of CT-derived outcomes ^[119], with the latter generally considered the gold standard with regard to quantifying these measures ^[120]. However, limitations may arise when examining obese individuals ^[121], with DXA previously shown to underestimate total body fat mass by up to 5.2 kg compared to CT-based protocols ^[119]. Therefore, the use of CT-derived measures of fat may provide increased accuracy in men treated with ADT, given the propensity of these men to gain fat mass and size during treatment ^[195]. We found that men treated with ADT had 29-36% greater forearm fat CSA when compared to both controls, and a trend for 18-22% greater lower leg CSA. Similarly, when expressed as a percent of total limb area, men treated with ADT had 4.8-5.8% greater forearm percent fat CSA compared to both controls. To our knowledge, this study is the first to examine pQCT-derived fat CSA in men treated with ADT when compared to appropriately selected controls. The similar magnitude of difference we observed between ADT-treated men and controls at these sites (both 3-4 cm²) further supports the notion that ADT likely systematically affects subcutaneous fat depots. Subsequently, the difference in forearm fat CSA and trend in lower leg fat CSA we observed between men treated with ADT and controls may not be of clinical relevance in terms of predicting increased risk of mortality. However, the accuracy associated with pQCT-derived fat outcomes strengthen the notion that these subcutaneous depots store greater amounts of fat in these men compared to men not treated with this therapy.

Effects of androgen deprivation therapy on forearm and lower leg muscle density

Greater amounts of intermuscular fat are represented by a decreased muscle density measured pQCT; thus, muscle density is often used as a marker of intermuscular fat [77]. Previous research has shown that the accumulation of fat within these ectopic depots may impact muscle performance, and has been suggested as one potential mechanism to help explain the non-parallel decrements of lean mass and muscle strength/power associated with ageing [40]. Furthermore, decreased muscle density was independently associated with both increased cardiovascular and all-cause mortality in a sample of 1,063 community-dwelling older men (mean age, 77 years) [181]. Therefore, the assessment of intermuscular fat via the quantification of muscle density appears to be a strong predictor of risk in population groups susceptible to its accumulation. Our study demonstrated that men treated with ADT had similar forearm muscle density when compared to PCa and healthy controls. However, we observed a trend towards ADT-treated men having lesser lower leg muscle density when compared to both controls (1.2-1.3 mg/cm³). The influence of ADT on intermuscular fat has received limited attention to date. The only study to date having quantified prospective changes in CT-derived intermuscular fat following 15-20 weeks of treatment observed a mean reduction of 19% [15]. In the aforementioned cohort of 1,063 healthy older men, each decrement of 3.5 mg/cm³ in muscle density of the lower leg was associated with an 18-39% increase in all-cause mortality, 34-66% increase in cardiovascular disease mortality and 14-29% increase in non-cardiovascular disease mortality [181]. Thus, the trend for a difference we observed may be of limited clinical relevance with regard to disease risk. Regardless, our study was the first to compare muscle density (as a marker of intermuscular fat) in men treated with ADT to appropriately selected controls, with our findings suggesting that ADT may not result in greater amounts of fat accumulation in intermuscular depots.

Duration of androgen deprivation therapy use

Recent advancements in the treatment of PCa have led to the incorporation of intermittent ADT protocols in usual care [4], with this approach aiming to reduce to time spent in a hypogonadal state due to the long-term adverse effects associated with continuous ADT [65]. There is evidence to suggest that duration of ADT use is associated with greater amounts of total body fat mass [18, 315], however, associations between ADT use duration and regional depots have not been previously examined. We found that duration of ADT use was positively correlated with all subcutaneous

regions of fat mass and CSA, bar android region. Moreover, duration of ADT use was negatively correlated with forearm muscle density with a negative trend observed for lower leg muscle density ($P=0.054$). These findings suggest that fat likely continues to accumulate in subcutaneous and intermuscular depots, but not within visceral regions, throughout treatment with ADT. These observations are of significance given that ADT may lead to the accumulation of fat mass beyond the plateau or gradual decrease in adiposity commonly reported in men following the seventh decade of life [142]. Notably, the correlations we observed may have been influenced by the few men treated with ADT for greater than five years; thus suggesting that these results should be interpreted with caution. Despite this limitation, these correlations should be considered during risk stratification and clinical decision making in men treated with ADT to ensure both the patient and clinician are aware of the long-term impact of this treatment on fat mass and CSA, and subsequent morbidity and mortality.

Mechanisms of fat accumulation during androgen deprivation therapy

Given the limited cross-sectional and prospective research to date that examined regional fat depots in men treated with ADT, the precise mechanisms behind the differences we observed are unknown. However, evidence from the androgen-receptor knockout mouse model indicated that hypogonadism decreased overall lipolysis and led to obesity [340] whereas, testosterone treatment increased lipolysis [341]. Hypogonadism has been suggested to increase adipocyte size and number through facilitating triglyceride uptake via increased lipoprotein lipase activity, as well as by stimulating pluripotent stem cells to mature into adipocytes [342]. However, the translation of these observations to humans is unclear, with the in vitro evidence to date having shown that testosterone treatment reduced lipolysis in subcutaneous, but not visceral fat depots [343]. This observation in part supports our findings that ADT-induced hypogonadism appeared to influence subcutaneous, rather than visceral or intermuscular fat depots. Whilst the understanding of these mechanisms remain in their infancy, current hypotheses propose a cycle in which the accumulation of fat due to hypogonadism leads to the inability of the hypothalamic-pituitary-testicular axis to respond to decreased androgens [342]; thus potentially explaining why men treated with ADT may continue to be hypogonadal following the cessation of ADT [194].

5.7 Strengths and limitations

The strengths of this study were discussed in Chapter 4. Furthermore, the quantification of region specific subcutaneous, visceral and intermuscular fat depots provided novel insight into potential complications associated with ADT-induced hypogonadism. Of these regional fat depots, this study was the first that examined forearm (66% radius) and lower leg (66% tibia) fat CSA and muscle density (as a marker of intermuscular fat) in men treated with ADT. Moreover, this study was the first to have examined a wide range of fat depots in men treated with ADT when compared to appropriately selected controls.

In addition to those outlined in Chapter 4, there are limitations associated with the data presented in this chapter which warrant caution when interpreting results. Due to DXA-estimated measurement of abdominal subcutaneous and visceral fat mass in this study, comparisons to CT- and MRI-derived outcomes may be limited. Additionally, muscle density was used as a marker of intermuscular fat due to noted limitations with current soft tissue analyses when assessing intermuscular fat directly ^[117]; therefore, these results were only an estimate of true intermuscular fat differences between groups.

5.8 Conclusion

In summary, the findings from this study found that men treated with ADT had greater amounts of fat stored in subcutaneous depots, but not within the visceral region of the abdominal cavity, when compared to PCa and healthy controls. Moreover, ADT-treated men did not possess compromised intermuscular fat compared to either control. Finally, we found that ADT use duration correlated with the majority of subcutaneous and intermuscular depots, indicating that the accumulation of fat mass at these sites likely continues throughout ADT. Collectively, the findings from this study indicate that ADT use has regional specific effects of fat depots, largely resulting in an increase in subcutaneous fat deposits.

In conclusion, differences in regional fat mass observed between men treated with ADT and controls tended to be within subcutaneous depots, rather than visceral or intermuscular depots, and thus may be of limited clinical relevance with regard to risk of adverse health outcomes. Given these observations, quantifying visceral and intermuscular fat in ADT-treated men may be of less importance in the clinical setting,

and these men may benefit from DXA-based monitoring of fat mass during therapy, similar to current recommendations with regard to bone mineral density ^[195]. Monitoring these changes are of increased clinical importance given the correlations observed in this study, which indicated that men treated with ADT do not experience the plateau/decline in various depots of fat mass commonly observed in healthy older men following the seventh decade of life. Therefore, interventions are required to manage this continued increase in fat mass during ADT to mitigate subsequent risk of adverse health outcomes. In the following chapter, the effects of a novel multi-component exercise program and nutritional supplementation intervention in men treated with ADT for PCa compared to usual care will be presented.

Chapter 6

The feasibility of combined exercise training and nutritional supplementation compared to usual care in men treated with androgen deprivation therapy for prostate cancer: a randomised controlled trial

6.1 Declaration statement

Under the guidance of supervisors, the candidate developed the study concept and initiated the project, provided significant input into the development of the protocol, implemented the protocol and oversaw the collection of the data, analysed and interpreted all data presented, and drafted, revised and approved the published protocol manuscript.

6.2 Overview

This chapter was initially planned to present the results of a 52-week randomised controlled trial (RCT) that examined the efficacy of a multi-component exercise program combined with protein, calcium and vitamin D supplementation (Ex+ProCaD) compared to usual care in men treated with androgen deprivation therapy (ADT) for prostate cancer (PCa; Appendix A). However, delays in the recruitment of this clinical population group beyond the control of the PhD candidate and the supervision team resulted in an extended study timeline, with recruitment still remaining active as of the submission of this thesis. Subsequently, this chapter presents the feasibility of conducting the first 26-weeks of the RCT from 2014 to 2017 with regard to recruitment, attrition, adherence, data collection and safety.

Additionally, baseline and follow-up descriptive data from the first 28 men who completed the 26-week intervention during this timeframe are presented in this chapter. Baseline data from the 42 ADT-treated men recruited in total are presented in Chapter 4 and Chapter 5. Notably, within- and between-group statistics are not presented based on the following reasons: 1) trial results may change with follow-up of the complete cohort of participants (n=70 target); 2) the reporting of preliminary results may introduce biases that jeopardise the eventual outcomes; and 3) the lack of adequate statistical power may increase the probability of a type II error^[302].

6.3 Introduction

In Australia, as in other developed countries, PCa is the most commonly diagnosed male cancer^[1]. Approximately 1.1 million new cases of PCa are diagnosed worldwide each year^[1]. It was estimated that approximately 13% of Australian male cancer-related deaths were attributed to PCa, which ranks second to lung cancer as the most common cause of male cancer-related death^[63]. Due to medical advancements in both the screening and treatment of PCa, 5-year relative survival rates are now approaching

100% internationally ^[344], and thus these patients are living longer, but susceptible to potential age-related and treatment-related declines in health. Therefore, the clinical paradigm is shifting to an increased focus on survivorship and improving the quality of years lived.

Various modalities of ADT, including those administered neoadjuvant or adjuvant with other treatments, are commonly used to treat PCa as it improves overall survival, particularly in men with advanced PCa ^[5, 6, 8, 9]. However, the evidence that ADT prolongs survival in men with localised PCa remains limited and therefore debated ^[68, 69]. Despite this lack of evidence, the use of ADT continues to increase for all stages and grades of PCa ^[345]. It was estimated that approximately 23,500 Australian men received pharmacological ADT via gonadotropin-releasing hormone (GnRH) agonists in 2008-09 ^[56]. After repeating this analysis for 2013-14, we estimated that approximately 25,500 men are currently receiving ADT via GnRH agonists ^[71]. Thus ADT remains the most common cause for severe male hypogonadism in Australia.

Despite benefits in overall survival, the hypogonadism induced via ADT has been associated with numerous adverse effects, such as those negatively influencing muscle, fat and performance outcomes. It has been reported that within the first three to 12 months of ADT, men experience losses in lean mass and muscle strength of up to 5% ^[21, 194, 346, 347] and 11% ^[25, 28, 29], respectively, which may partially contribute to the observed 23-65% increased fracture risk in this group ^[202, 214, 348]. There is also a profound gain (up to 15%) in fat mass which likely contributes to the 10-45% reported increased risk of diabetes, coronary heart disease, myocardial infarction and sudden cardiac death ^[207, 220, 333, 346, 349, 350]. Thus, there is a need to develop safe and effective interventions to manage the multiple treatment-induced adverse effects of ADT in men with PCa.

Exercise training has been recommended as a viable intervention to ameliorate many of the adverse effects of ADT ^[60, 231, 351]. Previous studies in men treated with ADT have shown that interventions including aerobic training, progressive resistance training (PRT) or the combination of both over periods of 12-52 weeks may improve total body (0.7 kg) ^[227, 246] and appendicular lean mass (ALM; 0.5 kg) ^[227, 238], lower total body (-0.6 kg) ^[234] and trunk fat mass (-0.5 kg) ^[234], increase upper body (up to 26%) ^[227, 232, 234, 238, 243, 246] and lower body muscle strength (up to 37%) ^{[227, 232, 234, 238,}

^{243, 246]}, improve upper (47%) ^[227] and lower body muscle endurance (69%) ^[227] and improve gait speed (6.4%) ^[227], when compared to usual care control groups. However, emerging evidence in healthy older men without PCa has suggested that the use of multi-nutrient supplementation, such as vitamin D and protein, may optimise the benefits of exercise training on certain muscle outcomes, including lean mass and muscle strength ^[195, 351].

Current nutritional guidelines for individuals with or at risk of sarcopenia have emphasised the importance of vitamin D and dietary protein ^[352]. Studies in healthy older adults have shown that 700-2,000 IU/day of vitamin D can improve muscle strength and functional capacity and reduce falls risk, however, these results were most commonly observed in individuals with the lowest serum 25-hydroxyvitamin D (< 30-60 nmol/L) ^[279, 353, 354]. While data on the vitamin D status of men with PCa is limited, in a small sample of 49 older men treated with ADT for PCa (mean age, 73 years) from Spain, it was reported that the average serum 25-hydroxyvitamin D was 21 ng/ml (52 nmol/L), with only 22% of men having levels > 30 nmol/L, whereas 30% and 48% were reported to have very low levels of < 15 nmol/L and levels between 15-30 nmol/L, respectively ^[249]. Therefore, supplementation with vitamin D in this susceptible population group should also be considered. With regard to protein supplementation, there is some evidence in healthy older adults that higher protein intakes (> 1.2 g/kg/d) may help to enhance weight loss, offset muscle loss, improve lipid profiles and insulin sensitivity ^[274]. While this is not a universal finding, this could be explained by the basal levels of protein intake prior to supplementation, the modest level of protein intake achieved in some studies and/or the type (quality) of protein consumed. To date, the efficacy of these nutritional supplementation protocols have not been investigated in men treated with ADT. It is well known that PRT stimulates muscle protein synthesis, but in a fasted state it also accelerates muscle protein breakdown ^[292]. Ingestion of a high quality, rapidly digested protein-rich source such as whey-protein, post-exercise can attenuate the increase in muscle protein breakdown and stimulate muscle protein synthesis to enhance the anabolic benefits of PRT ^[292]. Additionally, PRT prior to protein intake may facilitate greater use of protein-derived amino acids from the ingested protein ^[292]. Thus, combining PRT with whey-protein ingestion may represent an optimal strategy to enhance muscle hypertrophy. While questions still remain in terms of the optimal dose of protein needed to elicit a synergistic response with PRT, emerging evidence indicates that 20-40 g of high

quality protein be consumed early after a bout of PRT to enhance lean mass and/or muscle strength ^[292]. However, a critical but as yet unanswered question is whether ingestion of a whey-protein with PRT can improve these outcomes in ADT-treated men.

Previous studies that have examined the efficacy of exercise training and multi-nutrient supplementation in healthy older adults have shown mixed results with regard to muscle, fat and performance outcomes ^[355, 356]. Following an 18-month factorial design RCT in 180 healthy older men (age range, 50-79 years), the addition of a low-fat fortified milk product which provided approximately 13.2 g protein, 1,000 mg calcium and 800 IU vitamin D did not further augment the improvements observed following a multi-modal exercise program including PRT alone on dual-energy x-ray absorptiometry (DXA)-derived lean mass (0.6 kg), computed tomography (CT)-derived muscle cross-sectional area (CSA; 1.8%), muscle strength (20-52%) and gait speed (11%) ^[355]. The authors suggested that the lack of additional benefit of the multi-nutrient supplement likely stemmed from the adequate levels of serum 25-hydroxyvitamin D (mean, 86 nmol/L) in participants at baseline, as well as these participants having reported daily dietary protein and calcium intakes above or equivalent to current Australian daily recommendations (0.85 g/kg and 1,000 mg, respectively) ^[357]. In contrast, a 9-month RCT in 96 vitamin D deficient (serum 25-hydroxyvitamin D ≤ 16 ng/ml) adults aged 70 years or greater demonstrated that a multi-nutrient supplement (400 IU vitamin D and 800 mg calcium) and PRT intervention relative to a calcium-only supplement (800 mg) and PRT intervention resulted in greater improvements in functional capacity assessed via the timed-up-and-go (net difference, 3.9%), yet no within group changes or between group differences were observed for the change of DXA-derived lean or fat mass ^[356]. Emerging evidence has shown that in 130 older adults (mean age, 80 years) with pre-sarcopenia via low ALM adjusted for height (ALMI; men, < 7.26 kg/m²; women, < 5.5 kg/m²), a 12-week progressive exercise program combined with a daily multi-nutrient supplement (whey protein, 22 g; vitamin D, 100 IU) increased DXA-derived fat-free mass relative to a 12-week PRT program combined with a placebo supplement (net difference, 1.7 kg) ^[358]. These findings support the initial values principle of exercise training, in which those with the lowest physiological values have the greatest capacity to obtain improvements. Collectively, these findings suggest that multi-nutrient supplements may augment the effects of exercise training in those who are deficient

in the included nutrients and present with lower initial values, however, this notion is yet to be examined within men treated with ADT.

Given the demonstrated efficacy of previously mentioned exercise training and emerging evidence in support of nutritional supplementation to potentially counteract the range of treatment-induced adverse effects in men undergoing ADT, it is therefore plausible that the combination of these interventions may optimise benefits in these men ^[195]. There are currently no established guidelines for specifically managing the large range of adverse effects observed in men treated with ADT ^[231]. In terms of muscle, fat and performance, the guidelines are less evidence-based within this specific clinical population group ^[56, 59], and commonly recommend more generic exercise training guidelines for cancer survivors ^[221, 359-361], with no mention of nutrition and/or diet ^[195]. Therefore, well-designed long-term trials are needed to inform ADT-specific exercise training and nutritional guidelines for managing the myriad of adverse effects associated with ADT. However, whether these interventions are feasible in this clinical population group is unknown.

Potential feasibility issues in men treated with ADT for PCa primarily stem from the myriad of treatment-induced adverse effects often reported ^[11-14]. Whilst a recent pooled analysis of 1,366 cancer survivors (mean age, 75 years; PCa, 46%) concluded that average retention rates for exercise and diet-based lifestyle interventions were 91% ^[363], the potential influence of ADT-induced adverse effects is unknown. Similarly, whether these complications impede adherence and pose concerns to participant safety warrants investigation. In a study of 62 men treated with ADT (mean age, 68 years), 40% were precluded from muscle strength tests involving a handheld dynamometer due to pre-existing comorbidities ^[28]; thus the feasibility of collecting data should also be considered in this clinical population group. Moreover, it has been estimated that only 55% of funded clinical trials in the United Kingdom recruited their intended total sample ^[370]. Whilst these findings are not specific to ADT-treated men, the aforementioned concerns associated with treatment-induced adverse effects, as well as that poor physical and mental health has been shown to limit participation in physical activity in older adults ^[364, 365] highlight the need to determine the most effective pathways for recruiting and enrolling ADT-treated men into lifestyle interventions.

While the overall aim of this study was to examine the efficacy of Ex+ProCaD when compared to usual care in men treated with ADT for PCa, the specific aim of this chapter was to describe the feasibility of conducting the first 26-weeks of the RCT with regard to recruitment, attrition, adherence, data collection and safety. Secondary aims included the presentation of descriptive data from the 28 men who completed the 26-week intervention at the time of write up for this chapter.

6.4 Methods

Details on the methodology of this study are discussed in Chapter 3 and Appendix A. In brief, the study presented in this chapter was a single-blinded, parallel two-arm 26-week RCT in which men with PCa treated with ADT were randomly assigned to either Ex+ProCaD or a usual care control. The aspects presented in this chapter were undertaken within the Institute for Physical Activity and Nutrition, Deakin University, Australia from 2014 to 2017. The study was approved by the human research ethic committees at Deakin University (HREC 2013-184) and Alfred Health (Project No: 455/15) and was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12614000317695).

Participants were mainly recruited via clinician referral from Alfred Health (Melbourne, Australia) and six private practices (all within Victoria, Australia), as well as from 32 PCa support groups and advertisements in one state and 38 local newspapers. In addition, a state news report was aired on state television, advertisements were placed on Deakin University's website and in Deakin University's Clinical Exercise Learning Centre and mailing lists of the Prostate Cancer Foundation of Australia and Advanced Prostate Cancer Group were emailed. Eligible participants were men aged 50-85 years who were currently treated with pharmacological ADT for histologically diagnosed PCa for greater than 12 weeks at enrolment. Participants were excluded if they did not have the ability to complete surveys in the English language, had any disorder known to affect bone, calcium or vitamin D metabolism (other than hypogonadism), were currently receiving pharmacological intervention known to affect bone metabolism (other than ADT), had supplemented with protein, calcium (> 600 mg/day) or vitamin D (> 1,000 IU/day) in the past three months, had undertaken PRT (> 1 session/week) or regular weight-bearing impact exercise (> 150 min/week) in the past three months, were current smokers, had a weight greater than 159 kg, had plans to travel for greater than six

weeks continuously within the following 52 weeks, or had any absolute contraindications to exercise training (e.g. musculoskeletal, cardiovascular or neurological) according to the American College of Sports Medicine guidelines ^[24]. All eligible participants were required to provide informed consent before participating in the study and were required to obtain medical approval from their physician. Randomisation was at the level of the individual participant following baseline testing, stratified by age (< 65 or ≥ 65 years) and body mass index (BMI; < 30 or ≥ 30 kg/m²), using a computer-generated random number sequence and opaque envelopes to ensure allocation concealment by an independent researcher not affiliated with the study.

Participants randomised to the intervention group received Ex+ProCaD. The exercise program consisted of two gym-based supervised training sessions per week under the guidance of an Accredited Exercise Physiologist (tertiary trained exercise professional), as well as one unsupervised home-based training session. The exercise program followed key training principles of specificity, progressive overload and periodisation and was individually tailored to the health and functional status of each participant. Each supervised session (approximately 60 minutes) consisted of a warm-up and cool-down and a combination of aerobic, resistance, weight-bearing impact and challenging balance/functional exercises. Home-based sessions followed a similar format to supervised sessions, but were modified to be completed within the home-based setting. The nutritional supplementation consisted of a daily whey protein, calcium and vitamin D enriched drink (sachet) combined with a single 1,000 IU vitamin D tablet. Together, these provided 25 g protein (21 g whey protein), 1,200 mg calcium carbonate (480 mg elemental calcium) and 2,000 IU vitamin D per day. On exercise training days, participants were encouraged to consume the sachet within 1-2 hours of completing their exercise session and on the non-training days, participants were asked to take one sachet every morning before breakfast. This was designed to try and ensure a more even protein intake throughout the day. Participants allocated to usual care received ongoing care from their physician/specialist, but no additional access to the intervention. Due to current practice guidelines, all men randomised to usual care received 1,000 IU vitamin D per day in the form of a single tablet.

All data were collected at baseline and 26 weeks. Information with regard to feasibility outcomes are presented in Table 6.1, and include those pertaining to recruitment,

attrition, adherence, data collection and safety. Height and weight were assessed using standard techniques. BMI was calculated as weight (kg) divided by height (m) squared. Habitual physical activity and diet (excluding nutritional supplementation provide in the study) were assessed by self-reported questionnaire and 24-hour food recall, respectively. Demographical, clinical and lifestyle information was assessed by questionnaire. Total body and regional lean mass and total body fat mass and percentage fat mass were assessed by DXA. Specifically, DXA-derived abdominal subcutaneous and visceral fat were measured using CoreScan software. ALM was calculated as arm lean mass (kg) plus leg lean mass (kg) ^[77]. Muscle, subcutaneous fat and limb CSA and muscle density of the forearm (66% radius) and lower leg (66% tibia) was assessed by peripheral quantitative computed tomography (pQCT) ^[311, 312]. Percent muscle and subcutaneous fat CSA was calculated as muscle or fat CSA (cm²) divided by total limb CSA (cm²). Muscle strength was assessed by various three-repetition maximum (3-RM) protocols and handgrip dynamometry. Functional muscle power was assessed by the 30-second sit to stand. Functional capacity was assessed by a battery of common valid and reliable tests: timed-up-and-go with a secondary cognitive task (a measure of dual-task agility), four-square step test (a measure of dynamic mobility), Berg balance scale (a measure of static and dynamic balance), four metre usual walk (a measure of gait speed) and 400 metre walk (a measure of mobility limitations). Prostate-specific antigen (PSA; a measure of PCa activity) was assessed by immunoassay. Compliance was assessed by attendance record, self-reported diaries and counting all returned supplement. Adverse events potentially or confirmed to be associated with the study were monitored and documented by the exercise trainers at each exercise training sessions for the intervention group participants and via monthly phone calls by the research staff to the control group participants.

Table 6.1. Feasibility outcomes examined in the randomised controlled trial.

Outcome	Measures
Recruitment	Enrolled participants compared to total screened potential participants Reasons for ineligibility or declined participation Enrolment timeline Efficacy of recruitment pathways
Attrition	Number of participants available for follow-up Reasons for loss to follow-up
Adherence	Supervised, home-based and total exercise training sessions completed Sachet supplement consumed Vitamin D tablet supplement consumed (both groups)
Data collection	Collected data compared to missing data
Safety	Number, severity and relatedness to the study of adverse events Prostate specific antigen

All data were collated using STATA statistical software (STATA, College Station TX, United States of America). After data were screened for outliers, descriptive statistics were computed. Where possible, endpoint measures were obtained from any participant lost to follow-up and all randomised men who had completed 26-week follow-up by the time of data analysis for this chapter were included in descriptive statistics. Baseline measures and changes in outcome variables were computed as means $\pm$ standard deviation or 95% confidence intervals. Net differences were calculated by subtracting within-group changes for the control group from within-group changes for the intervention group.

6.5 Results

6.5.1 Recruitment

A total of 149 participants (expressions of interest) were assessed for eligibility (Table 6.2; Figure 6.1), from which 42 (28%) were included in the study. A total of 75 (50%) men did not meet specific inclusion criteria and 21 (14%) subsequently declined to participate, despite having met all inclusion criteria. At the time of write up for this chapter, an additional 11 potential participants were deemed ‘pending’ as they were still being assessed for eligibility and yet to complete baseline testing. The most common reasons for failing to meet inclusion criteria were not currently being treated with ADT (n=36; 24% of all potential participants) and vitamin D supplementation greater than 1,000 IU per day (n=12; 8.1% of all potential participants). For those participants who declined to participant, no reason (n=10, 6.7% of all potential participants) was the most frequent response.

Table 6.2. Reasons participants were excluded from the trial.

Failed inclusion criteria		Declined to participate	
Reason	Total, n (%)	Reason	Total, n (%)
Not currently on ADT	36 (48.0%)	No reason	10 (47.6%)
Vitamin D > 1,000 IU/day	12 (16.0%)	No time	4 (19.0%)
PRT > 1 session/week	6 (8.0%)	Disease progression	2 (9.5%)
Use of antiresorptive therapy	5 (6.7%)	Geographical location	2 (9.5%)
Located interstate	5 (6.7%)	Pain due to metastases	1 (4.8%)
Current smoker	5 (6.7%)	No clinician support	1 (4.8%)
No prostate cancer	2 (2.7%)	Not willing to be control	1 (4.8%)
Age > 85 years	1 (1.3%)	-	-
Calcium > 600 mg/day	1 (1.3%)	-	-
Lost to follow-up	1 (1.3%)	-	-
Orchiectomy	1 (1.3%)	-	-
Total	75 (100.0%)	Total	21 (100.0%)

Data are: number of participants and percentage of participants who failed inclusion criteria or declined to participate.

Figure 6.1. Flowchart of participants through the study.* Participants who had completed the 26-week follow-up period by write up of this chapter. ADT, androgen deprivation therapy; PRT, progressive resistance training.

A summary of recruitment pathway outcomes are presented in Table 6.3. Overall clinician referral (n=42; 28% of total screened), followed by PCa support groups and local newspaper advertisement (both, n=31; both, 21% of total screened) and then a State television news report (n=23; 15.4% of total screened) resulted in the highest number of participants screened. In terms of eligible participants who were included in the intervention, clinician referral (n=18; 43% of total screened from recruitment pathway) and PCa support groups (n=12; 39% of total screened from the recruitment pathway) were the most successful.

Table 6.3. Outcomes of all recruitment pathways.

Recruitment pathway	Outcome			Total screened
	Included	Excluded	Pending	
Clinician referral	18 (43%)	18 (43%)	6 (14%)	42
Prostate cancer support group	12 (39%)	18 (58%)	1 (3%)	31
Local newspaper advertisement	4 (13%)	27 (87%)	0 (0%)	31
State news television report	3 (13%)	18 (78%)	2 (9%)	23
Word of mouth	2 (29%)	4 (57%)	1 (14%)	7
Deakin University website	2 (67%)	1 (33%)	0 (0%)	3
State newspaper advertisement	1 (20%)	3 (60%)	1 (20%)	5
Advanced PCa Group Australia email	0 (0%)	3 (100%)	0 (0%)	3
PCa Foundation of Australia email	0 (0%)	2 (100%)	0 (0%)	2
Flyer in university exercise centre	0 (0%)	2 (100%)	0 (0%)	2
Total	42	96	11	149

Data are: number of participants and percentage of total screened from specific recruitment pathway. PCa, prostate cancer.

A timeline of participant recruitment is presented in Figure 6.2; notably, four clusters of enrolment occurred. The first cluster of enrolled participants (n=12) was predominantly attributed to the commencement of recruitment via PCa support groups and newspaper advertisement. The second cluster of enrolled participants (n=9) largely stemmed from contact with private urology practices and subsequent clinician referrals. The third cluster of enrolled participants (n=14) mainly resulted from clinician referrals from Alfred Health. The final cluster of enrolled participants (n=7) followed the state news television report that featured the trial.

Figure 6.2. Participants recruited throughout the randomised controlled trial.

6.5.2 Attrition

For this analysis, a total of 28 men with PCa on ADT were randomised to the exercise intervention (n=16) or usual care control group (n=12). Participant retention from baseline to 26-week follow up was 96% (27 of 28 men). One participant who was allocated to the Ex+ProCaD group was lost to follow-up due to complications associated with PCa progression.

6.5.3 Adherence

On average, participants within the Ex+ProCaD group completed 60% (range, 10-90%) of all training sessions (68% supervised gym-based [range, 12-90%]; 50% unsupervised home-based [range, 15-88%]; Figure 6.3). Notably, one participant (lost to follow-up) discontinued the intervention after completing 10% of total sessions due to complications associated with PCa progression. Compliance with the protein, calcium and vitamin D sachet and vitamin D tablet within the Ex+ProCaD group was 92% (range, 60-100%) and 93% (range, 55-100%), respectively (Figure 6.3). Due to gastrointestinal upset (constipation), one participant discontinued the sachet supplement and finished with a compliance of 60%. Participants allocated to the control consumed 94% (range, 64-100%) of the daily vitamin D tablets.

Figure 6.3. Histograms of the 26-week compliance for participants in the intervention group for the vitamin D tablet, multi-nutrient sachet and exercise training (all and supervised).

6.5.4 Data collection

Missing data at baseline and follow-up in men who completed the 26-week intervention period are presented in Table 6.4. All outcomes include some missing data at baseline and/or follow-up (range, 3.6-50%). Four outcomes only had missing data for the one participant who was lost to follow-up. Missing data for dietary intake ($n=8$), handgrip muscle strength ($n=6$), chest muscle strength ($n=6$) and gait speed ($n=6$) was due to the addition of secondary aims, outcome measures and confounding variables pertaining to sarcopenia and sarcopenic obesity after the initial commencement of the study. Global obesity prevented the acquisition of DXA total body scan outcomes for one participant, while central obesity limited the acquisition of DXA CoreScan outcomes for two participants. Upper arm obesity restricted the ability to obtain pQCT forearm outcomes for one participant. One participant refused radiological scans at follow-up due to concerns regarding radiation exposure, whereas one participant refused the PSA blood test at follow-up due to the self-reported inconvenience associated with providing a fasting blood sample. Six pQCT scans (forearm, $n=5$; lower leg, $n=1$) were excluded based on scoring four or five on the

visual inspection rating scale of participant movement (i.e. erroneous data due to movement artefact) proposed by Blew et al. ^[311]. The ethical approval granted for the study did not include the option for repeat scans due to the radiological nature of scan acquisition. Safety concerns associated with various pre-existing comorbidities prevented the collection of the following outcomes: chest muscle strength (n=3, shoulder injury; n=2, acute hypertension; n=1, inguinal hernia; n=1, bone metastases at shoulder; n=1, atrial fibrillation; n=1, fatigue), leg muscle strength (n=3, acute hypertension; n=2, knee injury; n=1, inguinal hernia; n=1, atrial fibrillation; n=1, fatigue), back muscle strength (n=2, acute hypertension; n=2, neck injury; n=1, inguinal hernia; n=1, atrial fibrillation; n=1, fatigue; n=1, recent cervical spine surgery), 400 metre walk (n=1, fatigue) and Berg balance scale (n=1, postural hypotension). Finally, due to the complete case approach adopted for the descriptive statistics of absolute and percent changes presented in this chapter, when analysable data was not collected at baseline, these participants were omitted from analyses (range, 0-46%).

Table 6.4. Missing data at baseline and 26 weeks in the Ex+ProCaD (INT; n=16) and control (CON; n=12) groups.

Measure	Added after study began		Missing at baseline		Unable to define ROI		Lost to follow-up		Participant refused		Movement artefact *		Pre-existing comorbidities		Total	
	INT	CON	INT	CON	INT	CON	INT	CON	INT	CON	INT	CON	INT	CON	INT	CON
Dietary intake																
Baseline	4	4	-	-	-	-	0	0	0	0	-	-	-	-	4	4
26 weeks	-	-	4	4	-	-	0	0	0	0	-	-	-	-	4	4
Weight																
Baseline	-	-	-	-	-	-	0	0	0	0	-	-	-	-	0	0
26 weeks	-	-	0	0	-	-	1	0	0	0	-	-	-	-	1	0
DXA total body scan																
Baseline	-	-	-	-	1	0	0	0	0	0	-	-	-	-	1	-
26 weeks	-	-	1	0	0	0	1	0	0	1	-	-	-	-	2	1
DXA CoreScan																
Baseline	-	-	-	-	1	1	0	0	0	0	-	-	-	-	1	1
26 weeks	-	-	1	1	0	0	1	0	0	1	-	-	-	-	2	2
pQCT forearm																
Baseline	-	-	-	-	1	0	0	0	0	0	1	4	-	-	2	4
26 weeks	-	-	2	4	0	0	0	0	0	0	0	0	-	-	2	4
pQCT lower leg																
Baseline	-	-	-	-	0	0	0	0	0	0	0	1	-	-	0	1
26 weeks	-	-	0	1	0	0	1	0	0	1	0	0	-	-	1	2
Handgrip muscle strength																
Baseline	3	3	-	-	-	-	0	0	0	0	-	-	0	0	3	3
26 weeks	-	-	3	3	-	-	0	0	0	0	-	-	0	0	3	3

Chest muscle strength																
Baseline	-	-	-	-	-	-	0	0	0	0	-	-	2	6	2	6
26 weeks	-	-	2	6	-	-	1	0	0	0	-	-	1	0	4	6
Leg muscle strength																
Baseline	-	-	-	-	-	-	0	0	0	0	-	-	2	4	2	4
26 weeks	-	-	2	4	-	-	1	0	0	0	-	-	1	1	4	5
Back muscle strength																
Baseline	3	3	-	-	-	-	0	0	0	0	-	-	2	5	5	8
26 weeks	-	-	5	8	-	-	0	0	0	0	-	-	0	1	5	9
Timed-up-and-go																
Baseline	-	-	-	-	-	-	0	0	0	0	-	-	0	0	0	0
26 weeks	-	-	0	0	-	-	1	0	0	0	-	-	0	0	1	0
Four-square step test																
Baseline	-	-	-	-	-	-	0	0	0	0	-	-	0	0	0	0
26 weeks	-	-	0	0	-	-	1	0	0	0	-	-	0	0	1	0
30-second sit-to-stand																
Baseline	-	-	-	-	-	-	0	0	0	0	-	-	0	0	0	0
26 weeks	-	-	0	0	-	-	1	0	0	0	-	-	0	0	1	0
Gait speed																
Baseline	3	3	-	-	-	-	0	0	0	0	-	-	0	0	3	3
26 weeks	-	-	3	3	-	-	0	0	0	0	-	-	0	0	3	3
400 metre walk																
Baseline	-	-	-	-	-	-	0	0	0	0	-	-	0	1	0	1
26 weeks	-	-	0	1	-	-	1	0	0	0	-	-	0	0	1	1

Berg balance scale																
Baseline	-	-	-	-	-	-	0	0	0	0	-	-	1	0	1	0
26 weeks	-	-	1	0	-	-	1	0	0	0	-	-	0	0	2	0
Prostate specific antigen																
Baseline	-	-	-	-	-	-	0	0	0	0	-	-	0	0	0	0
26 weeks	-	-	0	0	-	-	1	0	1	0	-	-	0	0	2	0

Data are: number of participants with missing data. DXA, dual energy x-ray absorptiometry; pQCT, peripheral quantitative computed tomography; ROI, region of interest. * Excluded based on scores of four or five on the visual inspection rating scale of participant movement proposed by Blew et al. ^[311].

6.5.5 Safety

Absolute changes in PSA over the 26-week follow-up are shown in Figure 6.4. On average, men allocated to Ex+ProCaD decreased PSA by 1.4 ng/mL (range, -8.2 to 15.2 ng/mL), whereas the control group increased by 1.0 ng/mL (range, -42.0 to 49.7 ng/mL).

Figure 6.4. Individual absolute changes in prostate specific antigen in the Ex+ProCaD and control groups from baseline to 26-week follow-up.

Overall, there were 37 adverse events reported in 13 participants (46% of total sample; all within the intervention group; 81% of intervention group) documented throughout the study (Table 6.5). Five participants reported one adverse event, three reported two, two reported four, one reported five, one reported six and one reported seven. On average, men who reported an adverse event experienced three. No adverse events were reported from the controls during monthly phone calls to them. Only one adverse event (2.7%) was deemed serious, in which a participant in the intervention group was hospitalised due to hyperglycaemia and was subsequently diagnosed with type 2 diabetes; however, this event was determined to be unrelated to the study. All other adverse events were either mild (n=22; 59%) or moderate (n=14; 38%) in terms of severity, which meant they caused limited inconvenience when completing activities of daily living. Collectively, six of 37 events (16%) were confirmed to be related to the study, two (5.4%) were deemed probable and six (16%) were deemed possible in terms of being study-related. No events resulted in a permanent discontinuation of the intervention, however, one participant discontinued the sachet supplement due to gastrointestinal upset (constipation). Moreover, two adverse events reported by the

same participant resulted in two and three sessions missed, respectively. The exercise program was also temporarily or permanently modified following 19 (51%) and 5 (14%) adverse events, respectively. The majority of temporary modification lasted one session (89%), whilst one event led to the cessation of the home-based training component for one week and another resulted in the removal of the bench press exercise indefinitely. Permanent modification of the exercise program tended to pertain to safety and resulted in increased emphasis on posture (n=1), support rails for balance (n=1), education and specific exercises (n=1) and monitoring of blood glucose levels (n=1) or blood pressure (n=1).

Table 6.5. Details of all recorded adverse events from baseline to 26-week follow-up.

ID	Adverse event	Severity	Study-related	Action taken with intervention	Outcome of adverse event	Expected	Serious
001	Acute illness (flu-like symptoms)	Mild	No	None	Resolved	No	No
001	Acute illness (diverticulitis flare-up)	Mild	No	None	Resolved	No	No
001	Muscle/Joint (lower leg muscle strain)	Mild	No	Temporarily modified (lower leg exercises removed for 1 session)	Resolved	No	No
001	Muscle/Joint (chest muscle strain)	Moderate	Probable	Temporarily modified (seated row modified for 1 session)	Resolved	No	No
002	Acute illness (gastroenteritis)	Mild	No	None	Resolved	No	No
003	Gastrointestinal upset (constipation)	Moderate	Definite	Permanently modified (sachet discontinued)	Resolved	No	No
004	Muscle/Joint (shoulder muscle strain)	Mild	Definite	Temporarily modified (upper limb exercise intensity reduced for 1 session)	Resolved	No	No
005	Gastrointestinal upset (constipation)	Mild	Possible	None	Resolved	No	No
006	Blood pressure (acute hypotension)	Mild	No	None	Still present, treatment (general practitioner)	No	No
006	Blood pressure (postural hypotension)	Mild	No	None	Still present, treatment (general practitioner)	No	No

006	Fall (during lunge; no injury)	Mild	Definite	Permanently modified (emphasised support rails)	Resolved	No	No
006	Fall (vasovagal; bruises)	Mild	No	None	Residual effects, no treatment	No	No
006	Muscle/Joint (foot pain; synovitis)	Mild	No	None	Resolved	No	No
007	Blood pressure (acute hypertension)	Mild	No	Permanently modified (emphasised monitoring of blood pressure)	Still present, treatment (general practitioner)	No	No
007	Muscle/Joint (back muscle strain)	Moderate	Possible	Temporarily modified (home-based exercises not completed for 1 week)	Resolved	No	No
008	Metabolic (hyperglycaemia; diagnosed with type 2 diabetes)	Severe	No	Permanently modified (emphasised monitoring of blood glucose levels)	Still present, treatment (general practitioner)	No	Yes
008	Muscle/Joint (radiating leg pain from pre- existing disc bulge)	Moderate	Probable	Permanently modified (specific exercises and education provided)	Still present, treatment (exercises)	No	No
008	Muscle/Joint (shoulder muscle strain)	Mild	Possible	Temporarily modified (upper limb exercise intensity reduced for 1 session)	Resolved	No	No
008	Muscle/Joint (lower limb muscle strain)	Mild	Definite	Temporarily modified (lower limb exercise intensity reduced for 1 session)	Resolved	No	No
009	Acute illness (flu-like symptoms)	Moderate	No	Temporarily modified (1 session missed; reduced intensity for 1 session)	Resolved	No	No

009	Blood pressure (acute hypertension)	Moderate	No	Temporarily modified (reduced intensity for 1 session)	Resolved	No	No
009	Muscle/Joint (chest muscle strain)	Moderate	No	Temporarily modified (upper limb exercise intensity reduced for 1 session)	Resolved	No	No
009	Muscle/Joint (fatigue)	Moderate	No	Temporarily modified (reduced intensity for 1 session)	Resolved	No	No
009	Muscle/Joint (fatigue)	Moderate	No	Temporarily modified (reduced intensity for 1 session)	Resolved	No	No
009	Muscle/Joint (knee pain)	Mild	Possible	Temporarily modified (lower limb exercise intensity reduced for 1 session)	Resolved	No	No
009	Muscle/Joint (ankle sprain)	Moderate	Definite	Temporarily modified (lower limb exercise intensity reduced for 1 session)	Resolved	No	No
010	Muscle/Joint (lower leg muscle strain)	Mild	Possible	Temporarily modified (lower limb exercise intensity reduced for 1 session)	Resolved	No	No
011	Muscle/Joint (ankle sprain)	Moderate	No	Temporarily modified (lower limb exercise intensity reduced for 1 session)	Residual effects, treatment (general practitioner)	No	No
011	Muscle/Joint (chest muscle strain)	Mild	Definite	Temporarily modified (upper limb exercise intensity reduced for 1 session)	Resolved	No	No
012	Metabolic (hyperglycaemic day prior to training session)	Mild	No	None	Still present, no treatment	No	No

012	Muscle/Joint (back pain during seated row)	Mild	Possible	Permanently modified (emphasised monitoring correct posture)	Resolved	No	No
012	Sleep disturbance (restlessness)	Mild	No	Temporarily modified (intensity reduced for 1 session)	Resolved	No	No
012	Respiratory (asthma flare-up)	Moderate	No	Intervention stopped temporarily (2 sessions missed)	Still present, treatment (general practitioner)	No	No
012	Respiratory (asthma flare-up)	Moderate	No	Intervention stopped temporarily (3 sessions missed)	Still present, treatment (general practitioner)	No	No
012	Respiratory (asthma flare-up)	Mild	No	None	Resolved	No	No
013	Blood pressure (vasovagal)	Mild	No	Temporarily modified (intensity reduced for 1 session)	Residual effects, no treatment	No	No
013	Muscle/Joint (wrist pain)	Moderate	No	Temporarily modified (bench press removed)	Still present, treatment (orthopaedic surgeon)	No	No

Identifiers (ID) generated for use in this table only. Severity: mild, awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities, symptoms do not require therapy or a medical evaluation; moderate, events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures, may cause some interference with functioning; severe, events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment, they are usually incapacitating.

6.5.6 Participant characteristics

Participant characteristics at baseline of the 28 men who had completed the 26-week intervention at the time of write up for this chapter are shown in Table 6.6. The mean age of the men in the Ex+ProCaD and control group was 72 and 75 years, respectively. More than half of the men in the Ex+ProCaD and control group had completed university or tertiary level education (56% and 58%, respectively) and most were retired from employment (81% and 83%, respectively) and of Caucasian decent (94% and 92%, respectively). Overall, 75% of the men within each of the two groups were classified as overweight or obese and the majority of all participants (83-94%) reported three comorbidities. Among men in the Ex+ProCaD and control group aware of the stage of their PCa, there was a similar distribution of localised (53% and 50%, respectively) and advanced disease (47% and 50%, respectively). Half of the total cohort had undergone a previous prostatectomy, whereas approximately two thirds (68%) had completed prior radiotherapy. Additionally, one participant from the intervention group had completed a course of chemotherapy. When compared to the control group, men within the Ex+ProCaD group were, on average, living with PCa for approximately five years less, treated with ADT for two years less, prescribed three less non-ADT medications, were 6.9 kg heavier and 37% more physically active. From baseline to follow-up, the average difference in the number of non-ADT prescription medications between groups remained the same (Ex+ProCaD, n=3; control, n=6). Both groups were administered a similar number of ADT doses on average throughout the 26-week period (Ex+ProCaD, n=3; control, n=2).

Table 6.6. Baseline characteristics of the 28 participants randomised to the Ex+ProCaD and control groups who completed the 26-week intervention.

	Ex+ProCaD	Control
n	16	12
Age (years)	72 ± 6	75 ± 6
Height (cm)	175.9 ± 6.2	171.4 ± 7.9
Weight (kg)	88.5 ± 21.8	81.6 ± 14.7
Body mass index (BMI; kg/m ²)	28.4 ± 5.3	27.8 ± 5.0
Overweight (BMI ≥ 25 to < 30), n (%)	7 (43.8)	7 (58.3)
Obese (BMI ≥ 30), n (%)	5 (31.3)	2 (16.7)
Highest level of education, n (%)		
Primary or some high school	2 (12.5)	0 (0.0)
Completed high school	3 (18.8)	4 (33.3)
Technical/trade certificate	2 (12.5)	1 (8.3)
University or tertiary level	9 (56.3)	7 (58.3)
Current work status, n (%)		
Full-time	2 (12.5)	0 (0.0)
Part-time	1 (8.3)	2 (16.7)
Retired	13 (81.3)	10 (83.3)
Ethnicity, n (%)		
Caucasian	15 (93.8)	11 (91.7)
Asian	0 (0.0)	1 (8.3)
African	1 (6.3)	0 (0.0)
Comorbidities*, n (%)	15 (93.8)	10 (83.3)
If yes, total (n)	3 ± 0	3 ± 0
Prescription medication, n (%)	12 (75.0)	8 (66.7)
If yes, total (n)	3 ± 2	6 ± 2
Energy expenditure (kJ/d)	2673 ± 1638	1846 ± 1299
Time since PCa diagnosis (months)	52 ± 17	113 ± 20
Stage of PCa, n (%)		
Localised	8 (50.0)	5 (41.7)
Advanced	7 (43.8)	5 (41.7)
Unknown	1 (6.3)	2 (16.7)
Duration of ADT (months)	18 ± 30	46 ± 53
Previous prostatectomy, n (%)	8 (50.0)	6 (50.0)
Previous radiotherapy, n (%)	11 (68.8)	8 (66.7)
Previous chemotherapy, n (%)	1 (6.3)	0 (0.0)

Data are: mean ± standard deviation unless stated otherwise. * Comorbidities included asthma/respiratory problems, chronic bronchitis, muscle/ligament problems, back pain, angina/stroke/heart condition, diabetes, hypertension and hypercholesterolaemia.

6.5.7 Dietary intake

Dietary intakes (excluding the nutritional supplement) of the two groups at baseline are presented in Table 6.7. Baseline and 26-week total protein and energy intake (including the nutritional supplement; calculated by adding supplemental daily protein [25 g] or energy [439 kJ] multiplied by individual compliance; 28 g and 417 kJ, respectively) are presented in Figure 6.5. When including the nutritional supplement, men allocated to Ex+ProCaD increased their total protein and energy intake, on average, by 28% (24 g/d) and 7.9% (722 kJ/d) between baseline and follow-up, respectively, whereas the control group decreased 9.8% (9 g/d) and 2.8% (224 kJ/d), respectively. Using current consensus criteria in terms of the recommended dietary protein intake for older adults ^[313], the proportion of men with a protein intake ≤ 1.2 g/kg/d at baseline was similar between the intervention (67%) and control group (63%). However, when a protein intake of ≤ 1.0 g/kg/d was considered at baseline, greater variation between the groups was observed (intervention, 33%; control, 50%). Based on Australian guidelines for acceptable macronutrient distribution ranges associated with reduced risk of chronic disease (20-35% from fat, 45-65% from carbohydrate and 15-25% from protein) ^[362], men within the two groups at baseline, on average, were within these ranges for total daily energy intake from fat (29-32%) and protein (19-20%), but not carbohydrate (42-44%). Average daily calcium intakes at baseline in both groups were 13-25% below Australian recommended daily intakes for adults aged 50 years or greater (1,000 mg) ^[362].

Table 6.7. Mean baseline dietary intake, within-group changes relative to baseline and between-group net differences for the change after 26 weeks in the Ex+ProCaD and control groups.

	Baseline values and within-group changes				Between-group changes
	Ex+ProCaD		Control		
	n	Mean $\pm$ SD Mean (95% CI)	n	Mean $\pm$ SD Mean (95% CI)	
Energy (kJ/d)					
Baseline	12	9194 $\pm$ 1811	8	8084 $\pm$ 2470	
Δ 26-week	12	305 (-343, 953)	8	-224 (-1988, 1541)	529 (-1117, 2174)
Protein (g/d)					
Baseline	12	99 $\pm$ 29	8	92 $\pm$ 25	
Δ 26-week	12	4 (-13, 21)	8	-9 (-29, 10)	14 (-13, 40)
Protein (g/kg/d)					
Baseline	12	1.13 $\pm$ 0.32	8	1.13 $\pm$ 0.35	
Δ 26-week	12	0.00 (-0.19, 0.19)	8	-0.11 (-0.35, 0.13)	0.11 (-0.19, 0.41)
Protein (% of energy/d)					
Baseline	12	19 $\pm$ 6	8	20 $\pm$ 4	
Δ 26-week	12	-1 (-4, 2)	8	-2 (-5, 2)	1 (-4, 5)
Carbohydrate (g/d)					
Baseline	12	256 $\pm$ 78	8	204 $\pm$ 67	
Δ 26-week	12	-18 (-45, 9)	8	-1 (-36, 35)	-17 (-61, 27)
Carbohydrate (% of energy/d)					
Baseline	12	44 $\pm$ 7	8	42 $\pm$ 14	
Δ 26-week	12	-1 (-7, 4)	8	-1 (-8, 5)	0 (-9, 9)

Fat (g/d)					
Baseline	12	72 ± 25	8	74 ± 49	
Δ 26-week	12	17 (5, 30)	8	-4 (-37, 29)	21 (-10, 53)
Fat (% of energy/d)					
Baseline	12	29 ± 8	8	32 ± 14	
Δ 26-week	12	4 (-1, 9)	8	2 (-7, 11)	2 (-8, 12)
Saturated fat (g/d)					
Baseline	12	29 ± 11	8	26 ± 18	
Δ 26-week	12	4 (-2, 11)	8	1 (-10, 12)	3 (-8, 15)
Saturated fat (% of energy/d)					
Baseline	12	12 ± 4	8	11 ± 6	
Δ 26-week	12	4 (-1, 9)	8	2 (-1, 4)	2 (-4, 9)
Calcium (mg/d)					
Baseline	12	882 ± 337	8	777 ± 235	
Δ 26-week	12	30 (-199, 178)	8	-84 (-304, 136)	114 (-143, 369)

Data are: baseline mean ± standard deviation (SD); within-group absolute changes with 95% confidence interval (CI); net difference (95% CI) were calculated by subtracting within-group absolute change for the control group from that of the Ex+ProCaD group. Dietary data for the Ex+ProCaD group does not include the supplement.

Figure 6.5. Total dietary protein and energy intakes (dietary plus daily supplemental adjusted for average compliance [shaded]) in the Ex+ProCaD (black) and control groups (white) at baseline and 26 weeks; data are: mean and standard deviation.

6.5.8 Body composition

Weight

Baseline and follow-up weight is reported in Table 6.8. On average, men allocated to Ex+ProCaD increased weight by 1.6 kg (1.8%), whereas the control group increased by 1.0 kg (1.2%; Figure 6.6).

Table 6.8. Mean baseline total body weight and lean mass and regional lean mass and muscle cross-sectional area (CSA), within-group changes relative to baseline and between-group net differences for the change after 26 weeks in the Ex+ProCaD and control groups.

	Baseline values and within-group changes				Between-group changes
	Ex+ProCaD		Control		
	n	Mean ± SD Mean (95% CI)	n	Mean ± SD Mean (95% CI)	
Weight (kg)					
Baseline	16	88.5 ± 21.8	12	81.6 ± 14.7	
Δ 26-week	15	1.6 (0.4, 2.9)	12	1.0 (-0.1, 2.2)	0.6 (-1.1, 2.3)
Total body lean mass (kg)					
Baseline	15	52.6 ± 7.5	12	51.1 ± 7.3	
Δ 26-week	14	1.1 (0.4, 1.9)	11	-0.3 (-1.0, 0.3)	1.4 (0.1, 2.4)
Arm lean mass (kg)					
Baseline	15	6.1 ± 1.3	12	5.8 ± 1.2	
Δ 26-week	14	0.1 (-0.1, 0.2)	11	-0.1 (-0.2, 0.1)	0.2 (-0.1, 0.4)
Leg lean mass (kg)					
Baseline	15	17.6 ± 2.7	12	17.4 ± 3.0	
Δ 26-week	14	0.9 (0.4, 1.3)	11	0.1 (-0.2, 0.3)	0.8 (0.2, 1.3)
Appendicular lean mass (kg)					
Baseline	15	23.7 ± 3.8	12	23.2 ± 4.2	
Δ 26-week	14	1.0 (0.5, 1.5)	11	0.0 (-0.2, 0.2)	1.0 (0.4, 1.6)
Forearm muscle CSA (cm²)					
Baseline	14	38.6 ± 5.6	8	38.4 ± 6.4	
Δ 26-week	14	0.7 (-0.2, 1.5)	8	1.3 (0.3, 2.3)	-0.6 (-2.0, 0.7)

Lower leg muscle CSA (cm²)					
Baseline	16	73.4 ± 12.1	11	68.3 ± 14.3	
Δ 26-week	15	-0.3 (2.1, 1.6)	10	0.2 (-1.9, 2.3)	-0.5 (-3.3, 2.4)

Data are: baseline mean ± standard deviation (SD); within-group absolute changes with 95% confidence interval (CI); net difference (95% CI) were calculated by subtracting within-group absolute change for the control group from that of the Ex+ProCaD group.

Figure 6.6. Individual absolute changes in weight in men treated with androgen deprivation therapy for prostate cancer in the Ex+ProCaD and control groups from baseline to 26-week follow-up.

Lean mass and muscle cross-sectional area

Baseline values, within-group changes and between-group changes in lean mass and muscle CSA are presented in Table 6.8. A high proportion of men treated with ADT responded positively (increase greater than zero) to the Ex+ProCaD with regard to total body lean mass (64%), ALM (87%) and forearm (64%) and lower leg muscle CSA (67%; Figure 6.7). On average, men allocated to the control group decreased total body lean mass (0.3 kg), but maintained ALM and increased forearm (1.3 cm²) and lower leg muscle CSA (0.2 cm²).

Figure 6.7. Individual absolute changes in total body and appendicular lean mass and forearm and lower leg muscle cross-sectional area (CSA) in men treated with androgen deprivation therapy for prostate cancer in the Ex+ProCaD and control groups from baseline to 26-week follow-up.

Fat mass and cross-sectional area

Baseline, within- and between-group values and changes in fat mass and CSA are shown in Table 6.9. Following Ex+ProCaD, participants tended to increase total body (mean, 0.8 kg) and regional fat mass (mean, 0.1-0.5 kg) and forearm and lower leg subcutaneous fat CSA (mean, 1.1-1.9 cm²), despite no change in total body percent fat mass (Figure 6.8). The majority of participants allocated to the control group gained total body and total body percent fat mass (both, 82% of group) and forearm (75% of group) and lower leg subcutaneous fat CSA (60% of group).

Table 6.9. Mean baseline total body fat mass and regional fat mass, subcutaneous fat cross-sectional area (CSA) and muscle density, within-group changes relative to baseline and between-group net differences for the change after 26 weeks in the Ex+ProCaD and control groups.

	Baseline values and within-group changes				Between-group changes
	Ex+ProCaD		Control		
	n	Mean ± SD Mean (95% CI)	n	Mean ± SD Mean (95% CI)	
Total body fat mass (kg)					
Baseline	15	28.9 ± 10.9	12	27.7 ± 10.5	
Δ 26-week	14	0.8 (-0.1, 1.7)	11	1.7 (0.5, 3.0)	-0.9 (-2.5, 0.5)
Total body fat mass (%)					
Baseline	15	34.5 ± 8.9	12	34.2 ± 7.7	
Δ 26-week	14	0.0 (-0.8, 0.9)	11	1.4 (0.5, 2.3)	-1.4 (-2.6, -0.1)
Arm fat mass (kg)					
Baseline	15	2.9 ± 1.2	12	2.7 ± 1.0	
Δ 26-week	14	0.0 (-0.1, 0.2)	11	0.0 (-0.1, 0.2)	0.0 (-0.2, 0.2)
Leg fat mass (kg)					
Baseline	15	7.8 ± 2.6	12	8.9 ± 4.6	
Δ 26-week	14	0.5 (0.1, 0.9)	11	0.6 (0.1, 1.1)	-0.1 (-0.7, 0.5)
Android fat mass (kg)					
Baseline	15	3.2 ± 1.6	12	2.7 ± 1.2	
Δ 26-week	14	0.1 (-0.1, 0.2)	11	0.3 (0.1, 0.4)	-0.2 (-0.4, 0.0)
Gynoid fat mass (kg)					
Baseline	15	4.1 ± 1.4	12	4.2 ± 1.5	
Δ 26-week	14	0.2 (0.0, 0.4)	11	0.3 (0.0, 0.5)	-0.1 (-0.3, 0.2)

Abdominal visceral fat mass (kg)					
Baseline	15	2.0 ± 1.4	11	1.5 ± 0.8	
Δ 26-week	14	0.1 (-0.1, 0.2)	10	0.2 (0.0, 0.4)	-0.1 (-0.4, 0.1)
Abdominal subcutaneous fat mass (kg)					
Baseline	15	1.2 ± 0.5	11	1.1 ± 0.5	
Δ 26-week	14	0.0 (-0.1, 0.1)	10	0.0 (-0.1, 0.1)	0.0 (-0.1, 0.2)
Forearm subcutaneous fat CSA (cm²)					
Baseline	14	10.6 ± 4.8	8	13.2 ± 10.0	
Δ 26-week	14	1.1 (0.4, 1.8)	8	0.7 (-0.4, 1.7)	0.4 (-0.7, 1.7)
Lower leg subcutaneous fat CSA (cm²)					
Baseline	16	17.9 ± 6.9	11	26.0 ± 18.6	
Δ 26-week	15	1.9 (0.7, 3.1)	10	0.6 (-0.3, 1.4)	1.3 (0.2, 3.0)
Forearm muscle density (mg/cm³)					
Baseline	14	78.3 ± 1.3	8	76.9 ± 3.5	
Δ 26-week	14	-0.3 (-1.0, 0.3)	8	-0.7 (-1.8, 0.5)	0.4 (-0.9, 1.5)
Lower leg muscle density (mg/cm³)					
Baseline	16	74.8 ± 2.7	11	73.3 ± 3.2	
Δ 26-week	15	0.2 (-0.6, 1.0)	10	0.4 (-0.4, 1.1)	-0.2 (-1.3, 0.9)

Data are: baseline mean ± standard deviation (SD); within-group absolute changes with 95% confidence interval (CI); net difference (95% CI) were calculated by subtracting within-group absolute change for the control group from that of the Ex+ProCaD group.

Figure 6.8. Individual absolute changes in total body and total body percent fat mass and forearm and lower leg subcutaneous fat cross-sectional area (SFCSA) in men treated with androgen deprivation therapy for prostate cancer in the Ex+ProCaD and control groups from baseline to 26-week follow-up.

Muscle density

Descriptive statistics for muscle density are presented in Table 6.9. Forearm muscle density tended to decrease in both groups by an average of 0.3-0.7 mg/cm³, whereas lower leg muscle density appeared to increase following Ex+ProCaD (0.2 mg/cm³) or usual care (0.4 mg/cm³; Figure 6.9).

Figure 6.9. Individual absolute changes in forearm and lower leg muscle density in men treated with androgen deprivation therapy for prostate cancer in the Ex+ProCaD and control groups from baseline to 26-week follow-up.

6.5.9 Muscle strength and functional capacity

Muscle strength

Muscle strength outcomes at baseline and follow-up are shown in Table 6.10. Men in the Ex+ProCaD group tended to improve chest (mean, 16%), leg (mean, 31%) and back muscle strength (mean, 18%), but not handgrip muscle strength (mean, -0.7%; Figure 6.10). Of those allocated to the control group, one third decreased chest muscle strength and approximately two thirds (67%) decreased handgrip muscle strength, however, no controls decreased back or leg muscle strength.

Table 6.10. Mean baseline muscle strength variables, within-group changes relative to baseline and between-group net differences for the change after 26 weeks in the Ex+ProCaD and control groups.

Muscle Strength	Baseline values and within-group changes				Between-group changes
	Ex+ProCaD		Control		
	n	Mean ± SD Mean (95% CI)	n	Mean ± SD Mean (95% CI)	
Handgrip					
Baseline (kg)	13	36.7 ± 7.0	9	37.4 ± 8.1	
Δ 26-week (%)	13	-0.7 (-5.9, 4.4)	9	2.8 (-8.2, 13.7)	-3.5 (-13.6, 6.6)
Chest					
Baseline (kg)	14	38.7 ± 12.8	6	33.7 ± 6.8	
Δ 26-week (%)	12	16.0 (-2.8, 34.9)	6	-2.6 (-10.7, 5.5)	18.6 (-7.9, 45.1)
Leg					
Baseline (kg)	14	131.1 ± 42.9	8	94.4 ± 40.1	
Δ 26-week (%)	12	30.7 (15.5, 45.8)	7	18.2 (3.7, 32.8)	12.5 (15.6, 36.5)
Back					
Baseline (kg)	11	49.2 ± 17.7	4	43.9 ± 11.6	
Δ 26-week (%)	11	17.9 (-5.6, 41.4)	3	9.9 (-14.5, 34.2)	8.0 (-37.7, 53.8)

Data are: baseline mean $\pm$ standard deviation (SD); within-group percent changes with 95% confidence interval (CI); net difference (95% CI) were calculated by subtracting within-group percent change for the control group from that of the Ex+ProCaD group.

Figure 6.10. Individual percent changes in handgrip, chest, leg and back muscle strength in men treated with androgen deprivation therapy for prostate cancer in the Ex+ProCaD and control groups from baseline to 26-week follow-up.

Functional capacity

Baseline values and percent within- and between-group differences for various outcomes of functional capacity are presented in Table 6.11. Men treated with ADT in the Ex+ProCaD group more commonly improved timed-up-and-go (53% of group) and four-square step test performance (80% of group), but not 30-second sit-to-stand, gait speed, 400 metre walk and Berg balance scale (all < 40% of group; Figure 6.11). Half of the participants allocated to the control group decreased 30-second sit-to-stand and four-square step test performance, whereas the majority decreased timed-up-and-go performance (58%; increase) and gait speed (67%; decrease), but not 400 metre walk (36%; decrease) and Berg balance scale (25%; decrease).

Table 6.11. Mean baseline functional capacity variables, within-group changes relative to baseline and between-group net differences for the change after 26 weeks in the Ex+ProCaD and control groups.

	Baseline values and within-group changes				Between-group changes
	Ex+ProCaD		Control		
	n	Mean ± SD Mean (95% CI)	n	Mean ± SD Mean (95% CI)	
Timed-up-and-go					
Baseline (sec)	16	11.11 ± 3.26	12	11.76 ± 5.71	
Δ 26-week (%)	15	6.7 (-13.3, 26.7)	12	18.9 (-13.6, 51.4)	-12.2 (-46.8, 22.4)
Four-square step test					
Baseline (sec)	16	10.54 ± 2.20	12	10.83 ± 2.66	
Δ 26-week (%)	15	-12.1 (-20.6, -3.6)	12	1.5 (-8.4, 11.5)	-13.6 (-25.9, -1.3)
30-second sit-to-stand					
Baseline (sec)	16	13 ± 4	12	12 ± 4	
Δ 26-week (%)	15	7.7 (-11.5, 26.8)	12	-0.9 (-14.9, 13.1)	8.6 (-15.2, 32.2)
Gait speed					
Baseline (m/s)	13	1.39 ± 0.16	9	1.36 ± 0.29	
Δ 26-week (%)	13	-0.4 (-4.6, 3.8)	9	0.2 (-5.9, 6.4)	-0.6 (-7.4, 6.0)
400 metre walk					
Baseline (sec)	16	278 ± 37	11	299 ± 47	
Δ 26-week (%)	15	8.5 (-3.1, 20.1)	11	2.4 (-5.5, 10.4)	6.1 (-8.0, 20.2)
Berg balance scale					
Baseline (n)	15	55 ± 1	12	54 ± 3	
Δ 26-week (%)	14	-0.9 (-2.5, 0.7)	12	-0.3 (-3.9, 3.3)	-0.6 (-4.1, 2.9)

Data are: baseline mean $\pm$ standard deviation (SD); within-group percent changes with 95% confidence interval (CI); net difference (95% CI) were calculated by subtracting within-group percent change for the control group from that of the Ex+ProCaD group.

Figure 6.11. Individual percent changes in the performance of timed-up-and-go, four-square step test, 30-second sit-to-stand, gait speed, 400 metre walk and Berg balance scale in men treated with androgen deprivation therapy for prostate cancer in the Ex+ProCaD and control groups from baseline to 26-week follow-up.

6.6 Discussion

The main findings from the preliminary analysis of this RCT that examined the feasibility of implementing a community-based multi-component exercise program combined with protein, calcium and vitamin D supplementation intervention in men treated with ADT for PCa were that participant retention rates (96%) and adherence to the supplement (mean, 92-93%) were high, but adherence to the exercise program was modest (mean, 60%). Furthermore, a relatively high proportion (81%) of participants in the intervention group reported an adverse event during the 26-week intervention, although only 16% were confirmed to be related to the intervention and the vast majority (97%) were determined by research staff to be mild (“Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient”) or moderate (“Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning”) in terms of severity.

Numerous issues pertaining to recruitment and data collection in this clinical population group were observed, which unforeseeably elongated the study timeline and prevented the collection of various outcome measures, respectively. Throughout the study, 10 separate recruitment pathways were considered, with clinician referral (43%) and PCa support groups (29%) yielding the greatest proportion of enrolled participants. Collectively, a total of 149 potential participants were screened for the RCT, which resulted in 42 participants at the time of write up for this thesis. The main reason for exclusion (n=75) was a lack of current ADT use (48%) and the men who declined to participate (n=21) most commonly cited no specific reason (48%). Among the first 28 participants to complete the 26-week intervention, there was a notable inability to completed all measures, in particular muscle strength assessed by 3-RM (21-50% were unable to complete these tests), which primarily stemmed from safety concerns with regard to previous comorbidities. Data from the initial 28 participants who completed the study tended to respond positively to the Ex+ProCaD intervention compared to usual care with regard to net differences in lean mass (0.2-1.4 kg), fat mass (-0.1 to -0.9 kg), muscle strength (8.0-19%), functional muscle power (8.6%) and functional capacity (12-14%). Together, these findings support the feasibility of implementing a multifaceted exercise and nutrition intervention in ADT-treated men,

but highlight the potential limitations associated with recruitment, safety and elements of data collection.

Attrition and adherence

Given the myriad of adverse effects associated with ADT ^[11-14], as well as the tendency for this treatment to be used for advanced PCa which may eventually progress and lead to additional comorbidities ^[3, 4], there is a need to consider retention rates and adherence when designing and implementing lifestyle interventions. In this study, only one participant of the first 28 men to complete the intervention was lost to follow-up; thus, the retention rate of our study at the time of write up of this chapter was 96%. On average, previous exercise-only RCTs of 12 weeks or greater have reported retention rates ranging from 66-96% ^[225, 227-229, 234, 238, 244, 246]. Notably, a recent study that pooled 1,366 cancer survivors (mean age, 75 years; PCa, 46%) from three diet and exercise-based lifestyle interventions found that overall retention (91%) was not influenced by factors that commonly reduce willingness to participate and adherence, such as sex, age, race, time since cancer diagnosis or cancer type ^[363]. These findings suggest that once ADT-treated men are enrolled in the study, the attention of researchers should shift towards ensuring adequate adherence to the prescribed intervention.

In terms of adherence, participants allocated to Ex+ProCaD completed 60% of all exercise training sessions (68% supervised gym-based; 50% unsupervised home-based) and consumed 92-93% of the nutritional supplement over the 26-week period. Similar compliance was observed for the vitamin D supplement in the control group (94%). On average, previous trials that have examined exercise training interventions of 12 weeks or greater in men treated with ADT have reported an adherence for supervised sessions ranging from 69-96%. It is difficult to explain the lower rates of adherence to supervised exercise training in our study, however, given the modest sample size (n=16) and the subsequent influence of outliers on mean adherence, the median adherence of 85% should be considered when interpreting the initial findings from our study. Compliance rates of unsupervised home-based exercise training tend to be omitted when RCT outcomes are reported, with only one study of 51 ADT-treated men (mean age, 70 years) having reported a 43% adherence to a once weekly session over a 52-week intervention; notably, unsupervised session compliance was approximately half of that of supervised sessions (84%) ^[244]. The authors suggested that the lower rates of compliance with unsupervised sessions may have stemmed from

training individually, whereas the supervised sessions were performed in a group-based setting ^[244]. Social support is a known facilitator to exercise training in older adults ^[364, 365] and may in part explain the compromised compliance of unsupervised sessions when compared to supervised sessions in our study.

To date, the feasibility of consuming a multi-nutrient supplement high in protein, calcium and vitamin D has not been examined in ADT-treated men, however, a previous multi-factorial RCT of 120 men treated for ADT (median age, 69 years) showed that a similar supplement delivery method (i.e. sachet of powder [soy isoflavones or placebo] and single tablet [venlafaxine or placebo]) had a compliance rate of 92% ^[366]. While this trial aimed to ameliorate ADT-induced hot flushes, the high compliance observed supports our findings that a powder sachet and single tablet appears to be a feasible approach for administering a multi-nutrient supplement in these men. Overall, our findings indicate that implementing a multifaceted lifestyle intervention incorporating supervised and home-based exercise with a multi-nutrient supplement is feasible in men treated with ADT in terms of retention and adherence over the initial 26-week follow-up. However, determining whether these rates are continued over the subsequent 26-week period in the larger RCT is warranted in order to assess the long-term likelihood of this clinical population group adopting such a lifestyle intervention.

Safety

To date, the safety of lifestyle interventions in men treated with ADT for PCa has predominately focused on the impact of these interventions on the efficacy of ADT itself, as measured by changes in PSA or testosterone, rather than potential adverse events associated with the intervention (e.g. exercise or nutritional factors) ^[60]. Moreover, given the novelty of the multi-nutrient supplementation examined in our study, its safety is currently unknown. In our study, the absence of robust statistical analyses limits the inference of safety associated with fluctuations in PSA, however, men randomised to Ex+ProCaD showed an average reduction of 1.4 ng/mL, whereas the control group increased by 1.0 ng/mL. Whilst these responses appear to support the safety of a multi-component exercise program combined with protein, calcium and vitamin D supplementation in terms of PSA, analyses of the complete dataset from the larger RCT are required before definitive conclusions may be drawn. With regards to the exercise training and nutritional supplements in our study, we observed no study-

related adverse events that led to permanent discontinuation of the complete intervention, however, one participant discontinued the sachet supplement due to gastrointestinal upset. Whilst the age-related changes in the gastrointestinal tract may impede the ability to digest protein and lead to gastrointestinal upset in some adults [367], protein supplementation has generally been shown to be well tolerated and accompanied by no serious adverse events in older adults [269, 270]. Previous RCTs that examined the efficacy of exercise programs in men treated with ADT have also reported the absence of intervention-based adverse events that resulted in permanent discontinuation [227, 229, 234, 238, 244, 246]. Of the reported adverse events in our trial that were study-related (n=6) or potentially study-related (n=8); the majority were muscle/joint-based from previously documented comorbidities and were resolved with temporary modification to the exercise program within a single training session. The presence of various comorbidities in older men, as well as in those treated with ADT for PCa, is well established [11-14], thus the prescription of exercise in these population group should be individually tailored and overseen by an appropriately qualified exercise trainers (e.g. a tertiary trained Accredited Exercise Physiologist in Australia). Collectively, the findings from our study support the safety of a multi-component exercise program combined with protein, calcium and vitamin D supplementation, yet highlight the potential for non-severe adverse events, primarily due to pre-existing comorbidities. Importantly, analyses of potential changes in PSA at the completion of the larger RCT are warranted before conclusions pertaining to the impact on the efficacy of ADT itself may be established.

Recruitment

There are a wide range of barriers to the recruitment of older adults with cancer into clinical trials, which often stem from trial design, clinician support and patient characteristics [368, 369]. In addition, poor physical and mental health has been shown to limit physical activity participation in older adults [364, 365]. Interestingly, a recent review of funded clinical trials conducted in the United Kingdom concluded that 45% of trials required an extended timeline due to recruitment-based delays and only 55% of trials eventually recruited their intended total sample, whereas 78% ultimately recruited 80% of their target sample size [370]. Despite these challenges, it has been noted that many clinical trials that recruited cancer patients did not include adequate details of the recruitment process in order to inform future research [371]. In our study, a total of 149 potential participants were screened from 2014 to 2017, with clinician

referral (n=42), PCa support groups (n=31), local newspaper advertisement (n=31) and state news television report (n=23) accounting for the majority of recruitment. Of these pathways, clinician referral and PCa support groups provided 43% and 29% of the total enrolled sample (n=42), respectively. A multi-pathway approach similar to our study (i.e. state cancer registry, clinician referral, support groups, community events and study advertisement) was utilised during the 2-year recruitment of men treated with ADT to a year-long exercise training RCT and resulted in 467 men screened and 51 randomised to the intervention ^[244]. Notably, the efficacy of each specific pathway was not reported and thus direct comparisons to the pathways utilised in our study are limited. Regardless, this previous approach screened greater than 300 more potential participants when compared to our trial ^[244], which may in part stem from our lack of utilisation of a cancer registry, which has previously been shown to be a successful recruitment pathway in cancer patients ^[372, 373]. Furthermore, two previous trials that adopted 14-16 month single pathway approaches that relied on clinician referral were only able to screen 97 ^[227] and 126 ^[234] men treated with ADT for inclusion in exercise-based RCTs, successfully enrolling 59% (n=57) and 50% (n=63) of potential participants, respectively. The greater efficacy of these approaches, when compared to our study, is difficult to explain and whilst counterintuitive may stem from the greater focus of resources on a singular recruitment pathway as opposed to several. Moreover, previous research has supported the importance of a clinician referral to an exercise program, with 80% of 47 men who recently received active treatment for PCa having cited that clinician involvement influenced their decision to participate in 12-week intervention ^[374]. Notably, these observations supported our findings that clinician referral led to a greater proportion of eligible participants, compared to those screened from other recruitment pathways. Collectively, our findings highlight the difficulty of recruiting ADT-treated men to a lifestyle intervention, and suggest that future trials should consider the development of a thoroughly designed recruitment plan that includes the clinical referral pathway to ensure predetermined sample sizes can be achieved.

The design of a clinical trial may also have significant implications on participant recruitment, especially when considering the strict inclusion/exclusion criteria often imposed to account for known confounding variables ^[369]. Approximately half (52%) of excluded participants were not eligible for our trial due to a lack of current pharmacological ADT for PCa and the remainder were precluded from involvement

due to various exclusion criteria designed to account for known confounding variables related to the main outcomes of the larger RCT (bone health). This was similar to a previous RCT that recruited men to a 52-week exercise training intervention, whereby the majority of exclusions were based on a lack of current ADT use ^[243]. Of ADT-treated men excluded in our study, vitamin D supplementation greater than 1,000 IU/day (16%) and PRT greater than one session/week (8.0%) were the most common reasons. Comparisons between our exclusion criteria and that of previous trials is difficult given the omission ^[225, 228, 241] or lack of detail ^[234, 238, 244, 246] when reporting these reasons, as well as the differences in primary outcomes. Exclusions based on current vitamin D supplementation and PRT align with current lifestyle guidelines for men treated with ADT for PCa that suggest these interventions to overcome the myriad of treatment-induced adverse effects ^[195]. Furthermore, in a survey of urologists and radiation oncologists, 47% recommended vitamin D supplementation for this susceptible population group ^[283]. The proportion of men treated with ADT who were precluded from our trial after expressing interest further highlights the importance of determining effective recruitment pathways.

Data collection

It is well established that men treated with ADT for PCa frequently present with additional comorbidities ^[11-14], which may in turn limit the ability to obtain certain outcome measures in research studies involving these men. In our study, men who presented with a current comorbidity reported three on average. These pre-existing comorbidities, which were most commonly musculoskeletal and haemodynamic in nature, predominantly impacted the acquisition of muscle strength measures of the three 3-RM protocols implemented (21-50% of data missing). Additionally, global and regional obesity limited the collection of some radiological scan outcomes due to an inability to define regions of interest (17-50% of data missing). To our knowledge, the majority of previous trials that have examined similar outcomes in studies that have examined lifestyle interventions in ADT-treated men have not reported these observations, which may in part stem from volunteer or reporting biases. In support of our limitations when muscle strength was assessed, 40% of men in a cohort of 62 men commencing ADT (mean age, 68 years) were unable to complete at least one of three assessment of handgrip strength over a 12-month follow-up ^[28]. Moreover, given the average annual gain of total body fat mass exceeds 11% in ADT-treated men ^[198] and the known limitations of DXA scan acquisition in those with obesity ^[76], the missing

data in our study appears to be in line with current limitations of these tools. However, our findings suggest that researchers should consider the feasibility of data collection when designing trials with clinical populations groups with multiple comorbidities, such as men treated with ADT for PCa.

Intervention responses to Ex+ProCaD versus usual care

Given that this chapter only reported descriptive statistics of the first 28 men to complete the intervention, responses to Ex+ProCaD and usual care (i.e. 1000 IU/day vitamin D) in these men should be interpreted with caution. Moreover, these observations may change following the analysis of the complete dataset of the larger RCT. Nonetheless, the following section presents the preliminary efficacy of Ex+ProCaD compared to usual care in men treated with ADT for PCa. Notably, due to the lack of previous studies in ADT-treated men that have examined the efficacy of multifaceted exercise and nutrition interventions similar to that of Ex+ProCaD in our study, comparisons will be primarily made with exercise-only trials in these men.

Men allocated to Ex+ProCaD demonstrated a 1.4 kg average net gain in total body lean mass compared to controls, which was primarily due to an improvement in ALM (net difference, 1.0 kg), particularly leg lean mass (net difference, 0.8 kg). Consistent with these findings, a previous 26-week RCT in 97 men treated with ADT (mean age, 69 years) that examined the efficacy of supervised PRT combined with aerobic exercise training reported an average net gain of 0.8 kg in DXA-derived total body lean mass compared to usual care; however, region-specific outcomes were not reported ^[246]. Moreover, following 12 weeks of PRT in a sample of 57 ADT-treated men (mean age, 70 years), total body lean mass increased compared to controls (adjusted net difference, 0.8 kg), which was due to gains in ALM (adjusted net difference, 0.8 kg), specifically leg lean mass (adjusted net difference, 0.5 kg). An explanation for these greater gains in leg lean mass when compared to that of the arms may in part stem from the exercise training principle of initial values, in which physiological outcomes with poorer results have the greatest capacity for improvement ^[24]. Indeed, multiple studies have observed age-related losses of muscle of the lower limb occur at more than double the rate of the upper limb ^[139-141]. However, the net effects of Ex+ProCaD on and lower leg muscle CSA (-0.5 cm²) appeared to contrast these observations and favoured usual care. Whilst difficult to explain, these findings potentially suggest that Ex+ProCaD led to gains in upper, rather than lower, leg lean

mass. Given the design of the PRT program in our study (e.g. targeting muscles with attachments to the hip and spine), muscles located within the upper leg likely received greater attention than those of the lower leg. To further investigate this notion, future studies should consider upper leg pQCT measures, such as those at the 25% or 50% femur ^[77]. Collectively, these findings support the use of lifestyle interventions that combine exercise training and nutritional supplementation to ameliorate the loss of lean mass often observed during ADT ^[195].

When compared to the control group, Ex+ProCaD resulted in a mean net loss of 0.9 kg in total body fat mass which corresponded with a reduction in total body percent fat mass (net difference, -1.4%). These changes in fat mass following Ex+ProCaD tended to span across multiple regions (i.e. leg, android, gynoid, abdominal visceral; net difference, -0.1 to -0.2 kg). Similarly, following a 52-week exercise program that combined PRT and impact exercise training, a sample of 51 men treated with ADT (mean age, 70-71 years) demonstrated net losses in total body fat mass (2.0 kg) and total body percent fat mass (1.3%) compared to stretching-only control group ^[242]. In contrast, multiple RCTs that examined the efficacy of lifestyle interventions including exercise training on adiposity showed no change compared to controls ^[227, 228, 238, 375]. For example, when compared to controls, no change in total body fat mass or total body percent fat mass was observed following 12 weeks of PRT in 57 ADT-treated men (mean age, 70 years) ^[227]. Many factors pertaining to the design of these exercise training programs (e.g. intensity, sets, repetitions and number of exercises) may in part explain these discrepancies. Particularly, it is possible that the trials that differed to our results and observed no change in adiposity achieved a training load below current recommendations (i.e. 150-250 minutes per week of moderate-intensity exercise) for weight loss and subsequent reductions in fat mass ^[376]. Interestingly, the loss of leg fat mass in men allocated to Ex+ProCaD compared to usual care was conflicted by the net gain in lower leg subcutaneous fat CSA (1.3 cm²). Similar to aforementioned discrepancies in leg lean mass and muscle CSA, these findings may further support that Ex+ProCaD resulted in decreased fat mass within the upper, but not lower leg, and further strengthens our recommendations for the incorporation of upper leg pQCT measures. Another factor may have been the difference in ADT duration between groups, with controls having reported two more years of treatment on average. A previous 6-month prospective study showed that 30 men treated with ADT for an average of three months gained 7.7% total body percent fat mass, whereas those treated

for an average of 33 months ($n=50$) showed no change ^[18]. Thus, there is a need to consider duration of ADT as a confounding variable in future analyses. Contrasting net differences were also observed in forearm (0.4 mg/cm^3) and lower leg muscle density (-0.2 mg/cm^3), which suggests effect of Ex+ProCaD on intermuscular fat may have been region-specific. To date, no other studies have examined muscle density in this clinical population group, however, given the small magnitude of change in comparison to decrements of 3.5 mg/cm^3 previously shown to be associated with mortality in a cohort of 1,063 healthy older men (mean age, 77 years), it is unlikely that these changes in muscle density are of clinical relevance with regard to mortality risk ^[181]. Therefore, these findings provide novel insight into the role of combining exercise training and nutritional supplementation to address the known gains in fat mass during ADT ^[195].

On average, participants randomised to Ex+ProCaD showed net increases of 8-19% in all measures of muscle strength, bar handgrip, when compared to controls. Previous exercise training studies of 12-52 weeks in men treated with ADT have shown improvements in various assessments of upper (4.0-26%) and lower body muscle strength (17-37%) when compared to controls ^[227, 232, 234, 238, 243]. Specifically, in a cohort of 58 ADT-treated men, 16 weeks of PRT resulted in a similar magnitude of improvement in leg, chest and shoulder muscle strength (10-26%) when compared to controls ^[238]. These improvements in muscle strength following Ex+ProCaD are important given that muscle strength tends to be a better independent predictor of adverse health outcomes when compared to lean mass alone ^[42, 44, 49, 182]. Among a sample of 5,995 older men (mean age, 74 years), men within the three highest quartiles of muscle strength had a reduced risk of falls when compared to those within the lowest quartile (relative risk, 0.74-0.84) ^[42]. Reducing the risk of falls in men treated with ADT is of clinical relevance given the established increased prevalence ^[201] and subsequent fractures ^[202-204]. Moreover, Ex+ProCaD resulted in mean net improvements in measures of functional muscle power (8.6%) compared to usual care. The only other known RCT that examined the effects of a lifestyle intervention on functional muscle power in 50 men treated with ADT (mean age, 72 years) demonstrated that a 12-week aerobic and PRT program combined with dietary advice improved 30-second sit-to-stand performance relative to the controls (net difference, 35% [four repetitions]) ^[375]. When compared to our absolute findings (net difference, one repetition), the variation in magnitude of improvement between intervention and

control participants likely stems from the lower initial values in the previous study (11 repetitions) compared to ours (13 repetitions).

Whilst Ex+ProCaD led to improvements in 30-second sit-to-stand performance in our study, an average baseline result of 13 repetitions was previously shown to be associated with physical independence in a sample of 2,140 older adults; thus the improvements observed in our study may be of limited clinical relevance. Similar to the improvements in Ex+ProCaD compared to usual care in our study with regard to functional capacity (net difference, 12-14%), various exercise training interventions in this clinical population group have also been shown to improve functional capacity, albeit variations in tests utilised limit the comparability between trials [227, 238, 375]. Regardless, the changes in functional capacity following Ex+ProCaD in our study are likely of limited clinical relevance given that average baseline results for outcomes such as timed-up-and-go (11.11 second), gait speed (1.39 m/s) and four-square step test (10.54 second) were within healthy ranges when compared to established cut-offs for predicting risk of adverse outcomes (i.e. timed-up-and-go ≥ 15 second, gait speed < 1.00 m/s and four-square step test ≥ 15 second). Overall, these findings demonstrate the potential role of lifestyle interventions that incorporate both exercise training and nutritional supplementation in mitigating the loss of muscle strength, functional muscle power and functional capacity that commonly accompany treatment-induced decrements in body composition [195].

6.7 Strengths and limitations

The strengths of this study were discussed in Chapters 4 and 5. More specific to the RCT however, this is the first study that examined a wide range of feasibility outcomes of a combined multi-component exercise program and multi-nutrient supplement in men treated with ADT for PCa. Similarly, the 26-week duration of the trial was longer than the majority of previously conducted lifestyle intervention studies in ADT-treated men. However, several limitations should be noted when interpreting the results from this study. First, due to the feasibility issues outlined in this chapter and the subsequent lack of a completed dataset, the descriptive statistics presented should be interpreted with caution given the modest sample size. Second, as with any study involving exercise training, those of greater functional capacity and/or a penchant for health and fitness, may have been more likely to participate. Third, the strict exclusion criteria, albeit a strength of our trial in terms of accounting for a range of confounding

variables, may have excluded men with characteristics that represent a large proportion of men treated with ADT, such as those with absolute contraindications to exercise training. Fourth, the assessment of safety was restricted to recorded adverse events and PSA, whereas testosterone and its precursors were not measured to assess whether the intervention impacted the intended therapeutic effects of ADT. Finally, apart from the analyses of radiological images, neither the participant nor the researchers were blinded to treatment allocation.

6.8 Summary and conclusion

In summary, our study showed that the implementation of Ex+ProCaD when compared to usual care in men treated with ADT for PCa was feasible in terms of participant retention, adherence to the intervention and safe with regard to changes in PSA. However, issues stemming from recruitment and data collection unforeseeably extended the study timeline and limited the ability to collect a complete dataset, respectively. Whilst various recruitment pathways were used to recruit participants, only clinician referral and PCa support groups resulted in meaningful numbers of enrolled participants. Of those included, data collection, particularly outcomes of muscle strength, were at times hindered by safety concerns associated with pre-existing comorbidities. Beyond these limitations, among the first 28 ADT-treated men to complete the 26-week follow-up, those allocated to Ex+ProCaD tended to improve various outcomes of muscle, fat and performance when compared to usual care.

In conclusion, our findings provide novel insight into the feasibility of implementing a multifaceted community-based exercise and nutrition intervention in men treated with ADT for PCa. Importantly, our observations support the notion that trials aiming to recruit these men should consider clinician referral and PCa support groups to ensure sample size targets are met in a timely manner. Moreover, the pre-existing comorbidities commonly observed in ADT-treated men should be considered when designing future trials to ensure realistically obtained outcome measures are utilised. Furthermore, these comorbidities may predispose these men to adverse events associated with lifestyle interventions, particularly exercise training, and therefore strategies to modify these exercise programs when required should be completed in advance. Finally, the safety in terms of PSA, adherence and retention associated with Ex+ProCaD, as well as the apparent positive responses among the initial participants suggest that this lifestyle intervention may be suitable for ameliorating the wide range

of ADT-induced adverse effects in this susceptible population group. However, outcomes of the large 52-week RCT should be considered before definitive conclusions are drawn with regard to the efficacy of multi-component exercise program combined with protein, calcium and vitamin D supplementation interventions in ADT-treated men. In the following chapter, the key themes and findings of this study, along with suggestions for future research, will be presented.

Chapter 7

Conclusions and future direction

7.1 Overview

This chapter presents concluding remarks pertaining to the key findings from the cross-sectional study and randomised controlled trial (RCT) reported within this thesis. Moreover, this chapter discusses the strengths and limitations of these studies and provides suggestions that should be considered for future research.

7.2 Summary

Worldwide, prostate cancer (PCa) continues to be one of the most frequently diagnosed male cancers and accounts for a substantial proportion of male cancer-related deaths ^[1]. However, as the five-year relative survival rate approaches 100% internationally ^[2], men diagnosed with PCa are now living longer and at risk of age- and treatment-related complications. PCa is commonly managed via androgen deprivation therapy (ADT) in both metastatic ^[3] and non-metastatic PCa survivors ^[4] and has been shown to increase survival in appropriately selected patients ^[5-9]. The treatment-induced hypogonadism is often accompanied by a range of adverse effects ^[11-14], including those that negatively impact lean mass and muscle cross-sectional area (CSA) ^[15-21], fat mass and CSA ^[17-23] and performance (e.g. muscle strength, muscle power and functional capacity) ^[25-34]. To date, the true extent in which these outcomes are affected by ADT is limited due to methodological limitations and inconsistencies in prior studies ^[15-23, 25-34, 36-38]. Moreover, the regional accumulation of fat in varying subcutaneous, visceral and intermuscular depots has received limited attention in this susceptible population group ^[15, 17-23]. A greater understanding of these ADT-induced adverse effects to muscle, fat and performance outcomes are of clinical importance given the propensity for these men to develop musculoskeletal, cardiometabolic and functional comorbidities ^[41-49]. Additionally, the application of pre-defined syndromes, such as sarcopenia ^[51-53] and sarcopenic obesity ^[54, 55], may assist in quantifying the risk of these comorbidities in ADT-treated men, although, these concepts are yet to be applied in these men. Emerging evidence has supported the use of lifestyle interventions, such as exercise training and to a lesser extent nutritional supplementation, to improve or maintain muscle, fat and performance outcomes in men treated with ADT ^[14, 56-59]. However, the majority of these interventions have been limited to singular modalities (e.g. exercise training only) and thus may not represent the most feasible approach to addressing the wide range of adverse effects associated with ADT. Therefore, the overall aim of this thesis was to quantify outcomes of muscle, fat and performance in men treated with ADT when compared to PCa and

healthy controls, and assess the feasibility of a multi-component exercise program combined with protein, calcium and vitamin D supplementation (Ex+ProCaD) when compared to usual care in ADT-treated men.

The specific aims of this thesis were the following:

1. To compare lean mass (total body, appendicular, arm and leg; dual-energy x-ray absorptiometry [DXA]) and muscle CSA (forearm [66% radius] and lower leg [66% tibia]); peripheral quantitative computer tomography [pQCT]) in men treated with ADT to PCa and healthy controls (Chapter 4).
2. To compare fat mass (total body, arm, leg, android, gynoid, abdominal visceral and abdominal subcutaneous; DXA) and fat CSA (forearm [66% radius] and lower leg [66% tibia]; pQCT) in men treated with ADT to PCa and healthy controls (Chapter 4 and Chapter 5).
3. To compare muscle strength (handgrip strength and three-repetition maximum leg press, chest press and seated row), functional muscle power (30-second sit-to-stand) and functional capacity (timed up-and-go, four-square step test, four metre walk and Berg balance scale) in men treated with ADT to PCa and healthy controls (Chapter 4).
4. To compare the prevalence of pre-sarcopenia, sarcopenia, obesity and sarcopenic obesity in men treated with ADT to PCa and healthy controls (Chapter 4).
5. To compare muscle density (forearm [66% radius] and lower leg [66% tibia]; pQCT) as a marker of intermuscular fat in men treated with ADT to PCa and healthy controls (Chapter 5).
6. To assess the influence of ADT use duration on lean mass, muscle CSA, fat mass and CSA, muscle density, muscle strength, functional muscle power and functional capacity in men treated with ADT (Chapter 4 and Chapter 5).
7. To assess the feasibility (recruitment, attrition, adherence, data collection and safety) of Ex+ProCaD when compared to usual care in men treated with ADT (Chapter 6).

7.3 Key findings, limitations and future direction

The key findings from this thesis were the following:

1. Men treated with ADT did not have compromised absolute total body and regional muscle mass and muscle CSA when compared to PCa and healthy

controls, however ADT-treated men had greater total body fat mass. When accounting for these differences via body size- or adiposity-based adjustments, men treated with ADT were shown to have significantly lower regional lean mass and muscle CSA compared to controls. Similar findings were observed when muscle strength outcomes were adjusted for weight. Men treated with ADT were also shown to differ in some, but not all, measures of functional capacity when compared to controls. Subsequently, men treated with ADT were more likely than both controls to present with pre-sarcopenia, sarcopenia, obesity and pre-sarcopenia/obesity concurrently.

2. Men treated with ADT had greater amounts of fat stored in subcutaneous depots, but not within the visceral region of the abdominal cavity, when compared to PCa and healthy controls. Moreover, ADT-treated men did not possess compromised muscle density (as a marker of intermuscular fat) compared to either control. However, duration of ADT use correlated with the majority of subcutaneous and intermuscular depots, indicating that the accumulation of fat mass at these sites likely continues throughout ADT.
3. The implementation of Ex+ProCaD when compared to usual care in men treated with ADT for PCa was feasible in terms of participant retention, adherence to the intervention and safe with regard to adverse events and changes in PSA. However, issues stemming from recruitment and data collection unforeseeably elongated the study timeline and limited the ability to collect a complete dataset, respectively. Whilst various recruitment pathways led to contact with potential participants, only clinician referral and PCa support groups resulted in meaningful numbers of enrolled participants. Of those included, the collection of data, particularly outcomes of muscle strength, were at times hindered by safety concerns associated with pre-existing comorbidities. Beyond these limitations, among the first 28 ADT-treated men to complete the 26-week follow-up, those allocated to Ex+ProCaD tended to respond positively in terms of improvement in lean and fat mass, muscle strength, functional muscle power and functional capacity.

7.3.1 Measures of muscle health should be considered relative to body size or adiposity in men treated with androgen deprivation therapy for prostate cancer

In Chapter 4, the effects of ADT on total body lean and fat mass, regional lean mass and muscle CSA and muscle strength were examined. The accelerated accumulation

of total body fat during ADT, when compared to normal ageing, is well established in men with PCa^[195] and was supported by our findings that these men had 3.3-5.0 kg greater DXA-derived fat mass than controls. Despite this notion, the application of methods for adjusting muscle-based outcomes for body size and adiposity have not been explored in ADT-treated men when compared to appropriately selected controls. We found that despite a lack of difference in absolute (unadjusted) measures of lean mass and muscle CSA, men treated with ADT tended to have compromised appendicular lean mass (ALM) adjusted for body mass index (BMI; ALM_{BMI} ; 10-12%), forearm muscle percent CSA (5.4-6.1%) and muscle strength expressed per kilogram of body weight (13-21%), when compared to controls. Reasons for the confounding influence of fat may stem from additional muscle contractile work required during locomotion and activities of daily living whilst carrying additional fat^[320], as well as the infiltration of fat around and/or within muscle tissue^[177]. Accounting for these adjustments rather than relying on absolute values is of clinical relevance given the potential to overlook men with compromised lean mass, muscle CSA or muscle strength that may predispose them to the adverse health outcomes more commonly reported in this susceptible population group than their non-ADT counterparts, such as falls, fractures, cardiometabolic disease and functional impairment^[41-49].

Strengths and limitations

These observations were strengthened by the inclusion of both a PCa and healthy control group, which allowed for the effects of ADT to be assessed independent of the ageing process and the diagnosis and non-hormonal treatment of PCa. Similarly, to our knowledge, this was the first study to compare pQCT-derived muscle CSA of the forearm and lower leg in men treated with ADT compared to both PCa and healthy controls. However, various limitations pertaining to the collection of outcome measures should be noted when interpreting these results. For example, DXA-derived outcomes of body composition may be confounded by the presence of excessive fat mass (e.g. global or regional obesity)^[121], whereas BMI may erroneously predict adiposity when compared to more robust radiological measures of body composition^[101]. Additionally, due to the cross-sectional design of this study, rationale for the confounding role of adiposity on muscle-based outcomes remains speculative, rather than causative in nature. Finally, there is a current lack of prospective trials that have assessed the risk of adverse health outcomes associated with compromised body size-

and adiposity-adjusted muscle outcomes in healthy older adults, let alone those undergoing ADT; thus, the true risk associated with compromised lean mass relative to body size or adiposity in men treated with ADT for PCa is unknown.

Future direction

Future studies should consider reporting body size and adiposity adjustments of muscle-based outcomes in men treated with ADT for PCa when compared to appropriately selected controls, to avoid potential erroneous conclusions pertaining to the effect of ADT on these outcomes. A time- and cost-effective way to further address this question is via retrospective analyses of previously collected datasets and researchers should consider performing and publishing these analyses or making their datasets available to other researchers. Moreover, the quantification of the risk of adverse health outcomes associated with differences in these adjusted outcomes is warranted in both healthy older men and this specific clinical population group, particularly in prospective cohorts in which a wide range of risk factors and adverse events are reliably documented.

7.3.2 Current definitions of sarcopenia and sarcopenic obesity are limited in men treated with androgen deprivation therapy for prostate cancer

In Chapter 4, various definitions of sarcopenia and sarcopenic obesity were examined in men treated with ADT and appropriately selected controls. While there is no international consensus definition of sarcopenia in terms of clinical cut-offs, recently proposed definitions tend to include low lean mass and compromised muscle strength or functional capacity, most commonly measured via DXA, handgrip dynamometry and gait speed, respectively ^[51, 53]. Despite a worldwide prevalence of approximately 8.0% in older men ^[158], our study only observed two cases (< 6.0%) in men treated with ADT for PCa, a cohort that has been previously shown to lose lean mass at an accelerated rate when compared to natural ageing (2.0-3.6% vs 0.5-1.0% per year) ^[195]. Notably, the low prevalence of sarcopenia was largely related to the limited evidence of impaired gait speed (< 0.8 or < 1.0 m/s) in these men, with only one case observed. Additionally, the lack of ability for current definitions of sarcopenia to detect cases in our sample of men treated with ADT may have stemmed from the aforementioned confounding role of fat on muscle-based outcomes. This concept was supported when we examined pre-sarcopenia (low lean mass only) and observed that when adjusted for adiposity (ALM_{BMI} and ALM adjusted for height and fat mass; ALM_{HFM}), 7.2-34%

more ADT-treated men were pre-sarcopenic when compared to either control. These findings were not evident when considering ALM adjusted for height alone (ALMI), thus supporting the notion that adiposity, rather than body size, likely played a role in these observations. Given the influence of adiposity, we also examined the prevalence of sarcopenic obesity, yet observed no cases among men treated with ADT. However, there was some evidence in our study that ADT-treated men were more likely to have pre-sarcopenic obesity. Collectively, these findings suggest that current definitions of sarcopenia and sarcopenic obesity are limited in their ability to detect men treated with ADT at risk of adverse health outcomes. Alternatively, our observations may suggest that ADT does not lead to sarcopenia or sarcopenic obesity, albeit this notion appears counterintuitive given the high prevalence of musculoskeletal, cardiometabolic and functional comorbidities in men treated with ADT for PCa [41-49]. Therefore, our findings highlight the potential use of adiposity-adjusted pre-sarcopenia and pre-sarcopenic obesity given these consider the role of fat accumulation associated with ADT.

Strengths and limitations

To our knowledge, this was the first study to consider composite definitions of sarcopenia and sarcopenic obesity in men treated with ADT. Additionally, our findings were strengthened by the use of various established criteria for these syndromes, rather than reliance on a single set of criteria. Although, these findings are not without notable limitations. Firstly, given that men treated with ADT included in our cross-sectional study were enrolled in a lifestyle intervention RCT, volunteer bias may have resulted in a cohort less representative of the broader population of these men in terms of overall health and fitness. Moreover, as the definitions of sarcopenia and sarcopenic obesity investigated in our study were initially developed and validated in larger cohorts, our results may be limited by the comparatively modest sample size.

Future direction

As various definitions of sarcopenia and sarcopenic obesity have been shown to predict greater risk of falls [81, 88, 89], fractures [48, 88, 90], functional impairment [88, 91-94] and mortality [88, 91, 95, 96] in healthy older men, men treated with ADT may benefit from the development of population-specific cut-offs. Whilst amassing a cohort large enough to represent the broader population of men and allow for robust conclusions to be drawn may pose logistical difficulties, pooled data may be pertinent to the feasibility

of this approach. This may be facilitated by the pooling of retrospective cohorts in which these measures were collected and/or the integration of these measures into current clinical practice, which would allow for prospective data to be collected.

7.3.3 The accumulation of fat associated with androgen deprivation therapy for prostate cancer more commonly occurred in subcutaneous depots and superseded expected age-related plateaus/declines

In Chapter 5, the effects of ADT on regional fat depots were examined. The risk of adverse health outcomes associated with the accumulation of fat differs pending regional distribution [40, 102, 177, 178]. For example, the accumulation in visceral and intermuscular depots tends to be associated with greater risk than fat stored in subcutaneous depots [40, 102, 177, 178]. In our study, men treated with ADT tended to have 15-36% greater subcutaneous fat, but similar visceral and intermuscular fat, when compared to controls. Our findings suggest that the accelerated fat accumulation previously shown in men treated with ADT [195] predominantly affects subcutaneous depots, which suggests that these effects of ADT may be of limited importance in terms of risk of adverse health outcomes. From a clinical practice perspective, our findings proposes that the quantification of visceral (DXA CoreScan) and intermuscular fat (pQCT) in ADT-treated men may be of less importance when compared to traditional measures of fat mass via DXA. The monitoring of DXA-derived fat mass in men treated with ADT is further supported by our findings that duration of ADT use tended to correlate with the increase storage of fat in subcutaneous and intermuscular depots, which appeared to supersede the age-related plateau or gradual decrease of fat storage at these sites commonly observed in men following the seventh decade of life [142].

Strengths and limitations

Our findings were strengthened by the use of robust radiological measures (i.e. DXA and pQCT), as well as the quantification of various depots of fat accumulation (i.e. subcutaneous, visceral and intermuscular). Although, these findings are primarily limited by the cross-sectional design of our study and subsequent lack of ability to infer causality and discount reverse causality (e.g. increased fat may have led to PCa progression and thus the need for ADT [332]). Moreover, the associations between ADT use duration and various outcomes may have been influenced by a few participants who had been treated for greater than five years. Finally, it should be noted that

abdominal subcutaneous and visceral fat mass were estimated via DXA CoreScan software and pQCT-derived muscle density was used as a marker of intermuscular fat, rather than quantified by more robust measures such as those involving computed tomography (CT) and magnetic resonance imaging (MRI).

Future direction

Further research is required to elucidate the risk of adverse health outcomes associated with the regional accumulation of fat during ADT for PCa. These studies would benefit from the use of radiological scanning protocols, ideally CT or MRI-based [40, 77, 111, 112], and should be prospective in design. A valuable study design would involve an assessment immediately prior to the commencement of ADT, assessments at several intervals throughout treatment and then several assessments at similar intervals following the cessation of therapy, coupled with a comprehensive and ongoing health and medical assessment. These observations would allow for a greater understanding of the long-term impact of ADT on the accumulation of fat in regional depot and inform clinical decision-making for men suitable for commencing or stopping this treatment.

7.3.4 The recruitment of men treated with androgen deprivation therapy for prostate cancer into a lifestyle intervention was challenging

In Chapter 6, the efficacy of various recruitment pathways utilised while conducting an RCT examining the efficacy of Ex+ProCaD compared to usual care in men treated with ADT for PCa was described. Clinical trials are often hindered by recruitment-based issues and it has been previously estimated that 45% of trials require an extended timeline due to these issues and only 55% eventually recruit their intended sample size [370]. In our study, 149 potential participants were screened, which resulted in 42 enrolled participants; thus, our initial target sample size for adequate statistical power was not met by the time of thesis write up. Clinician referral emerged as the most successful recruitment pathway in terms of the greatest number of participants screened (n=42; 28%) and enrolled (n=18; 43%). Notable success was also attained via PCa support groups, with 31 screened (21%) and 12 enrolled (29%) participants. Collectively, the seven other recruitment pathways resulted in only 12 enrolled (29%) participants. These findings suggest that clinician referral and PCa support groups should be utilised to increase the likelihood of attaining intended sample sizes in a timely manner.

The inclusion and exclusion criteria of a clinical trial has been shown to have significant implications on participant recruitment ^[369]. Among potential participants who were screened for inclusion in our study, the majority of excluded participants were deemed illegible due to a lack of pharmacological ADT for PCa (52%), whereas the remainder were excluded based on criteria designed to account for known confounding variables (e.g. vitamin D supplementation > 1,000 IU/day and progressive resistance training [PRT] > one session/week) of the main outcomes in the larger trial (bone health). The proportion of men treated with ADT who were precluded from our trial after expressing interest further highlights the importance of establishing effective recruitment pathways.

Strengths and limitations

This study provided novel insights into a wide range of feasibility outcomes of a combined multi-component exercise program and multi-nutrient supplement in men treated with ADT for PCa. These findings were strengthened by the 26-week duration of the trial, which was longer than most previously conducted lifestyle interventions in these men. However, our reporting of recruitment pathway efficacy was primarily limited by the retrospective nature of analysis. Data on the number of potential participants who were not interested in pursuing participation after face-to-face discussion or receiving a letter from their clinician was not recorded. Similarly, the total number of men who attended PCa support group presentations, received mailing list emails and viewed the trial information on the university website is unknown. Moreover, it is difficult to determine how many potential participants saw study-related flyers or the state news television report and received information via word of mouth and opted not seek involvement. Furthermore, a large proportion (48%) of men who declined to participant provided 'no reason', which may have been further explored if an anonymous feedback process was implemented. Finally, the 52-week study duration of the larger RCT may have deterred some men from expressing interest.

Future direction

Future research examining lifestyle interventions in men treated with ADT for PCa should report further details pertaining to the efficacy of recruitment pathway. Additionally, a larger clinical trial could include cost-effective analyses which would

provide valuable data on the potential cost-benefit of a combined exercise training and nutritional supplementation intervention on health outcomes and potential reductions in emergency department presentations or unplanned hospital admissions due to comorbidities associated with ADT. Qualitative research studies may also lead to a better understanding of the barriers and facilitators for ADT-treated men pursuing involvement in lifestyle interventions and research projects.

7.3.5 Men treated with androgen deprivation therapy for prostate cancer tended to respond positively to a multi-modal exercise training combined with multi-nutrient supplementation

Exercise training continues to gain traction as a viable intervention to ameliorate a wide range of ADT-induced adverse effects [60, 231, 351] and evidence in healthy older men without PCa highlights the many benefits which may be augmented by multi-nutrient supplements, such as those high in protein, calcium and vitamin D [195]. Despite these benefits, to our knowledge, our study was the first RCT to compare Ex+ProCaD to usual care in men treated with ADT for PCa. Data from the first 28 men to complete the 26-week follow-up indicated that men randomised to Ex+ProCaD tended to respond positively when compared to usual care with regard to net differences in lean mass (0.2-1.4 kg), fat mass (-0.1 to -0.9 kg), muscle strength (8.0-19%), functional muscle power (8.6%) and functional capacity (12-14%). These findings are promising and support our recent recommendations [195] that ADT-treated men should be prescribed exercise training and nutritional supplementation under the guidance of their clinical care team.

Strengths and limitations

Strengths associated with these outcomes included the novelty of the lifestyle intervention investigated with regard to this clinical population group, as well as the use of robust and valid measures of muscle, fat and performance. Although, multiple limitations associated with these findings warrant caution during interpretation. Primarily, the incomplete dataset and subsequent lack of preliminary within- and between-group analyses resulted in the presentation of descriptive statistics only. Subsequently, some responses deemed positive may be limited in terms of clinical significance. Additionally, potential volunteer bias of those capable and interested in exercise training may limit the generalisability of these findings. Similarly, the strict inclusion and exclusion criteria implemented to participant safety may have precluded

men with comorbidities commonly present in the broader ADT-treated population. Moreover, during the collection of data, neither participants nor researchers were blinded to treatment allocation.

Future direction

In light of the aforementioned limitations, there is a need to consider the outcomes of the larger 52-week RCT before definitive conclusions may be drawn with regard to the efficacy of Ex+ProCaD in men treated with ADT for PCa. Assuming our observations persist following the completion of the RCT, a factorial RCT should be considered to elucidate the individual and comparatively synergistic effects of the multi-modal exercise program and multi-nutrient supplement. Similarly, examining the feasibility of integrating Ex+ProCaD into clinical practice or a community-based setting is warranted.

7.4 Conclusion

This thesis provided new information on muscle, fat and performance in men treated with ADT for PCa when compared to PCa and healthy controls, and assessed the feasibility of implementing a lifestyle intervention designed to address these differences when compared to usual care. The main findings were that men treated with ADT had greater stores of subcutaneous fat when compared to controls, which tended to impair the quantification of muscle-based outcomes; thus, the consideration of muscle-based outcomes relative to body size or adiposity is warranted. Moreover, the recruitment of ADT-treated men into an Ex+ProCaD intervention was challenging, yet men randomised to Ex+ProCaD tended to respond positively in terms of improvement in lean and fat mass, muscle strength, functional muscle power and functional capacity.

The following key themes emerged from this thesis and may be used (in context with the aforementioned strengths and limitations) to guide clinical practice guidelines and future research along with the proposed recommendations for managing the adverse effects of ADT on muscle, fat and performance outcomes in Table 7.1:

1. Men treated with ADT for PCa had greater amounts of fat when compared to non-ADT counterparts; therefore, muscle-based outcomes should be considered relative to body size or adiposity in these men

2. Current definitions of sarcopenia and sarcopenic obesity were limited in men treated with ADT for PCa; thus, the development of additional risk stratification tools specific to this clinical population group are warranted
3. The greater amounts of fat observed in men treated with ADT for PCa tended to be stored in subcutaneous depots and supersede age-related plateaus/losses; hence, the long-term risk associated with this pattern of fat accumulation should be explored in these men
4. The recruitment of men treated with ADT for PCa into a lifestyle intervention was challenging; therefore, future trials should consider clinician referral and PCa support groups to increase the likelihood of attaining intended sample sizes in a timely manner.
5. Men treated with ADT for PCa tended to respond positively to a multi-modal exercise training combined with multi-nutrient supplementation; thus, the incorporation of similar interventions into usual care for this susceptible population group should be considered pending results of the larger 52-week RCT.

Table 7.1. Recommendations for managing adverse effects of androgen deprivation therapy (ADT) in men with prostate cancer on muscle, fat and performance.

Densitometry

- Prior to commencing ADT, men should undergo a DXA total body scan for the assessment of total and regional lean and fat mass. These measures should be repeated yearly (or even 6-monthly) until the cessation of ADT.
-

Exercise Training

- It is recommended that clinicians discuss and refer men to an individualised, multi-component exercise program incorporating the elements below:
 - Progressive resistance training: at least twice per week, 8-10 exercises (targeting major muscle groups, specifically the muscle attached too or near the hip and spine), 2-3 sets of 8-10 repetitions at moderate to high-intensity (70-85% of 1-RM or 5-8 'hard to very hard' on the 10-point Borg RPE scale).
 - Weight bearing impact exercises (jumping, bounding, hopping, skipping, bench stepping): at least 4 days per week, 2-4 impact exercises varying in magnitude and direction, progress to 50-100 jumps per session divided into 2-3 sets of 10-20 repetitions. **progressive resistance training is recommended first for those with low muscle strength and/or poor muscle function prior to commencing some impact activities.*
 - Aerobic exercises: 5-7 days per week, 30 minutes of continuous, 55-75% of predicted heart rate maximum, modalities including cycling, walking, rowing or sports such as tennis. Aerobic training can be divided into shorter bouts if required (three by 10 minutes sessions).
 - The concept of specificity and progressive overload should be applied to all exercises and when possible, programs should initially be performed under the supervision of a tertiary trained exercise professional (e.g. an Accredited Exercise Physiologist in Australia).
-

Vitamin D

- Prior to commencing ADT, men should have their serum 25-hydroxyvitamin D assessed and those with levels > 50 nmol/L (> 20 ng/ml) should consider a daily supplement of 800 IU. Men with < 50 nmol/L should supplement with 3,000-5,000 IU/day for at least 6-12 weeks under the guidance of a clinician.
-

Calcium

- Include 3-4 serves of dairy food each day and if daily calcium intake is below the recommended dietary intake of 1,000-1,300 mg/day, supplement with 600 mg/day.
-

Protein

- Daily protein intake of at least 1.2 grams per kilogram body weight per day.
 - Consume 25-30 g of high quality protein with each meal and on exercise training days, within the first few hours post-exercise.
-

Tobacco and alcohol

- Smoking cessation should be considered.
 - Alcohol consumption should be limited to < 2 standard drinks per day.
-

DXA, dual-energy x-ray absorptiometry; RM, repetition maximum; RPE, rating of perceived exertion. Adapted from Owen et al. ^[195].

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STUDY PROTOCOL

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Efficacy of a multi-component exercise programme and nutritional supplementation on musculoskeletal health in men treated with androgen deprivation therapy for prostate cancer (IMPACT): study protocol of a randomised controlled trial

Patrick J. Owen^{1*}, Robin M. Daly¹, Patricia M. Livingston², Niamh L. Mundell¹, Jack Dalla Via¹, Jeremy L. Millar³ and Steve F. Fraser¹

Abstract

Background: Prostate cancer is the most commonly diagnosed cancer in men in developed countries. Androgen deprivation therapy (ADT) is a systemic treatment shown to increase survival in selected patients with prostate cancer. The use of ADT continues to increase for all stages and grades of prostate cancer despite known treatment-induced adverse effects. The primary aim of this study is to examine the efficacy of a targeted, multi-component resistance and impact-loading exercise programme together with a daily protein-, calcium- and vitamin D-enriched supplement on bone health in men treated with ADT for prostate cancer. Secondary aims are to determine the effects of this intervention on measures of total body and regional body composition, cardiometabolic risk, inflammatory markers, health-related quality of life and cognitive function.

Methods: This study is a two-arm randomised controlled trial. Men currently treated with ADT for prostate cancer will be randomised to either a 52-week, community-based, exercise training and nutritional supplementation intervention ($n = 51$) or usual care control ($n = 51$). Participants will be assessed at baseline, 26 weeks and 52 weeks for all measures. The primary outcome measures are proximal femur and lumbar spine areal bone mineral density (BMD). Secondary outcomes comprise: changes in tibial and radial bone structure and strength, total body and regional body composition, muscle strength and function, as well as cardiometabolic health, catabolic/inflammatory and anabolic/anti-inflammatory cytokines, health-related quality of life and cognitive function.

Discussion: This study investigates whether a multi-component intervention incorporating a targeted bone and muscle-loading programme in combination with a protein-, calcium- and vitamin D-enriched supplement can ameliorate multiple adverse effects of ADT when compared to usual care. The results will contribute to the development of exercise training and nutrition guidelines for optimising overall health in men treated with ADT for prostate cancer.

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* Correspondence: powen@deakin.edu.au
¹Deakin University, Institute for Physical Activity and Nutrition (IPAN), School of Exercise and Nutrition Sciences, Geelong, Australia
Full list of author information is available at the end of the article

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Trial registration: Australia New Zealand Clinical Trial Registry (ANZCTR), ID: ACTRN12614000317695. Registered on 25 march 2014.**Keywords:** Prostate cancer, Androgen deprivation therapy, Bone mineral density, Body composition, Cardiometabolic health, Exercise training, Protein, Calcium, Vitamin D, Randomised controlled trial

Background

In Australia, as in other developed countries, prostate cancer (PCa) is the most commonly diagnosed cancer in men [1]. Approximately 1.1 million new cases of PCa are diagnosed worldwide each year [1]. In Australia, a 2014 report estimated that approximately 13% of cancer-related deaths in men were attributed to PCa, which ranks second to lung cancer as the most common cause of cancer-related death in men [2]. Due to medical advancements in both the screening and treatment of PCa, 5-year relative survival rates of all PCa cases are now approaching 100% internationally [3], and thus these patients are living longer, but are susceptible to potential age-related and treatment-related declines in health. Therefore, the clinical paradigm is shifting to an increased focus on improving the quality of years lived.

Various modalities of androgen deprivation therapy (ADT), including those administered as neoadjuvant or adjuvant therapies with other treatments, are commonly used to treat PCa as it improves overall survival, particularly in men with advanced PCa [4–7]. However, the evidence that ADT prolongs survival in men with localised PCa remains limited and, therefore, debated [8, 9]. Despite this lack of evidence, the use of ADT continues to increase for all stages and grades of PCa [10]. It was estimated that approximately 23,500 Australian men received pharmacological ADT via gonadotropin-releasing hormone (GnRH) agonists in 2008–2009 [11]. After repeating this analysis for 2013–2014, we estimated that approximately 25,500 men are currently receiving ADT via GnRH agonists [12]. Thus, ADT remains the most common cause for severe hypogonadism in men in Australia.

Despite benefits in overall survival in appropriately selected men, the hypogonadism induced via ADT has been associated with numerous adverse effects, particularly with regard to musculoskeletal and cardiometabolic health. It has been reported that within the first 3 to 12 months of ADT, men experience a rapid and dramatic loss in bone mass (up to 11%) and concomitant losses in muscle mass (2–5%) [13–17] which may explain the observed 23–65% increased fracture risk in this group [18–20]. There is also a profound gain (up to 15%) in fat mass (FM) which likely contributes to the 10–45% reported increased risk of diabetes, coronary heart disease, myocardial infarction and sudden cardiac death [13, 17, 21–25]. Thus, there is a need

to develop safe and effective interventions to manage the multiple treatment-induced adverse effects of ADT in men with PCa.

Exercise training has been strongly suggested as a viable intervention to ameliorate many of the adverse effects of ADT [17, 26–28]. In terms of musculoskeletal health outcomes, a number of interventions have shown that progressive resistance training (PRT) can increase muscle strength [29–33], muscle endurance [30, 34] and balance [30] in men treated with ADT. While there is also some evidence that PRT can improve or preserve lean body mass (LBM) [30, 32, 33, 35], a systematic review found that there was inconclusive findings on the effects of exercise training in men treated with ADT on bone health [26]. To date, only four studies have examined the efficacy of exercise training on areal bone mineral density (aBMD) in ADT-treated men, three of which were conducted over interventional periods of no longer than 20 weeks and observed no benefit [32, 36, 37]. This is perhaps not unexpected given that the typical bone remodelling cycle and new steady state that is measurable takes 6–8 months to complete, and thus it is unlikely that any true physiological skeletal adaptations would occur prior to this period. However, a recent 12-month randomised controlled trial (RCT) also reported no marked skeletal benefits of a targeted PRT and impact-loading exercise programme in men treated with ADT [36]. This may be due to a number of factors. First, the sample size of approximately 25 per group was below the target sample which may have limited the power to detect any between-group differences. Second, the impact exercise programme was non-progressive and only consisted of two-footed jumps (plus 10% body weight), and thus did not incorporate diverse loading patterns which are known to be important for bone remodelling. Third, the mean calcium intake was <750 mg/day, well below the recommended dietary intake of 1200 mg/day. There is some evidence that insufficient calcium intakes can attenuate the skeletal responses to exercise in older adults [38]. Finally, this study was limited to an assessment of aBMD by dual-energy X-ray absorptiometry (DXA), which provides no information on other determinants of bone strength (e.g. trabecular volumetric BMD (vBMD), cortical structure), which may change following exercise training, independent of aBMD. This is important because the findings from a prospective study using high-resolution, peripheral,

quantitative computed tomography (pQCT) found that treatment with ADT for 12 months was associated with losses of up to 11.3% in cortical and 3.5% in trabecular vBMD, which are two- to three-fold greater than changes observed in DXA aBMD [14]. In healthy older men, the findings from an 18-month RCT found that a targeted and progressive multi-component exercise programme incorporating PRT and a diverse range of weight-bearing, impact activities was safe and effective for improving lumbar spine trabecular vBMD and femoral neck aBMD, cross-sectional area and strength as well as muscle strength, mass and size [39]. Further long-term RCTs are required to examine whether similar well-designed and progressive multi-component exercise programmes in combination with adequate nutrition can ameliorate bone and muscle loss in men treated with ADT for PCa.

Clinical guidelines for optimising bone health in men on ADT recommend calcium and vitamin D treatment [11]. While direct evidence from RCTs to support their role in preventing bone loss in this group is lacking, a review based on secondary analyses of clinical trials reported that treatment with 500–1000 mg/day of calcium and 200–500 IU/day of vitamin D in ADT-treated men was inadequate to prevent bone loss [40]. In healthy older adults, there is level-1 evidence that calcium (>1000 mg/day) plus vitamin D (>800 IU/day) can reduce fracture risk [41]. Studies have also shown that 2000 IU/day of vitamin D can improve muscle strength and function [41, 42], and that daily consumption of calcium-vitamin D fortified milk for 2 years prevented aBMD loss at multiple sites in healthy men aged older than 50 years [43]. While a systematic review and meta-analysis of prospective studies reported that increased dairy or calcium intake was associated with an increased risk of PCa, no association was observed with supplemental or non-dairy calcium, which suggest that other components of dairy rather than fat and calcium may increase PCa risk [44]. In line with these mixed findings, supplementation at doses <1500 mg/day have been shown to either have no influence on PCa progression [45], reduce PCa risk [46] or decrease PSA velocity [47]. In addition, in men diagnosed with PCa, total milk/dairy intake after diagnosis was not associated with a greater risk of lethal PCa, with evidence of a decreased risk in those with a high intake of low-fat dairy [48].

There is also evidence that increased dietary protein in older adults can have favourable effects on both health, particularly when combined with calcium and vitamin D at recommended levels [38]. This has been attributed to several factors: a higher protein intake can increase serum insulin-like growth factor-1 (IGF-1), enhance intestinal calcium absorption, suppress parathyroid hormone levels as well as increase muscle mass and strength, which may improve bone health via increased

loading on bone [49]. There is also evidence in older adults without PCa that higher protein intakes (>1.2 g/kg) can enhance weight loss, offset muscle loss, improve lipid profiles and insulin sensitivity [50]. While this is not a universal finding, this could be explained by the modest level of protein intake achieved in some studies and/or the type (quality) of protein consumed. Currently there are no guidelines with regard to dietary protein for men with PCa using ADT.

It is well known that PRT stimulates muscle protein synthesis (MPS), but in a fasted state it also accelerates muscle protein breakdown (MPB) [51]. Ingestion of a high-quality, rapidly digested, protein-rich source, such as whey-protein, post-exercise can attenuate the increase in MPB and stimulate MPS to enhance the anabolic benefits of PRT [51]. Thus, combining PRT with whey-protein ingestion may represent an optimal strategy to enhance muscle hypertrophy. While questions still remain in terms of the optimal dose of protein needed to elicit a synergistic response with PRT, emerging evidence indicates that 20–40 g of high-quality protein be consumed early after a bout of PRT to enhance muscle mass and/or strength [51]. Moreover, Hanson et al. [52] recently demonstrated that consumption of 40 g of whey-protein alone, or following a single session of unilateral knee extension exercises, increased MPS beyond basal rates in men treated with ADT; albeit these increments were suboptimal when compared to healthy, age-matched men. However, a critical, but as yet unanswered, question is whether ingestion of a whey-protein-, vitamin D- and calcium-enriched drink with PRT can improve the multiple musculoskeletal health outcomes in ADT-treated men.

Therefore, the primary aim of this 12-month RCT is to determine whether a multi-component exercise programme targeting muscle and bone health combined with a protein-, calcium- and vitamin D-enriched drink can enhance hip and lumbar spine aBMD in men with PCa currently treated with ADT. The secondary aims are to examine the effects of the intervention on tibial and radial bone structure and strength, total body and regional body composition, muscle strength and function, as well as cardiometabolic health, catabolic/inflammatory and anabolic/anti-inflammatory cytokines, health-related quality of life (HR-QoL) and cognitive function.

Methods

Study design

This will be a 52-week, single-blinded, two-arm RCT consisting of a supervised and structured multi-component exercise programme in combination with a daily nutritional supplement. Men treated with ADT will be randomised to either an intervention consisting of a

multi-component exercise programme and a daily protein-, calcium- and vitamin D-enriched supplement ($n = 51$) or a usual care control group ($n = 51$). Men allocated to usual care will not receive a placebo drink as typical ingredients used to develop a placebo drink (e.g. maltodextrin as a food additive) have the potential to alter blood glucose levels and muscle mass. A factorial 2×2 trial will not be conducted for several reasons: (1) the large sample size that would be required to detect an interaction and (2) findings from previous research in older adults which indicates that the benefits of exercise training on musculoskeletal health require adequate nutrition (e.g. dietary calcium > 1000 mg/day) [38]. This study will not evaluate whether the combination of protein, calcium and vitamin D with exercise training is more effective than either of these treatments alone, but will determine if combining the two approaches is effective for improving multiple health outcomes. This trial will be managed by the Institute for Physical Activity and Nutrition at Deakin University. The study has been approved by the Human Research Ethics Committees at Deakin University (HREC 2013-184) and Alfred Health (Project No: 455/15) and is registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12614000317695). A summary of trial registration data and compliance with SPIRIT guidelines are shown in Additional files 1 and 2, respectively.

Participants

Eligible participants will be men aged 50–85 years who are currently treated with ADT for histologically diagnosed PCa. Treatment with ADT must be pharmacological (surgical orchiectomy excluded) and administered for longer than 12 weeks at enrolment. Participants will be excluded if they do not have the ability to complete surveys in the English language, have any disorder known to affect bone, calcium or vitamin D metabolism (other than hypogonadism), are currently receiving pharmacological intervention known to affect bone metabolism (other than ADT), have supplemented with protein, calcium (> 600 mg/day) or vitamin D (> 1000 IU/day) in the past 3 months, have undertaken PRT (more than one session/week) or regular weight-bearing, impact exercise (> 150 min/week) in the past 3 months, are current smokers, have a weight greater than 159 kg, have plans to travel for longer than 6 weeks continuously within the following 52 weeks or have any absolute contraindications to exercise training (e.g. musculoskeletal, cardiovascular or neurological disorders) according to the American College of Sports Medicine guidelines [53].

Recruitment and screening

Participants will be recruited via direct referral from clinicians across various hospitals, private practices and health networks in combination with promotion via PCa

support groups and advertisements in state/local newspapers within Melbourne and surrounding areas in Victoria, Australia. The direct referral process will include mass mail-outs to potential participants and face-to-face discussions during regular consultations with physicians/specialists. PCa support groups will be initially contacted via email with information regarding the study, with an option to provide a brief presentation to groups interested. All potential participants will be screened initially via telephone to determine their eligibility based on the criteria outlined above. All eligible participants will be required to obtain medical approval from their physician and provide informed consent before participating in the study.

Randomisation and blinding

Randomisation will be at the level of the individual participant following baseline testing, stratified by age (< 65 or ≥ 65 years) and Body Mass Index (< 30 or ≥ 30 kg/m²), using a computer-generated, random number sequence by an independent researcher. Due to limited funding, neither the participants nor researchers involved in the testing will be blinded to the group allocation, with the exception of the DXA and pQCT scans which will be assessed independently. A flow diagram of the study protocol is outlined in Fig. 1.

Intervention group

Multi-component exercise programme

The 52-week exercise programme will consist of two gym-based sessions and one home-based session per week. During the first 26 weeks, the two gym-based sessions will be supervised by an accredited exercise physiologist (tertiary-trained exercise professional) in a community-based health and fitness facility. For the final 26 weeks, only one gym-based session will be supervised. All home-based sessions will be unsupervised and performed in the participant's own time. All intervention-group participants will be provided with a yearly membership at a community-based health and fitness centre and will have the opportunity to complete their home-based sessions in this setting at their own discretion.

The exercise training programme is a multi-component programme that will follow key training principles of specificity and progressive overload and will be individually tailored to the participant's health and functional status. The programme will follow similar exercise prescription guidelines in terms of the structure, type and dose (frequency, sets, repetitions, intensity) of training to our previous 'Osteo-cise: Strong Bones for Life' community-based osteoporosis prevention exercise programme in healthy older adults in which we observed significant improvements in musculoskeletal health and

function (Table 1) [39, 54, 55]. To ensure progressive overload and promote a sense of achievement for the men, the 52-week programme will be divided into five mesocycles (training phases). The first mesocycle (4 weeks – adoption phase) will focus on orientation to the exercise programme, with an emphasis on correct technique. The four subsequent 12-weekly mesocycles will focus on progression through three 4-weekly microcycles (preparatory phase, challenge phase and consolidation phase). Each gym-based session (approximately 60 min) will consist of a warm-up and cool-down and a combination of aerobic training, PRT, weight-bearing, impact activities and challenging balance/functional exercises. More specific details about each training component are provided below.

Aerobic training

For the aerobic exercise, participants will be prescribed 15 to 25 min of continuous aerobic training at 55–75% of predicted heart rate maximum via modalities such as stationary cycling, treadmill walking or rowing. The type of aerobic exercise prescribed will be based on each participant's preference and functional capabilities.

Progressive resistance training

For PRT, participants will be prescribed five or six targeted hip, spine and forearm resistance exercises using

machine and free weights (two sets of 12–15 repetitions at moderate intensity (3–4 on the 10-point Rating of Perceived Exertion (RPE) scale) for each exercise for the first 4–8 weeks, progressing to two sets of 8–12 repetitions at moderate to hard intensity (4–6 on the RPE scale) thereafter; resistance will be increased as tolerated to maintain intensity and ensure progressive overload). During the first mesocycle, five resistance exercises will be available to choose from for each training session (leg press, bench press, one hip-targeted, one-spine targeted and one upper body exercise). New resistance exercises will be introduced at the start of each subsequent mesocycle (three hip-targeted, three spine-targeted and one upper-body-targeted). Varying combinations of the nine resistance exercises in each of these mesocycles will be prescribed each session. After the initial 8 weeks of training, participants will be progressively taught to perform the concentric (lifting) phase of all lower body exercises at high velocity. This is designed to improve movement speed and muscle power. When possible, participants will perform resistance exercises standing with the aim to also improve balance and physical function.

Weight-bearing, impact exercise

For the weight-bearing, impact-loading exercises, participants will be prescribed three exercises (interspersed amongst the PRT exercises) consisting of three sets of

Table 1 Structure of the exercise programme and training doses for 52 weeks

Phase	Anaerobic training					Progressive resistance training					Weight-bearing, impact training			Functional and core stabilisation training	
	Microcycle	Week	Mesocycle	Duration	%1RM ¹	Sets	Reps	RPE ²	Speed ³	Rest ⁴	Sets	Reps	Intensity ⁵	Sets	Duration/Reps
#1	1-4	1-4	Orientation	15-25 min	55-75%	2	12-15	3-4	Slow	1-2 min	3	10-20	Low	2	Balance exercises, 30-60 s or until fatigue
	5-8	5-8	Preparatory	15-25 min	60-75%	2	10-15	3-4	Slow	1-2 min	3	10-20	Low to moderate	2	Core stabilisation exercises, 15 reps or up to 30 for abdominal based exercises
	9-12	9-12	Challenge	15-25 min	60-75%	2	8-12	5-8	Rapid	2 min	3	10-20	Moderate	2	
	13-16	13-16	Consolidation	15-25 min	60-75%	2	8-12	5-8	Rapid	2 min	3	10-20	Moderate	2	
#3	17-20	17-20	Preparatory	15-25 min	60-75%	2	10-15	3-4	Slow	1-2 min	3	10-20	Moderate	2	
	21-24	21-24	Challenge	15-25 min	60-75%	2	8-12	5-8	Rapid	2 min	3	10-20	Moderate	2	
	25-28	25-28	Consolidation	15-25 min	60-75%	2	8-12	5-8	Rapid	2 min	3	10-20	Moderate to high	2	
	29-32	29-32	Preparatory	15-25 min	60-75%	2	10-15	3-4	Slow	1-2 min	3	10-20	Moderate to high	2	
#4	33-36	33-36	Challenge	15-25 min	60-75%	2	8-12	5-8	Rapid	2 min	3	10-20	Moderate to high	2	
	37-40	37-40	Consolidation	15-25 min	60-75%	2	8-12	5-8	Rapid	2 min	3	10-20	Moderate to high	2	
	41-44	41-44	Preparatory	15-25 min	60-75%	2	10-15	3-4	Slow	1-2 min	3	10-20	High	2	
	45-48	45-48	Challenge	15-25 min	60-75%	2	8-12	5-8	Rapid	2 min	3	10-20	High	2	
#5	49-52	49-52	Consolidation	15-25 min	60-75%	2	8-12	5-8	Rapid	2 min	3	10-20	High	2	

Adapted from Garandis et al. ¹RPE Rating of Perceived Exertion (1-10). ²Speed: slow (2-3 sec concentric and 2-3-4 eccentric contractions), rapid (rapid concentric and 2-3-4 eccentric contractions). ³Intensity: low (ground reaction force (GRF) = 1-3 x body weight), moderate (GRF = 3-6 x body weight), high (GRF = 6-9 x body weight)

10–20 repetitions that will utilise body weight as the primary load. The programme will focus on lower-limb exercises designed to load the hips. The exercises prescribed will be based on a battery that we have previously shown to be safe and effective for improving femoral neck and lumbar spine aBMD in older men [54]. This battery includes a range of exercises from low to high intensity (magnitude of peak ground reaction forces) and difficulty (easy, moderate, hard) and is divided into three broad categories: stationary movements (e.g. marching on the spot, mini-tuck jumps), forward/backwards movements (e.g. forward bench step-ups, drop jumps) and lateral movements (e.g. side-to-side jumping). Training intensity will be increased progressively by increasing the height of jumps, by adding additional weight, increasing the rate of impact-loading or multi-directional movement patterns (e.g. diagonal loads).

Challenging balance/functional exercise

Challenging balance and functional exercises will include a range of static and dynamic exercises, including fit ball exercises (e.g. sitting on fit-ball with knee extension), standing balance activities (e.g. single-leg standing) and dynamic functional tasks (e.g. heel-to-toe walking). Participants will be prescribed two exercises per session and asked to complete two sets of 30–60 s or for a given number of repetitions. To ensure progression, participants will be prescribed a new exercise or advance to a more challenging level (e.g. closing eyes, reducing base of support, confounding visual fixation, changing centre of mass or adding a second manual or cognitive task) once they have mastered the previous exercise (e.g. it is no longer challenging).

Core stabilisation exercise

Key muscle groups known to help maintain good posture, improve pelvic floor function and trunk stability (e.g. rotator cuff, scapular stabilisers, transverse abdominis, pelvic floor muscles) will be targeted with these exercises, which are important for balance and muscular performance [56]. Participants will be prescribed two exercises per session with light to moderate resistance in two sets of 10 to 15 repetitions. Of note, abdominal-based exercises will be prescribed in two sets of up to 50 repetitions.

Home-based exercise programme

The home-based exercise programme will consist of similar types of exercise to the gym-based sessions, but body weight and resistive tubing (provided to participants) will be used for resistance exercises. This will provide participants with knowledge and experience of ways to exercise relatively inexpensively in a home-based setting following the completion of the study. The home-

based programme will be explained and demonstrated to the participants during the initial gym-based sessions and instructions will be provided. Three resistance exercises, three weight-bearing, impact-loading exercises and three functional exercises following the same training principles as gym-based sessions will be prescribed for each home-based session. The home-based programme will be progressed and new exercises will be introduced once the previous exercises are no longer challenging for the participant.

Nutritional supplement

The nutritional supplement will consist of a daily whey-protein-, calcium- and vitamin D-enriched drink (powder) combined with a single vitamin D tablet. Participants will be provided with 6-monthly supplies of powder in single-use sachets and tablets. Each sachet is to be mixed with 150 ml of water and shaken vigorously in a 'shake-and-take' container (provided to participant). Each sachet of powder will contain approximately 25 g of whey-protein concentrate 80% (WPC80), containing approximately 2.4 g of leucine, 1200 mg calcium carbonate (~480 mg elemental calcium) and 1000 IU vitamin D (Omniblend, Campbellfield, VIC. Australia). The vitamin D tablet will contain 1000 IU (Ostelin, Macquarie Park, NSW, Australia). On the non-training days, participants will be asked to take one sachet every morning before breakfast. This is designed to try and ensure a more even protein intake throughout the day which has been reported to optimise muscle protein balance [57]. On exercise training days, participants will be encouraged to consume the sachet within 1–2 h of completing their exercise session as early post-exercise consumption of protein has been shown to promote an increase in MPS and muscle hypertrophy in older adults [58, 59].

Usual-care control group

Participants allocated to usual care will receive ongoing care from their physician/specialist but will not receive additional education or access to exercise training or the protein-, calcium- and vitamin D-enriched nutritional supplement powder sachet. Due to current practice guidelines [40] and a pilot study we conducted in 31 men undergoing ADT for PCa in which 65% reported taking vitamin D supplementation (90% at least 1000 IU/day), all men randomised to usual care will receive 1000 IU vitamin D per day. There is no evidence that vitamin D alone (without calcium supplementation) at these doses can prevent bone loss in these men [40].

Measurements

All measures will be collected at baseline, 26 and 52 weeks. Additionally, 24-h food recalls will also be administered at 13 and 39 weeks to monitor any habitual

fluctuations in dietary factors. With the exception of blood samples, 24-h food recalls and questionnaires, all data will be collected at Deakin University. Blood samples will be collected at an external commercial pathology clinic. The 24-h food recalls will be administered via telephone. Questionnaires will be completed by participants at home prior to each testing sessions (i.e. baseline, 26 and 52 weeks) and checked by the research staff during these face-to-face testing sessions. A summary of the proposed outcome measures is shown in Table 2. All participants will undergo all measures except those specific to treatment allocation (i.e. compliance to the intervention). All data collected will be in a continuous format, aside from the outcomes from some of the questionnaires, which will be categorical in nature.

Primary and secondary outcome measures

The primary outcome for this study will be changes in proximal femur and lumbar spine aBMD. Secondary outcomes will comprise: changes in 4% and 66% tibial and radial vBMD, bone structure and strength, total body and regional body composition, muscle strength, functional capacity, cardiometabolic health, inflammatory biomarkers, HR-QoL and cognitive function.

Bone mineral density

Total hip, femoral neck and lumbar spine (L1–L4) aBMD (g/cm^2) will be assessed using DXA (Lunar Prodigy, GE Lunar Corp., Madison, WI, USA) using software version 12.30.008. The short-term coefficient of variation (CV) for aBMD measures range from 0.6 to 1.0% within our laboratory.

Volumetric BMD, bone geometry and strength

Proximal (66%) radial and tibial cortical vBMD (mg/cm^3), cortical area (mm^2), total bone area (mm^2), medullary area (mm^2) and polar Strength Strain Index (SSI_{polar}, mm^3), and distal (4%) radial and tibial total and trabecular vBMD (mg/cm^3), total bone area (mm^2) and the Bone Strength Index (BSI, mg^2/mm^4) of the non-dominant upper limb and dominant lower limb will be assessed using pQCT (XCT 3000, Stratec Medizintechnik GmbH, Pforzheim, Germany). Briefly, tibial length will be determined by measuring from the distal edge of the medial malleolus to the medial joint cleft of the knee and radial length will be determined by measuring ulnar length from the ulnar styloid process to the olecranon. After obtaining a scout-view slice of the distal endplate of the radius or tibia, scans will be performed at the 4% and 66% sites. The slice thickness will be 1 mm and voxel size will be 0.5 mm at a scanning speed of 20 mm/s. All pQCT bone and body composition parameters will be assessed using BoneJ [60] ImageJ-plugin (rsbweb.nih.gov/ij/) as previously reported [61]. Distal radial and tibial (4%) total

bone area and density will be analysed based on thresholding at $169 \text{ mg}/\text{cm}^3$, with trabecular density assessed using a threshold of $480 \text{ mg}/\text{cm}^3$. BSI will be calculated as follows: $\text{BSI} = \text{total area multiplied by the square of total vBMD}$ [62]. For the proximal radius and tibia (66%), the periosteal surface will be determined based on a threshold of $280 \text{ mg}/\text{cm}^3$, and cortical bone a threshold of $710 \text{ mg}/\text{cm}^3$. Medullary area will be calculated by subtracting cortical area from total area. SSI_{polar} will be determined using the bone threshold of $480 \text{ mg}/\text{cm}^3$ [63]. The short-term CVs for repeated measures in a sample of healthy premenopausal women range from 0.9 to 2.2% for the 4% radius, 0.7 to 2.5% for the 4% tibia and 0.6 and 1.8% for the 66% tibial outcome measures [64].

Body composition

Total and regional (arms and legs) LBM (kg), FM (kg) and percentage body fat will be assessed by DXA as described above. The short-term CV for LBM and FM repeated measures range from 1.0 to 1.7% within our laboratory. Muscle and subcutaneous fat cross-sectional area (CSA) and muscle density (as a measure of inter-muscular adiposity) at the proximal (66%) radius and tibia will be assessed using pQCT. Thresholds of -40 to $+40 \text{ mg}/\text{cm}^3$ hydroxyapatite density will be used for estimating subcutaneous fat CSA. Muscle CSA will be estimated by subtracting the total bone CSA and subcutaneous fat CSA from the total area of the 66% tibia or radius. The following CVs have been reported for muscle CSA (radius, 2.1 to 5.3%; tibia, 2.5 to 3.7%), muscle density (radius, 1.4 to 3.2%; tibia 0.7 to 3.2%) and subcutaneous fat CSA (radius, 2.4 to 3.2%; tibia, 6.0 to 6.3%) for repeated measures in a sample of postmenopausal women [65].

Muscle strength

Muscle strength will be obtained via chest press (BodySolid, Powerline Smith Machine PSM144X, Forest Park, IL, USA), leg press (Synergy Omni Leg Press S-31-OPD, Yatala, QLD, Australia) and seated row (Nautilus tower pulley system, F3ATFS, Independence, VA, USA) three-repetition maximum (3-RM) protocols [53]. The 3-RM protocols assess the maximum weight that can be lifted for three repetitions while maintaining correct form and technique and were selected rather than one-repetition maximum protocols to reduce participant exertion. Prior to attempting these protocols, participants will complete a 5-min aerobic warm-up. Thereafter, each participant will perform a warm-up set of eight to 10 repetitions with a light load. The participant will then complete six to eight repetitions at a heavier weight. The load will be increased incrementally until only three repetitions can be completed. A 2–3-min recovery period

Table 2 Summary of data collection

Variables	Data collection method	Data collection points		
		Baseline	26 weeks	52 weeks
Primary outcome measures				
Areal bone mineral density	DXA proximal femur and lumbar spine	x	x	x
Secondary outcome measures				
Bone structure and strength	pQCT scan at 4% and 66% radial and tibial site	x	x	x
Body composition	DXA total body and regional lean mass, fat mass and % body fat	x	x	x
	pQCT 66% radial and tibial muscle cross-sectional area and muscle density	x	x	x
Muscle strength	Chest press, leg press and seated row	x	x	x
	Grip strength	x	x	x
Functional capacity	30-s sit-to-stand	x	x	x
	Timed-up-and-go with cognitive task	x	x	x
	Four-square step test	x	x	x
	Berg balance scale	x	x	x
	Four-metre usual walk	x	x	x
	400-metre walk	x	x	x
Biochemistry and lipids	Overnight, fasted serum and plasma collection	x	x	x
Inflammatory markers	Overnight, fasted serum and plasma collection	x	x	x
Blood pressure	Automated measurement	x	x	x
Cognitive function	CogState Brief Battery computerised tests	x	x	x
	Rey Auditory Verbal Learning Test	x	x	x
	Trail Making Test (Part A and B)	x	x	x
	Digit Span Test	x	x	x
	National Adult Reading Test	x		
Health-related quality of life, fatigue and mood	Functional Assessment of Cancer Therapy-Fatigue questionnaire	x	x	x
	Functional Assessment of Cancer Therapy-Prostate questionnaire	x	x	x
	Assessment of Quality of Life 8D questionnaire	x	x	x
	Geriatric Depression Scale questionnaire	x	x	x
	Depression Anxiety and Stress Scale questionnaire	x	x	x
Additional measures				
Anthropometry	Height, weight, Body Mass Index, waist and hip circumference	x	x	x
Habitual physical activity	Community Healthy Activities Model Programme for Seniors physical activity questionnaire	x	x	x
Diet	24-h food recalls	Collected every 13 weeks		
Additional questionnaire	Demographic questionnaire	x		
	Clinical and lifestyle questionnaire	x	x	x
	Sun exposure habits and practices questionnaire	x	x	x
	Alcohol consumption questionnaire	x	x	x
	Medical questionnaire	x	x	x
	Medication questionnaire	x	x	x
	Falls questionnaire	x	x	x
Exercise programme adherence	Calculated from monthly calendars collected every 4 weeks	Collected every 4 weeks		
Supplement compliance	Calculated from supplement returned at 26 and 52 weeks		x	x
Adverse events	Calculated from monthly calendars collected every 4 weeks	Collected every 4 weeks		

DXA dual-energy X-ray absorptiometry, pQCT peripheral quantitative computed tomography

will be provided between each set. The 3-RM result will be used in a formula to calculate each participant's one-repetition maximum [66]. The 3-RM protocol has been shown to have a test-retest intraclass correlation coefficient (ICC) of 0.97 in a sample of untrained men [67] and strongly correlates with 1-RM results [68].

Maximal muscle (grip) strength will be assessed using a digital grip-strength dynamometer (Jamar Plus Digital, Lafayette Instrument Company, IN, USA) [69]. The participant will be seated with their forearm resting on the arm of chair while maintaining a 90° angle at the elbow. Participants will be asked to squeeze the dynamometer maximally. Six trials will be completed (three with each hand alternating) with the single highest score recorded. A CV of 6.3% was reported for grip-strength repeated measures with the same device in a sample of advanced lung and gastrointestinal cancer patients [70].

Functional capacity

Functional capacity will be assessed using the 30-s sit-to-stand, timed-up-and-go (TUG) with cognitive task test, the four-square step test, the Berg Balance Scale, the 4-m usual walk and the 400-m walk. The 30-s sit-to-stand, four-square step test and 4-m usual walk will be performed in triplicate, with the best result recorded. All other tests will be performed once.

The 30-s sit-to-stand test measures lower-limb muscle strength and function [71]. Participants begin in a seated position with their arms folded across their chest on a chair without arms. Participants are instructed to stand fully upright and then return to a seated position as many times as possible in 30 s. This test was observed to have a test-retest ICC of 0.84 in a sample of community-dwelling men aged 60 years and over [71].

The TUG with cognitive task test is a measure of dynamic balance and dual-tasking [72]. Participants will be seated in a chair (height 45 cm) that will be placed at the end of a 3-m walkway. Once instructed to begin, the participant will stand up, walk at a regular pace for 3 m, turn, walk back to the chair and sit down. During this task, the participant will be provided with a mental arithmetic task (e.g. counting backwards from 100 by 3s from a random number) and the number of correct digits will be recorded. A stopwatch will be used to record the time taken (to the nearest ms) to complete each test. This test was observed to have an interrater ICC of 0.99 [73].

The four-square step test is a measure of dynamic balance and stepping speed in four directions [74]. Participants will be instructed to step forward, sideways, and backwards over four canes resting flat on the floor in a cross formation in a clockwise sequence and then back to in an anticlockwise sequence. The participant will be instructed to complete the test as fast as possible

without touching the raised canes, and to face forward during the entire sequence. They will also be instructed to ensure that both feet make contact with the floor in each square. The time (to the nearest ms) taken to complete the sequence will be measured with a stopwatch. This test has been observed to have an interrater and test-retest ICC of 0.99 and 0.98, respectively, in a sample of community-dwelling adults aged 65 years and over [74].

The Berg Balance Scale is an overall measure of balance including both dynamic and static components [75]. The test rates participants on 14 different tasks on an ordinal scale ranging from zero (unable to perform the task) to 4 (performs the task independently). Assessments include variations of sitting, standing, reaching, leaning, turning and stepping. The scores of the 14 tasks are summed to produce a total score ranging from 0 to 56 points. Higher scores indicate better performance. This test was observed to have an interrater and test-retest ICC of 0.98 and 0.97, respectively, in a sample of adults aged 65 years and over [75].

The 4-m usual walk is a measure of gait speed [76]. Participants will be instructed to walk at a usual pace between two cones 8 m apart (2-m acceleration zone, 4-m timed zone and 2-m deceleration zone). Time will be recorded when the participant's front foot enters the timed zone and stopped when their front foot exits the timed zone. The time (to the nearest ms) to complete the timed zone was recorded with a stopwatch. This method has an ICC of 0.96 within our laboratory.

The 400-m walk test provides an estimate of cardiorespiratory fitness [77]. Participants will be instructed to walk as fast as possible between two cones placed 20 m apart (turning when they approach each cone). The time (to the nearest ms) taken to complete 10 laps (400 m) will be recorded. This test was observed to have a test-retest ICC of 0.95 in a sample of middle-aged women [78].

Biochemical, lipid and lipoprotein measures

Fasted, resting, morning blood samples will be collected at a commercial pathology clinic and sent to a central laboratory accredited by the National Association of Testing Authorities Royal College of Pathologists Australasia. The following parameters will be assessed using standardised techniques: creatinine, albumin, inorganic phosphate and corrected calcium. Fasting plasma glucose will be assessed using the hexokinase method (Roche Diagnostics, Mannheim, Germany). Total cholesterol, high-density lipoprotein cholesterol and triglycerides will be determined using an enzymatic colorimetric method (Roche Diagnostics, Mannheim, Germany). Low-density lipoprotein cholesterol will be calculated using Friedewald's formula. The estimated glomerular filtration rate (eGFR) will be calculated using the participants' serum creatinine,

age and sex according to the abbreviated 'modification of diet in renal disease' formula, which is now used by most laboratories in Australia:

$$eGFR \left[\text{ml}/(\text{min } 1.73 \text{ m}^2) \right] = 1.75 \times [\text{serum creatinine} (\mu\text{mol/l}) \times 0.0113]^{-1.234} \times \text{age} (\text{years})^{-0.203}$$

High-sensitivity C-reactive protein (CRP) will be assessed using an immunoturbidimetric assay (Roche Diagnostics, Mannheim, Germany). Total prostate-specific antigen (free and complexed) will be assessed via immunoassay (Roche Diagnostics, Mannheim, Germany).

Serum aliquots will also be collected and stored at -80°C so that the following parameters can be assessed in a single batch at the completion of the study if sufficient funding is obtained: serum insulin, serum 25-hydroxyvitamin D (25(OH)D), IGF-1, serum adiponectin and resistin, and a battery of pro-inflammatory and anti-inflammatory cytokines, including interleukin (IL)-6, IL-1 β , IL-8, tumour necrosis factor (TNF)- α and IL-10.

Blood pressure

Blood pressure will be assessed three times using an automated machine (TM-2655P, A&D, Tokyo, Japan) [79] after a 10-min rest, with 1-min intervals between trials. The mean of the second and third measures will be used.

Cognitive function

Previous research has shown that ADT use is associated with cognitive decline, particularly in the domains of verbal memory, visuospatial function, attention and executive function [80]. Thus, this study will include a number of established and valid cognitive tests to assess the different cognitive domains. The CogState Brief Battery computerised test (<http://cogstate.com/>) will be administered to assess cognitive function including psychomotor function, attention, learning, reaction time, processing speed, visual attention and working memory [81, 82]. The CogState battery involves five computerised tests (Groton maze, detection task, identification task, one card learning task, one back task) conducted in a quiet environment, with scripted instructions and a practice attempt prior to completing each task.

The Rey Auditory Verbal Learning Test will be administered to assess memory and learning [83]. A list of 15 common words is read to the participant five times, with the participant asked to immediately recall as many words as possible following each recital. An interference list is then presented, after which the participant must recall words from the original list. Following a 20-min delay, during which other non-verbal tests are conducted, the participant is asked to recall the original list

again. Finally, the participant will be asked to visually identify the words from the original list from a list of 50 words. Participants are scored on the total number of words recalled in trials 1–5, total number recalled after interference, loss after interference number (trial 5 minus trial 2) and long-delay free recall.

The Trail Making Test (Parts A and B) will be administered to assess executive function [84]. Participants will be instructed to accurately draw lines to connect circled numbers in sequential order as fast as possible (Part A). Participants will then be instructed to draw lines to connect circled numbers and letters in an alternating numeric and alphabetic order (Part B).

The Digit Span Test measures working memory and will be administered forwards and backwards to assess short-term memory and working memory, respectively [85]. In the first condition, the researcher presents the participant with a string of non-sequential numbers which gradually increase in length, which the participant must then immediately recall in the same order in which they were presented. In the second condition, the researcher also presents the participant with a string of non-sequential numbers which gradually increase in length, but the participant must immediately recall them in the reverse order to which they were presented.

The National Adult Reading Test will be administered to calculate verbal, performance and full-scale intelligence quotes as an estimate of cognitive reserve [86]. The test comprises of 50 irregular words which are read aloud by the participant. The number of errors regarding pronunciation are recorded.

Health-related quality of life, fatigue and mood

The Functional Assessment of Cancer Therapy-Fatigue (FACT-F) [87] and the Functional Assessment of Cancer Therapy-Prostate (FACT-P) [88] questionnaires will be used to assess fatigue and HR-QoL, respectively. The Assessment of Quality of Life 8D will also be used to assess HR-QoL [89]. The Geriatric Depression Scale will be used to assess depression [90]. The Depression Anxiety Stress Scale 21-item will be used to assess depression, anxiety, stress and psychological distress [91].

Anthropometry

Height and body mass will be assessed using a portable stadiometer and scales, respectively. Body Mass Index will be calculated using height and body mass. Girth measurements of the chest, waist and hips will be assessed using standard techniques.

Habitual physical activity

The Community Healthy Activities Model Programme for Seniors physical activity questionnaire will be used to assess participation in a comprehensive list of low,

moderate and vigorous physical activities [92]. Participants will document the frequency and duration of their participation in a 'typical week' of the preceding 4 weeks. The results will be reported as estimated kilojoules per week spent in moderate- to high-intensity activities and hours per week spent undertaking weight-bearing exercise.

Diet

Diet will be assessed using a 24-h food recall performed during a one-on-one interview via telephone. Prior to the telephone interview, the participant will complete a 24-h food diary with instructions that will be discussed at the baseline testing session. These instructions will include how to use household measures (e.g. measuring cups, plates, bowls, glasses) to help estimate food portion sizes. In addition, a standard script will be used during the telephone interview to maximise the ability of participants to recall what was consumed. Dietary analysis will be performed using Australia-specific dietary analysis software (FoodWorks, Xyris software, Highgate Hills, QLD, Australia).

Additional questionnaires

A demographic, clinical and lifestyle questionnaire will be used to obtain background information from participants (e.g. age, education history, marital status, employment status, cultural background, PCa and ADT-use details). Sun-exposure habits and practices, alcohol consumption, past and current medical conditions, use of prescription and non-prescription medication (type and dose) and falls and fracture history will also be included in the questionnaire.

Compliance

Compliance with the exercise training programme (i.e. attendance at each training session) and nutritional supplement (i.e. consumption) will be assessed via attendance record and self-reported diaries, respectively. Diaries will be monitored weekly and calendars will be monitored monthly by the participant's accredited exercise physiologist and researchers. In addition to the calendars, compliance with the sachets and vitamin D tablets will be checked by counting all returned at the 26- and 52-week testing sessions.

Adverse events

Any adverse events potentially associated, or confirmed to be associated, with the exercise programme or protein, calcium and vitamin D supplementation will be recorded by the exercise trainers at each exercise training session for the intervention-group participants and monthly telephone calls by the research staff to the control-group participants. For this trial, an adverse event will consist of any health-related unfavourable or unintended medical

occurrence (e.g. sign, symptom, syndrome, illness) that develops or worsens during the trial. All adverse events will be assessed for seriousness, causality and expected outcome by the researchers and followed during the trial. Although there will be no formal data monitoring committee, all data will be reviewed at regular intervals throughout the study and researchers involved in recruitment, testing and implementing the trial will update the research team monthly about the study progress.

Data management and archiving

All data will be stored on password-protected computers and in locked filing cabinets at Deakin University (Burwood). All study-related documents will be archived at Deakin University at the end of the study for 7 years which is in line with current ethical requirements.

Dissemination plan

Findings from the primary outcomes of this trial will be reported in journal articles, which will include results regardless of the direction or magnitude of the effect. The results will also be presented at leading national and international conferences, clinical forums and to other relevant health professionals and stakeholders, as well as to the participants. All investigators will have the opportunity to be listed as an author of future publications in accordance with journal-specific guidelines.

Sample size calculation

The sample size calculations are based on our previous research in healthy and ADT-treated men. The mean (standard deviation (SD)) annual loss in femoral neck, hip and spine BMD in ADT-treated men was 3.0% (4.5), 2.6% (2.8) and 3.9% (3.0), respectively [14]. Our previous exercise trials in healthy older men have shown that 12 months of training can increase spine aBMD by 1.5–2.0% (SD 2.9) and hip aBMD by 1.2–1.8% (SD 2.8) [39, 55]. We estimate a conservative net difference in aBMD in favour of the intervention of ~3.5–4.0% at the hip and spine. Based on these estimates, 29 men in each group will provide 90% power ($P < 0.05$, two-tailed) to detect a difference of this magnitude (assuming a SD of 4.0). A net benefit of this magnitude is clinically relevant as there is evidence that a 1–2% gain in aBMD translates into a 7–14% reduction in fracture risk [36, 93]. For pQCT bone measures, radial and tibial cortical area decreased by 11.5% (8.8) and 12.5% (7.4), respectively, over 12 months in ADT-treated men [14]. While few long-term trials have examined the effect of exercise training on pQCT bone geometry in older men, several intervention trials in older adults have shown that a targeted, weight-bearing, impact-exercise programme can have beneficial effects on cortical bone [94, 95]. Assuming that the proposed intervention can half the rate of loss in cortical area, we estimate that we will require 39 men per

group (SD 8.0; 90% power, two-tailed, $P < 0.05$). Based on a previous study and a meta-analysis showing that ADT is associated with an average 7.7% gain in fat and a 2.8% loss in lean mass over 3–12 months [96, 97], and that exercise training can prevent the gain in FM and increase (1–5%) or preserve LBM relative to usual care in men on ADT [30, 32], we estimate a sample size of 24–32 in each group will be required to observe a preservation in LBM and FM in the intervention group vs. usual care (90% power, two-tailed, $P < 0.05$). Assuming a conservatively projected 30% dropout, an estimated sample size of 51 men per group (102 in total) will be required. Based on previous studies in ADT-treated men focussing on a number of our secondary outcomes [32, 37, 98], we estimate that we will have sufficient power (80–90%, $P < 0.05$, two-tailed) to detect the following intervention effects: 20–40% for muscle strength; 8–22% for functional capacity; 4 points for fatigue (FACT-F), 15% for fasting plasma glucose and 14% for serum IL-6 and 20% for CRP. We will also have sufficient sample to detect a clinically meaningful difference of 0.5 SD in the Assessment of Quality of Life 8D questionnaire (AQoL-8D) and 9 points on the FACT-P (disease-specific QoL).

Statistical analysis

Primary analyses will be conducted on an intention-to-treat basis using STATA statistical software (STATA, College Station, TX, USA). Per-protocol analysis will also be performed by including all participants who are at least 66% compliant to the exercise (two of three sessions per week) and 80% compliant to taking the supplements. Initially, descriptive statistics will be computed to compare the intervention and usual-care groups on background variables and baseline measures. All data will be screened for outliers and the normality of the distribution of all data will be assessed using Kolmogorov-Smirnov tests, with skewed data log transformed prior to analysis. Linear mixed models with random effects will be used to evaluate the effects of the intervention compared to usual control. Potential covariates to be included will be: age, duration of ADT use, other chronic conditions, change in medication and change in habitual physical activity or diet. Where possible, we will obtain endpoint measures from all withdrawals and include all randomised subjects in the final analysis. For participants who are lost to follow-up, missing data will be handled with multiple imputation, with subsequent sensitivity analyses to evaluate the effect of potential non-random attrition. Baseline measures and changes in outcome variables will be presented as means $\pm$ SD or 95% confidence intervals. A significance level of $P < 0.05$ will be adopted for all statistical tests.

Discussion

This trial will be the first to assess the efficacy of combining a targeted, bone-specific, resistance and

impact exercise training programme with nutritional supplementation on musculoskeletal health in men treated with ADT for PCa. Importantly, this is one of the few known trials to examine such a lifestyle intervention over an extended period of time (52 weeks) in this population group, with a focus on both DXA areal bone density and pQCT measures of bone structure and cortical and trabecular volumetric BMD, all of which are important determinants of whole bone strength. There are currently no established guidelines for specifically managing the large range of adverse effects observed in men treated with ADT [28]. Current guidelines mainly focus on pharmacological interventions for bone health, such as antiresorptive therapy with bisphosphonates, which have been extensively evaluated and shown to prevent losses in bone density commonly reported with ADT [11, 99–101]. However, these drugs have no effect on ameliorating the many other adverse effects associated with ADT. In terms of muscle health, functional capacity and cardiometabolic risk, the guidelines are less evidence-based within this specific clinical population group [11, 99], and commonly recommend more generic exercise guidelines for cancer survivors [102–105]. A recent study evaluating the most robust ADT-specific guidelines [11] in a cohort of 113 men commencing ADT concluded that over a 2-year follow-up, despite maintaining bone density at the lumbar spine and reducing various cardiometabolic risk markers via additional therapies (e.g. statins), bone losses were still reported at the total hip, and risk factors of cardiometabolic risk, such as waist circumference, increased. Therefore, further well-designed, long-term trials are needed to inform ADT-specific exercise training guidelines for managing bone health and cardiometabolic risk. Furthermore, there are limited guidelines on addressing declines in HR-QoL and the large range of additional ADT-induced adverse effects. We expect that the findings from this study will provide a unique opportunity to explore whether combining exercise training with nutritional supplementation may also be effective at ameliorating multiple ADT-induced adverse effects when compared to usual care.

Trial status

The IMPACT trial is concurrently recruiting and administering the intervention to a number of participants.

Additional files

Additional file 1: Trial registration data. (DOCX 15 kb)

Additional file 2: SPIRIT checklist. (DOC 120 kb)

Abbreviations

3RM: Three-repetition maximum; aBMD: Areal bone mineral density; ADT: Androgen deprivation therapy; BSI: Bone Strength Index; CRP: C-reactive protein; CV: Coefficient of variation; DXA: Dual-energy X-ray absorptiometry; eGFR: Estimated glomerular filtration rate; FACT-F: Functional Assessment of Cancer Therapy-Fatigue; FACT-P: Functional Assessment of Cancer Therapy-Prostate; FM: Fat mass; GnRH: Gonadotropin-releasing hormone; HR-QoL: Health-related quality of life; ICC: Intraclass correlation coefficient; IGF-1: Serum insulin-like growth factor-1; IL: Interleukin; LBM: Lean body mass; MPB: Muscle protein breakdown; MPS: Muscle protein synthesis; PCA: Prostate cancer; pQCT: Peripheral quantitative computed tomography; PRT: Progressive resistance training; RCT: Randomised controlled trial; RPE: Rating of Perceived Exertion; SSE: Stress Strain Index; TNF: Tumour necrosis factor; TUG: Timed-up-and-go; vBMD: Volumetric bone mineral density

Acknowledgements

We acknowledge the contribution of Deakin University Honours student Stephen J. Foulkes.

Funding

The study received in-kind support from YMCA Victoria, Ostelin and Omnibond. Facilities, equipment and internal funding were provided by Deakin University.

Availability of data and materials

Not applicable

Authors' contributions

PJO, RMD and SFF developed the study concept and initiated the project. PJO, RMD, PML, NLM, JD, JLM and SFF provided significant input into the development of the protocol. PJO drafted the manuscript. PJO, NLM, JD and JLM will implement the protocol and oversee collection of the data. PJO, RMD, PML, NLM, JD, JLM and SFF read, contributed to, and approved, the final manuscript.

Ethics approval and consent to participate

The study has been approved by the Human Research Ethics Committees at Deakin University (HREC 2013-18-4) and Alfred Health (Project No: 455/15) and is registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12614000317695). All eligible participants will be required to obtain medical approval from their physician and provide informed consent before participating in the study.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author details

¹Deakin University, Institute for Physical Activity and Nutrition (IPAN), School of Exercise and Nutrition Sciences, Geelong, Australia. ²Deakin University, Faculty of Health, Geelong, Australia. ³Alfred Health Radiation Oncology, The Alfred, Melbourne, Australia.

Received: 1 January 2017 Accepted: 8 September 2017

Published online: 03 October 2017

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The Role of Exercise Training in Men With Prostate Cancer

Patrick J. Owen, B. Exercise and Sports Science (Hons); Steve F. Fraser, PhD

Prostate cancer is the most commonly diagnosed cancer in older men worldwide. Advancements in diagnosis and treatment have resulted in 5-year relative survival rates approaching 100%. Therefore, men diagnosed with prostate cancer are now living longer, but treatment-induced adverse effects are regularly reported and may result in various comorbidities that may impair quality of life. Exercise training has been suggested as an intervention to ameliorate these adverse effects and improve multiple aspects of health. Despite the lack of specific guidelines, exercise training can play a critical role following the diagnosis and treatment of prostate cancer.

Key words: adverse effects, exercise training, prostate cancer

Prostate cancer (PCa) is the second most frequently diagnosed male cancer worldwide and the most commonly diagnosed cancer in developed countries.¹ The probability of PCa diagnosis increases with age, from 0.3% between birth and 49 years to 11.2% after the age of 70 years.² Thus, PCa is a disease more commonly diagnosed in older men.

The treatment of PCa varies depending on the stage, grade, and aggressiveness of the cancer.^{3,4} Once PCa has been histologically confirmed, multiple treatment options become available including active surveillance, watchful waiting, radical prostatectomy (surgery), radiotherapy, androgen deprivation (hormone) therapy (ADT), and chemotherapy.^{3,4} Active surveillance is reserved for men with early stage PCa and involves delaying active treatment until PCa progression or the threat of progression occurs.⁵ This approach aims to reduce the number of men who are overtreated for PCa that may never progress to cause harm.⁵ Watchful waiting also avoids active treatment; however, this method is for men who are not candidates for curative treatment due to preexisting comorbidities.⁵ Radical prostatectomy is an active treatment that involves the surgical removal of the prostate gland and is common in men with

PCa confined or assumed to be confined to the prostatic capsule.⁵ Radiotherapy is another active treatment that utilizes radiation to damage deoxyribonucleic acid in PCa cells to increase their likelihood of undergoing apoptosis, with two common methods being external beam radiation therapy and brachytherapy.⁵ Men with more aggressive PCa may be required to undergo ADT to prevent progression.⁴ ADT aims to reduce the activity and/or concentration of androgens, such as testosterone, to castration levels to prevent PCa growth and spread.⁵ Finally, chemotherapy may be used for PCa that has metastasized or PCa that has become resistant to ADT.⁴ Chemotherapy is a systemic treatment that damages cells while they divide to promote apoptosis; thus, PCa cells are a likely target of these agents.⁴ Combinations of treatment methodologies are common when treating PCa and may include approaches such as neoadjuvant radiotherapy before radical prostatectomy or adjuvant ADT following radiotherapy.^{5,6}

Advancements in these treatment options, as well as the increased use and availability of diagnostic tests (such as prostate specific antigen), have increased the 5-year relative survival rate for all stages of PCa to 99.9%.⁶ Furthermore, the 10-year and 15-year rates are 97.8% and 91.4%, respectively.⁶ Thus, men diagnosed with PCa are now living longer but are susceptible to age-related and treatment-related declines in health.

TREATMENT-INDUCED ADVERSE EFFECTS

As PCa is a disease of older men, age-related declines in various aspects of health are common. These may include negative alterations to fitness, functionality, body composition, cardiometabolic risk, and overall health-related quality of life (HRQOL).⁷ In addition, various treatment-induced adverse effects are reported following the aforementioned therapies. Commonly reported treatment-induced adverse effects following a prostatectomy and/or radiotherapy include incontinence, sexual dysfunction, and fatigue, with men who have undergone radiotherapy reporting greater perceptions of fatigue.^{8,9} Moreover, prostatectomies may result in general surgical complications.⁸ As men undergoing ADT have their testosterone reduced to castration levels, they report additional adverse effects including negative alterations to muscle, bone, adiposity, cognition, cardiometabolic risk, sexual function, and HRQOL.¹⁰ Finally, men treated with chemotherapy also report further adverse effects such as gastrointestinal

Author Affiliation: Centre for Physical Activity and Nutrition Research, School of Exercise and Nutrition Sciences, Deakin University, Burwood, Victoria, Australia.

The authors declare no conflicts of interest.

Correspondence: Steve F. Fraser, PhD, Centre for Physical Activity and Nutrition Research, School of Exercise and Nutrition Sciences, Deakin University, Burwood, VIC 3125, Australia (steve.fraser@deakin.edu.au).

complications, fluid retention, and more severe fatigue.¹¹ Because of high survival rates following treatment, these adverse effects may contribute to long-term comorbidities in these men.

Comorbidities associated with these treatment-induced adverse effects may directly or indirectly limit physical activity in men diagnosed with PCa.¹² In addition, diagnosis of PCa alone has been shown to decrease physical activity in men.¹³ Inadequate physical activity is likely to decrease cardiorespiratory fitness and therefore increase all-cause mortality.¹⁴ Therefore, low levels of physical activity may partially explain why men diagnosed with earlier stage PCa are more likely to die from cardiovascular disease than from PCa.¹⁵ Lifestyle interventions such as exercise training have been suggested to ameliorate a number of PCa treatment-induced adverse effects.

THE ROLE OF EXERCISE TRAINING

Exercise training has been suggested to have an important role both pre- and post-diagnosis of cancer.¹⁶ There is also emerging evidence that increased physical activity levels may decrease PCa incidence¹⁷ and prevent cancer recurrence through the reduction and maintenance of body fatness.¹⁸ Exercise training has been extensively implemented and reviewed across a range of treatments in men diagnosed with PCa.^{10,19} Safety concerns regarding injury and increased prostate specific antigen (a marker of PCa disease progression) following exercise training were dismissed in various trials.^{20,25} Moreover, no long-term testosterone increases were observed following exercise training in men treated with ADT.²²⁻²⁵ There is also emerging evidence that exercise training is safe and well tolerated in men with bone metastases of prostatic origin.²⁶ The effects of exercise training in men diagnosed and/or treated for PCa are displayed in Figure 1.

FITNESS

Cardiorespiratory fitness has been shown to increase following aerobic exercise training in men previously treated for PCa.^{20,22,25,27-29} In addition, there is evidence that pro-

grams predominantly focusing on resistance exercise training can also improve cardiorespiratory fitness.^{25,26} Muscular fitness (endurance and strength) increased following programs that included resistance exercise training.^{20,22-26} These improvements in cardiorespiratory and muscular fitness may contribute to improved functionality (the ability to complete tasks of daily living) following exercise training.^{20,22,25,28} Maintaining this independence into older age may significantly improve the quality of the additional years of life following PCa treatment. Increased cardiorespiratory fitness is also strongly associated with reductions in all-cause mortality.¹⁴

BODY COMPOSITION

Measures of body composition, including body mass index³⁰ and waist circumference,²¹ have decreased following exercise training. Changes in more robust measures of body composition, such as those assessed via dual-energy x-ray absorptiometry, have shown lean body mass to increase^{20,22,25,26,30} and fat mass decrease^{20,30} following both aerobic and resistance exercise training. These alterations to body composition may reduce cardiometabolic risk associated with PCa treatment and the risk associated with natural aging.⁷ Increased lean body mass may also reduce falls risk in older individuals, which is higher in men treated with ADT.³¹

Trials that have examined the role of exercise training on bone mineral density, predominantly in men treated with ADT due to the accelerated loss associated with treatment,³² are yet to report improvements and have observed no change.^{20,33} However, the preservation of bone mineral density should not be overlooked in these men, as significant declines over similar periods of time have been frequently reported.³² To potentially improve bone mineral density in men treated with ADT, walking or swimming is inadequate. Bone-specific exercises, such as those that involve repeated impact and progressive resistance training, are required.³⁴ Increasing bone mineral density in areas prone to fracture (such as at the hip and spine) may reduce the high fracture risk in men treated with ADT.³²

Figure 1. The benefits of exercise training in men diagnosed and/or treated for prostate cancer.

HEALTH-RELATED QUALITY OF LIFE

Various self-report measures assessed via questionnaire have shown that exercise training increased HRQOL.^{20,22,24,25,28} Decreased psychological distress may be one factor that helps explain this increase.²⁰ The aforementioned benefits of exercise training may also contribute to these improvements. Perceptions of HRQOL are important to men diagnosed/treated with PCa and therefore these men should be informed of the benefits of exercise training.

FATIGUE

Self-report measures of fatigue have decreased following exercise training in men who had recently undergone various PCa treatments.^{20,24,25,28} Reductions in cancer-related fatigue via exercise training play a significant role in perceptions of general health in men previously treated for PCa.³⁵ Reducing the severity of fatigue may also increase the likelihood of these men adopting and complying with exercise training programs for sustained benefit.

GENITOURINARY AND SEXUAL HEALTH

The number and severity of urinary incontinence issues are decreased following pelvic floor muscle exercise training.³⁶ These reductions may increase the likelihood of men seeking exercise training options in a community and individual setting due to decreased concerns of continence issues. Men have also reported increased practice and interest in sexual activity following exercise training.³⁷ Providing men with this information may be a strong motivational tool for exercise training, as many men who have undergone PCa treatment report sexual dysfunction as an important issue in their relationships that should be addressed.

CARDIOMETABOLIC RISK

There is some evidence that exercise training can positively impact markers of cardiometabolic risk in men with PCa. Exercise training has been reported to increase high-density lipoprotein cholesterol,²² decrease C-reactive protein,²⁵ and decrease triglycerides²⁵; however, further trials are required to confirm the efficacy of exercise training on these measures. If these exercise training studies yield similar beneficial effects on cardiovascular and diabetic risk (such as reduced blood pressure, improved insulin sensitivity, and reduced systemic inflammation) as with other populations then exercise training could potentially decrease cardiometabolic risk, reduce cardiovascular or diabetes disease progression, or reduce the reliance on pharmacotherapy in these men.

IMPLEMENTING EXERCISE FOR MEN WITH PROSTATE CANCER

A diagnosis of PCa is a challenging time for men and historically clinicians have advised them to rest or avoid exercise. At various time points from diagnosis through treat-

ment, exercise training can reduce psychological distress and ameliorate adverse effects, from reducing incontinence post prostatectomy to minimizing bone mineral density and lean body mass loss in men treated with ADT. The recommendations for exercise training is compelling yet despite the large body of evidence to support the safety and efficacy of exercise training in men diagnosed and treated for PCa, there is currently a lack of extensively evaluated specific guidelines. General guidelines for cancer survivors are usually suggested for these men due to common symptoms and comorbidities shared with other cancers.³⁸ Guidelines suggest appropriate pre-exercise screening taking into consideration the potential increased risk of fracture and cardiovascular event in some men with PCa.¹⁶ Prescription should be individualized relative to fitness, strength, comorbidities, and exercise preference.²⁷

Guidelines commonly include recommendations to meet physical activity guidelines, which typically suggest a minimum of 150 minutes of moderate-intensity physical activity with at least 2 sessions of resistance-based activities per week.³⁸ More specifically, aerobic exercise training should include large muscle groups and be performed for 20 to 30 minutes, 3 to 5 times per week.³⁹ These exercises should be performed at an intensity of 50% to 75% $\dot{V}O_2$ maximum, 60% to 80% heart rate maximum, or 11 to 14 rating of perceived exertion on the Borg Scale.³⁹ In men with more severe comorbidities, such as those with increased cancer-related fatigue, short bouts with adequate rest intervals may be required.³⁹ Resistance exercise training should target large muscle groups with an emphasis on dynamic and functional movements.³⁹ These exercises should use a combination of machine weights, free weights, and body weight exercises.³⁹ Training sessions should include 6 to 10 resistance exercises and be performed 1 to 3 times per week with at least 1 rest day between sessions.³⁹ Exercises should be prescribed in sets of 1 to 4 at 50% to 80% of 1-repetition maximum or at 6 to 12 repetition maximum.³⁹ Progression for both aerobic and resistance exercise training should work within the limitations of the individual, but ensure that gains are continually being achieved.³⁹ Programs should be modified as fitness improves or treatment-induced adverse effects emerge.³⁹

Although generic guidelines are beneficial for providing health benefits to the vast majority of these men, specific guidelines for varying treatment-induced adverse effects may be required for addressing other health issues. For example, men treated with ADT may receive added benefit from impact exercise training that aims to improve bone mineral density and balance training to reduce falls and fracture risk, whereas men recently treated with prostatectomy may require pelvic floor exercise training to help treat incontinence. The development and assessment of PCa treatment-specific guidelines are therefore warranted.

FUTURE DIRECTION

In addition to the development of treatment-specific guidelines, the efficacy of exercise training in various cohorts of men diagnosed with PCa is yet to be evaluated. To date, no studies have examined the potential benefits of exercise training in men treated primarily with chemotherapy or those treated with palliative intent. In addition, the assessment of long-term outcomes common in men treated with ADT, such as fall and fracture risk, is warranted. Finally, the combination of exercise training and other lifestyle interventions, such as dietary modification, may yield additional benefits. Research in these areas may strengthen the rationale for incorporating exercise training into the usual care model for treatment of PCa.

CONCLUSION

There is strong evidence that exercise training can play a critical role following diagnosis and during and after treatment of PCa. Although this period can be stressful to the individual and may be accompanied with complications, it provides a unique teaching moment in which appropriately trained individuals can educate these men on the benefits of exercise training. Appropriately prescribed exercise training can reduce prostate cancer recurrence, minimize the impact of treatment-related adverse effects, and reduce the likelihood of comorbid conditions such as diabetes and cardiovascular disease. Exercise training can empower these men and provide them with the knowledge to take control of an aspect of their health and potentially improve both the quality and quantity of their own lives.

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OPEN

Prostate Cancer and Prostatic Diseases (2017) 00, 1–9
www.nature.com/pcan

REVIEW

Lifestyle guidelines for managing adverse effects on bone health and body composition in men treated with androgen deprivation therapy for prostate cancer: an update

PJ Owen¹, RM Daly¹, PM Livingston² and SF Fraser¹

BACKGROUND: Men treated with androgen deprivation therapy (ADT) for prostate cancer are prone to multiple treatment-induced adverse effects, particularly with regard to a deterioration in bone health and altered body composition including decreased lean tissue mass and increased fat mass. These alterations may partially explain the marked increased risk in osteoporosis, falls, fracture and cardiometabolic risk that has been observed in this population.

METHODS: A review was conducted that assessed standard clinical guidelines for the management of ADT-induced adverse effects on bone health and body composition in men with prostate cancer.

RESULTS: Currently, standard clinical guidelines exist for the management of various bone and metabolic ADT-induced adverse effects in men with prostate cancer. However, an evaluation of the effectiveness of these guidelines into routine practice revealed that men continued to experience increased central adiposity, and, unless pharmacotherapy was instituted, accelerated bone loss and worsening glycaemia occurred.

CONCLUSIONS: This review discusses the current guidelines and some of the limitations, and proposes new recommendations based on emerging evidence regarding the efficacy of lifestyle interventions, particularly with regard to exercise and nutritional factors, to manage ADT-related adverse effects on bone health and body composition in men with prostate cancer.

Prostate Cancer and Prostatic Diseases advance online publication, 24 January 2017; doi:10.1038/pcan.2016.69

INTRODUCTION

Prostate cancer (PCa) is the most commonly diagnosed male cancer in developed countries.¹ Treatment for PCa includes surgery, radiotherapy, androgen deprivation therapy (ADT) and chemotherapy, which is influenced by the stage and aggressiveness of the cancer.^{2,3} Although usually reserved for non-localised or more aggressive PCa, ADT is a standard systemic treatment that aims to reduce the activity and/or concentration of androgens, such as testosterone, to castration levels to prevent PCa growth and spread.⁴ Various modalities of ADT, including those administered neoadjuvant or adjuvant with other treatments are associated with improved survival in appropriately selected men with advanced PCa.^{5–9} In contrast, evidence that ADT prolongs survival in men with localised PCa remains limited and, therefore, debated.^{10–12} Despite this, ADT is commonly prescribed for both metastatic⁴ and non-metastatic PCa.¹³

Although ADT has been shown to improve survival outcomes, treatment-induced hypogonadism has been associated with multiple interconnected adverse effects such as decreased bone mineral density (BMD) and a loss in the structure and strength of bone,^{14–25} a loss in lean tissue mass and muscle cross-sectional area,^{17,18,20,26–31} an increase in fat mass and intermuscular adipose tissue,^{17,18,20,26–28,31,32} and an increased risk of falls³³ and subsequent fractures in this clinical population group.^{34–36} Other commonly observed adverse effects of ADT include negatively altered blood lipid profiles, decreased insulin sensitivity, increased arterial stiffness, increased fatigue, increased depressive

symptoms and sexual dysfunction.^{37–39} Collectively, these alterations may lead to increased cardiometabolic risk and decreased health-related quality of life in men treated with ADT.^{40,41} The aim of this paper was to review the current guidelines available for management of various bone and metabolic ADT-induced adverse effects in men with PCa. A secondary aim was to propose new recommendations based on emerging evidence regarding the efficacy of lifestyle interventions, particularly with regard to exercise and nutritional factors, to manage ADT-related alterations to bone health and body composition in men with PCa.

MATERIALS AND METHODS

An electronic search of the National Institute of Health MEDLINE database was performed to identify all peer-reviewed articles published in English between January 2000 and June 2016. The following search terms were used: ('androgen deprivation therapy' or 'hormone therapy') and ('guidelines' or 'strategies' or 'practice') and ('bone' or 'muscle' or 'fat' or 'body composition'). Overall, 276 articles were found, of which the titles and abstracts were evaluated by two authors (PJO and SFF). Additional articles were located via manual searches of relevant reference lists. Five articles discussing recently proposed and relevant lifestyle guidelines for the management of ADT-induced adverse effects on bone health and body composition were determined as the basis for this review.

¹Institute for Physical Activity and Nutrition (IPAN), School of Exercise and Nutrition Sciences, Deakin University, Geelong, VIC, Australia and ²Faculty of Health, Deakin University, Geelong, VIC, Australia. Correspondence: PJ Owen, Institute for Physical Activity and Nutrition (IPAN), School of Exercise and Nutrition Sciences, Deakin University, Geelong, VIC 3220, Australia.

E-mail: pow@deakin.edu.au

Received 5 September 2016; revised 15 November 2016; accepted 29 November 2016

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Figure 1. Effects of ADT on bone mass, structure and strength. aBMD, areal bone mineral density; ADT, androgen deprivation therapy; vBMD, volumetric bone mineral density.

Changes to bone health and body composition associated with androgen deprivation therapy

Bone mineral density, structure and strength. It is well established that there is a progressive age-related loss in areal BMD (aBMD) in healthy men, as commonly measured via dual-energy X-ray absorptiometry (DXA), which equates to ~0.5–1.0% per year at various skeletal sites including the femoral neck, total hip and lumbar spine^{42,43} (Figure 1). In contrast, it has been reported that men treated with continuous pharmacological ADT experience aBMD annual losses of 0.6–3.9% at the femoral neck^{4–16,21–23,25,44} and 2.3–4.8% at the lumbar spine,^{15,18,21–23,25,44} particularly during the initial 6 months of treatment (Table 1 and Figure 1). Accelerated aBMD loss has also been observed at the hip,^{17–20,22–25,44,45} radius^{18,22,24,44} and whole body,^{17,18} indicating that ADT has a systemic effect on bone (Table 1). The findings from a 12-month prospective study using high-resolution peripheral quantitative computed tomography, which quantifies changes in appendicular cortical and trabecular volumetric BMD and microarchitecture, reported that men treated with ADT (mean age; 71 years) experienced losses in distal radius and tibia cortical volumetric BMD of up to 11.3% and 6.0% per year, respectively⁴⁴ (Figure 1). Losses in trabecular volumetric BMD of 3.5% and 1.5% were also observed at the distal radius and tibia, respectively⁴⁴ (Figure 1). In addition, cortical area at the distal radius and tibia decreased by 5.1–5.2% within the first 6 months which increased to 11.5–12.5% after 12 months⁴⁴ (Figure 1). This study indicates that both the density and structure of bone, which are both important determinants of whole-bone strength, are compromised in men treated with ADT. Furthermore, the study indicates that DXA-based measures of aBMD may underestimate the magnitude of bone loss associated with ADT.

There is also evidence that the rate of bone loss in men with PCa may be dependent on the modality of treatment. For instance, orchiectomy appears to lead to greater aBMD loss when compared with pharmacological ADT,^{14,16} whereas anti-androgen monotherapy has been associated with reduced bone loss compared with gonadotropin-releasing hormone agonists.²⁵ Duration of ADT may also influence the rate of bone loss, with the greatest losses occurring within the first 6 months of treatment.¹⁸ From a clinical perspective, accelerated loss of bone density and structure during ADT is important because it likely contributes to the marked increase in fracture risk (34–65%) in this susceptible population group, which has been associated with twice the rate of mortality when compared with men on ADT who did not sustain a fracture.^{34,46} Importantly, there is also evidence of a significant dose-response relationship between the number

of ADT doses received during the 12 months post diagnosis and the subsequent risk of fracture.^{35,47} In addition to ADT, residual effects of radiotherapy have been postulated to influence androgen concentration,⁴⁸ which supports the findings from a meta-analysis indicating that men who had not received ADT for PCa had lower aBMD than healthy older males, but not as low as men treated with ADT.⁴⁹

Lean tissue mass. In healthy adult men, age-related losses in lean tissue mass range from 1.0–2.0% per year after the age of 40–45 years, with a more accelerated loss after the fifth decade of life.^{50,51} However, lean tissue mass losses of 2.0–3.6% have been reported after a year of ADT^{18,20,28,44} (Table 2). In addition, findings from a study of 25 men (mean age; 68 years) who had commenced ADT reported that lean tissue mass decreased by 1.4% in the first 12 weeks of treatment.²⁹ Although the mediating factors contributing to muscle loss with ADT are multifaceted, duration of treatment and patient age appears to be important. For instance, men treated with ADT demonstrated the greatest losses in lean tissue mass (2.6–3.2%) during the initial 6–9 months of treatment.^{18,44,52} Furthermore, men on ADT aged >70 years have been shown to lose three times the amount of lean tissue mass when compared with men aged <70 years.⁵² These changes to lean tissue mass may adversely affect functional performance as observed during a follow-up of 50 men (median age; 78 years) treated with ADT in which 24% of the men demonstrated impairment during activities of daily living.³³ Moreover, 22% of these men reported a recent fall,³³ which may further increase the risk of fracture. Notably, after cessation of ADT and recovery of eugonadal testosterone level, lean tissue mass losses were not reversed over a 2-year follow-up in a cohort of 49 men (mean age; 73 years).³² This suggests that the associated complications of ADT may be prolonged after cessation of treatment.

Fat mass. During the ageing process, fat mass and percentage body fat commonly increases in men until the seventh decade, after which it typically remains stable or decreases slightly throughout the remainder of life.⁵³ Conversely, men on ADT have been shown to experience a continuous increase in fat mass beyond this age-associated plateau (Table 2) with an average annual gain exceeding 11%.¹⁴ Furthermore, following a 2-year period after cessation of ADT, negative alterations to fat mass remained.³² To date, limited studies have quantified if there are region-specific gains in fat mass during ADT,^{27,55,56} but of the limited research available, ADT has been associated with an 11–13% increase in subcutaneous abdominal fat mass^{27,55} and either an increase (22%)⁵⁵ or no change²⁷ in visceral abdominal fat mass after 48–52 weeks. In addition, findings from a study of 39 men (median age; 73 years) commencing ADT reported increased fat infiltration of lower limb muscles (anterior compartment of thigh), as assessed via computed tomography, after 14.6–20 weeks of treatment.⁵⁶ Clinically, there are multiple adverse consequences associated with these ADT-related gains in total and regional fat mass and intramuscular fat. For instance, potential increases in subcutaneous and visceral fat may contribute to the marked increase in cardiometabolic disorders in men treated with ADT.^{28,40,57} In addition, increased fat infiltration within muscle has been shown to impair muscular function in non-ADT-treated older adults.⁵⁸ As obesity is associated with an increase in inflammatory cytokines (or adipokines),⁵⁹ and chronic systemic inflammation has been shown to contribute to age-related muscle wasting,⁶⁰ it is possible that ADT-induced gains in fat mass may exacerbate losses in muscle in men with PCa.

Table 1. Non-randomised controlled trials examining the effects of continual ADT in men with prostate cancer on aBMD

Authors	N	Average age (years)	Change in aBMD
GnRH agonist only			
<i>6 months</i>			
Diamond <i>et al.</i> ⁴⁶	18	78	FN – 6.5%; WT – 7.5%; Troch – 6.2%
Maillefert <i>et al.</i> ²¹	12	70	LS – 3.0%; FN – 2.7%
Hamilton <i>et al.</i> ⁴⁴	26	71	LS – 1.7%; FN – 1.5%; Hip – 1.5%; 1/3Rad +9.1%
<i>12 months</i>			
Maillefert <i>et al.</i> ²¹	12	70	LS – 4.6%; FN – 3.9%
Berruti <i>et al.</i> ¹⁵	35	75	LS – 2.3%; FN – 0.6%
Mittan <i>et al.</i> ²²	15	75	Hip – 3.3%; DRad – 5.3%; MRad – 2.7%; 1/3Rad – 1.6%; LS – 2.8%; FN – 2.3%
Bergstrom <i>et al.</i> ¹⁴	10	73	FN – 3.2%
Smith <i>et al.</i> ²³	26	65	LS – 2.5%; Hip – 1.4%
Lee <i>et al.</i> ²⁰	65	66	Hip – 1.9%
Morote <i>et al.</i> ²³	31	70	LS – 4.8%; FN – 3.0%; WT – 5.6%; Troch – 3.6%; Hip – 3.8%
Hamilton <i>et al.</i> ⁴⁴	26	71	LS – 3.9%; FN – 3.0%; Hip – 2.6%; 1/3Rad +9.2%
<i>18 months</i>			
Maillefert <i>et al.</i> ²¹	12	70	LS – 6.6%; FN – 7.1%
Anti-androgen only			
<i>12 months</i>			
Smith <i>et al.</i> ²⁵	25	63	LS +2.9%; Hip +1.1%
CAB			
<i>9 months</i>			
Higano <i>et al.</i> ¹⁹	17	69	LS – 4.5%; Hip – 2.5%
Galvão <i>et al.</i> ¹⁷	69	74	Hip – 1.5%; LS – 3.9%; WB – 2.4%
Pharmacological (any modality)			
<i>12 months</i>			
Daniell <i>et al.</i> ¹⁶	16	72	FN – 3.4%
Greenspan <i>et al.</i> ¹⁸	80	69–71	Acute ADT: Hip – 2.5%; Troch – 2.4%; TRad – 2.6%; WB – 3.3%; LS – 4.0%; Chronic ADT: TRad – 2.0%
<i>24 months</i>			
Daniell <i>et al.</i> ¹⁶	16	72	FN – 6.5%
Preston <i>et al.</i> ²⁴	23	73	FN – 1.9%; Hip – 1.5%; Troch – 2.0%; LS – 0.2%; DRad +9.4%
Ochlectomy only			
<i>12 months</i>			
Daniell <i>et al.</i> ¹⁶	10	77	FN – 2.4%
Bergstrom <i>et al.</i> ¹⁴	12	79	FN – 4.5%
<i>24 months</i>			
Daniell <i>et al.</i> ¹⁶	10	77	FN – 10.0%

Abbreviations: 1/3Rad, one-third radius; aBMD, areal bone mineral density; ADT, androgen deprivation therapy; CAB, combined androgen blockade; DRad, distal radius; FN, femoral neck; GnRH, gonadotropin-releasing hormone; Hip, total hip; LS, lumbar spine; MRad, mid radius; N, number; TRad, total radius; Troch, trochanter; WB, whole body; WT, Ward's triangle.

Potential treatment options for addressing bone health and body composition changes associated with androgen deprivation therapy

Current guidelines for managing ADT-induced adverse effects on bone, muscle and fat generally apply a similar approach, that is, monitoring known risk factors, pharmacotherapy and/or lifestyle interventions, but these management guidelines appear to vary by country, organisation and expert opinion.^{37,40,61–63} Although these guidelines are often based on numerous evidence-based studies, it remains uncertain as to whether these guidelines are routinely implemented and followed over time and if they are effective in ameliorating or attenuating many of the adverse effects of ADT. To date, only one set of guidelines,⁴⁰ focusing on bone and metabolic outcomes of ADT, has been implemented and evaluated.⁶⁴ In a 2-year prospective study, 236 men with PCa commencing ADT attended a baseline clinic visit and received diet and lifestyle advice, with overweight and obese men offered referral to a dietician.⁶⁴ If required, men also received treatment for hypertension, hypercholesterolaemia and osteoporosis as per standard management guidelines.⁴⁰ Men attending this clinic were assessed at 3–6 monthly intervals.⁶⁴ A summary of the

assessment and management strategies used in this study is shown in Table 3. At the initial assessment, 87% of the men were overweight/obese, 61% had hypertension, 56% had hypercholesterolaemia, 27% had prior cardiovascular disease, 11% had osteoporosis and 40% had osteopenia.⁶⁴ For the prospective study, 153 men had data available after 2 years of continuous ADT use.⁶⁴ The main findings from this study were a mean loss of 3.4% and 2.5% in lumbar spine (L1–4) and hip aBMD, respectively, over 2 years, unless the men were treated with antiresorptive therapy ($n = 14$), in which case aBMD was maintained at both the sites.⁶⁴ No measures of muscle or fat mass or functional performance were assessed in this study, however, an increase in waist circumference of 2.7 cm was indicative of an increase in abdominal fat mass.⁶⁴ In contrast, reductions were observed in blood pressure, total cholesterol and low-density lipoprotein cholesterol with treatment.⁶⁴ Although it is important to acknowledge that this was an observational study, which precludes inferences about causality, these findings provide some evidence that adhering to the current management guidelines for men with PCa treated with ADT may not mitigate some of the metabolic and bone adverse effects associated with this treatment.

Bone mineral density, structure and strength. Current guidelines for managing bone health during ADT include several key recommendations.^{37,40,61–63}

Table 2. Non-randomised controlled trials examining the effects of continual ADT in men with prostate cancer on lean tissue mass and fat mass

Authors	N	Average age (years)	Change in lean tissue mass (total body)	Change in fat mass
GnRH agonist only				
26 weeks				
Boxer <i>et al.</i> ³¹	30	72	–2.1%	+9.5%
Hamilton <i>et al.</i> ⁴⁴	26	71	–3.2%	+12.0%
48 weeks				
Smith <i>et al.</i> ²⁷	32	66	–2.7%	+9.4%
52 weeks				
Lee <i>et al.</i> ²⁰	65	66	–2.0%	+6.6%
Hamilton <i>et al.</i> ⁴⁴	26	71	–3.6%	+14.1%
CAB				
12 weeks				
Smith <i>et al.</i> ²⁹	25	68	–1.4%	NA
36 weeks				
Galvão <i>et al.</i> ¹⁷	72	74	–2.4%	+13.8%
52 weeks				
Smith <i>et al.</i> ²⁸	26	65	–3.6%	+11.2%
Pharmacological (any modality)				
24 weeks				
Smith <i>et al.</i> ³⁰	22	67	–2.7%	NA
48 weeks				
Smith ²⁶	79	71	–3.8%	NA
52 weeks				
Greenspan <i>et al.</i> ¹⁸	80	69–71	Acute ADT: –3.5%; Chronic ADT: NC	Acute ADT: +10.4%; Chronic ADT: NC

Abbreviations: ADT, androgen deprivation therapy; CAB, combined androgen blockade; GnRH, gonadotropin-releasing hormone; N, number; NA, not applicable; NC, no change.

First, aBMD and fracture risk assessment should be performed prior to commencing ADT, after the first 2 years of treatment, and beyond this point pending individualised circumstances^{37,40,61} (Table 4). The use of DXA aBMD assessment within this population group has previously been deemed a cost-effective strategy to evaluate fracture risk.⁶⁵ Despite these recommendations, it was reported that only 10.2% of a cohort of 28 960 men were referred to a DXA aBMD assessment prior to commencing ADT or within the first year of treatment.⁶⁶

Second, dietary and supplemental calcium and vitamin D are recommended, with recommended intakes varying from 1000–1500 mg per day and 800–2000 IU per day, respectively.^{37,40,62,63} For men who are vitamin D deficient (serum 25-hydroxyvitamin D (25OHD) < 50 nmol l^{–1}), it is recommended that they supplement with 3000–5000 IU per day of vitamin D (pending level of deficiency) for at least 6–12 weeks under the guidance of a clinician.⁶⁷ These recommendations are in line with a recent review, which concluded that 500–1000 mg calcium and 200–500 IU vitamin D per day was not adequate to prevent bone loss in men treated with ADT.⁶⁸ In addition, Level 1 evidence from healthy older adults indicates that daily calcium plus vitamin D supplementation of > 1000 mg and > 800 IU can reduce fracture risk.⁶⁷ Although it has been reported that an increased calcium intake (or dairy consumption) may be associated with an increased risk of PCa,⁶⁹ calcium supplementation at doses of < 1500 mg per day were not found to be associated with PCa progression.⁷⁰ Similarly, vitamin D supplementation of 4000 IU per day for 1 year was associated with no adverse effects or PCa progression in men with PCa.⁷¹ Although further studies are needed to evaluate the efficacy of calcium and vitamin D on bone health in men with PCa treated with ADT, based on the available evidence it is advised that these men consider supplementation with calcium and vitamin D under the guidance of their urologist and/or general practitioner (Table 4).

Third, for patients who have experienced a minimal trauma fracture have an initial aBMD hip or lumbar spine T-scores of < 2.0 or have a 10-year absolute risk of major osteoporotic fracture of > 20% as determined by FRAX (<http://www.shef.ac.uk/FRAX>), antiresorptive therapy is recommended.^{37,40,61–63} The efficacy of antiresorptive therapy, such as bisphosphonates, has been extensively reviewed and shown to prevent bone loss and fragility fractures in men treated with ADT.⁷² However, in countries such as Australia, the Pharmaceutical Benefits Scheme only subsidises

Table 3. Clinical assessment and management guidelines for ADT-associated cardiometabolic and skeletal adverse effects

<p>Cardiometabolic health</p> <p>Metabolic risk assessment prior to ADT commencement: body mass index, waist circumference, blood pressure, fasting blood glucose, oral glucose tolerance test (if fasting glucose between 5.5 and 6.9 mmol l^{–1}) and fasting lipid profile.</p> <p>Six-monthly to yearly metabolic assessment during the first 24 months of ADT.</p> <p>Lifestyle intervention and/or dietician to prevent weight gain and worsening of insulin resistance.</p> <p>Smoking cessation.</p> <p>Blood pressure < 130/80 mm Hg.</p> <p>Lipid targets according to NCEP ATP III treatment guidelines.</p> <p>In men with diabetes, intensification of management as necessary to main HbA1c target.</p> <p>Skeletal health</p> <p>At commencement of ADT: assessment for history of minimal trauma fractures and risk factors for osteoporosis; aBMD measurement by DXA and, in men with osteopenia, postero-anterior as well as lateral thoracolumbar spine X-rays.</p> <p>Yearly aBMD measurement during the first 24 months of ADT.</p> <p>Advice regarding regular physical exercise, smoking cessation and alcohol consumption of ≤ 2 standard drinks per day at each visit.</p> <p>Total daily calcium intake of 1200–1500 mg through diet, supplements, or both, unless there is a history of renal calculi.</p> <p>Vitamin D supplementation as necessary to achieve a target serum 25-hydroxyvitamin D level ≥ 75 nmol l^{–1}.</p> <p>Commencement of treatment with a bisphosphonate in men with a minimal trauma fracture, an aBMD T-score of ≤ –2.5, or if 10-year absolute risk of a major osteoporotic fracture is > 20%.</p>	<p>Abbreviations: aBMD, areal bone mineral density; ADT, androgen deprivation therapy; DXA, dual-energy X-ray absorptiometry; HbA1c, glycated haemoglobin; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III. Adapted from Cheung <i>et al.</i>⁶⁴ on behalf of the Endocrine Society of Australia, the Australian and New Zealand Bone and Mineral Society and the Urological Society of Australia and New Zealand.</p>
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Table 4. Recommendations for managing adverse effects of ADT in men with prostate cancer on bone health, lean tissue mass and fat mass

Densitometry
Prior to commencing ADT, men should undergo a DXA scan for the assessment of hip and spine bone mineral density and a total body scan for the assessment of total and appendicular lean tissue mass and fat mass. These measures should be repeated yearly until the cessation of ADT.
Antiresorptive therapy
Clinicians should consider antiresorptive therapy if men: (1) experience a minimal trauma fracture, (2) have a hip and/or lumbar spine DXA-assessed bone mineral density T-score of < 2.0 or (3) have a 10-year absolute risk of major osteoporotic fracture of $> 20\%$ as determined by FRAX (http://www.shef.ac.uk/FRAX).
Exercise training
It is recommended that clinicians discuss and refer men to an individualised, multi-component exercise program incorporating the elements below:
Progressive resistance training: at least twice per week, 8–10 exercises (targeting major muscle groups, specifically the muscle attached to or near the hip and spine), 2–3 sets of 8–10 repetitions at moderate-to-high-intensity (70–85% of 1-RM or 5–8 'hard to very hard' on the 10-point Borg RPE scale).
Weight-bearing impact exercises (jumping, bounding, hopping, skipping and bench stepping): at least 4 days per week, 2–4 impact exercises varying in magnitude and direction, progress to 50–100 jumps per session divided into 2–3 sets of 10–20 repetitions. *PRT is recommended first for those with low muscle strength and/or poor muscle function prior to commencing some impact activities.
Aerobic exercises: 5–7 days per week, 30 min of continuous, 55–75% of predicted heart rate maximum, modalities including cycling, walking, rowing or sports such as tennis. Aerobic training can be divided into shorter bouts if required (three by 10 min sessions).
The concept of specificity and progressive overload should be applied to all exercises and when possible, programs should initially be performed under the supervision of a tertiary-trained exercise professional (for example, an Accredited Exercise Physiologist in Australia).
Vitamin D
Prior to commencing ADT, men should have their serum 25(OH)D assessed. Men with 25(OH)D levels $> 50 \text{ nmol l}^{-1}$ ($> 20 \text{ ng ml}^{-1}$) should consider a daily supplement of 800 IU. Men with $< 50 \text{ nmol l}^{-1}$ should supplement with 3000–5000 IU per day for at least 6–12 weeks under the guidance of a clinician.
Calcium
Include 3–4 serves of dairy food each day and if daily calcium intake is below the recommended dietary intake of 1000–1300 mg per day, supplement with 600 mg per day.
Protein
Daily protein intake of at least 1.2 g kg^{-1} body weight per day.
Consume 25–30 g of high-quality protein with each meal and on exercise training days, within the first few hours post exercise.
Tobacco and alcohol
Smoking cessation should be considered.
Alcohol consumption should be limited to < 2 standard drinks per day.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; ADT, androgen deprivation therapy; DXA, dual-energy X-ray absorptiometry; PRT, progressive resistance training; RM, repetition maximum.

antiresorptive therapy for secondary prevention for those who have suffered a minimal trauma fracture and primary prevention for those aged over 70 years with T-scores ≤ -2.5 or ≤ -3.0 , pending therapy already prescribed. There may be a potential lack of accessibility to these therapies in men treated with ADT in some countries. Furthermore, there are concerns surrounding the overall safety of antiresorptive therapy with adverse effects such as flu-like symptoms, hypercalcaemia and hepatic failure reported in men treated with ADT.⁷³ Finally, as antiresorptive therapy has no effect on other key fracture risk factors, such as muscle strength, muscle mass, balance and gait, all of which are associated with an increased risk of falls and fracture, independent of BMD, alternative or adjunct interventions should be made available to patients currently undergoing ADT (Table 4).

Lifestyle measures such as exercise training, smoking cessation and limited alcohol consumption (< 2 standard drinks per day) are an alternative to pharmacological intervention and are commonly recommended in men treated with ADT.^{40,62} Suggested exercise training modalities include weight-bearing aerobic training (AT; for example, walking), progressive resistance training (PRT) and balance training.^{40,62} However, these guidelines provide limited information on the precise exercise prescription variables such as the training intensity, frequency and duration. Despite initial concerns, regular exercise training has been shown to have no effect on PSA or testosterone levels.⁷⁴ Currently only four studies have examined the role of exercise on skeletal adaptations in men treated with ADT.^{75–78} Galvao *et al.*⁷⁵ reported that a 20-week PRT program, including two training sessions per week utilising exercises that progressed from two sets at

12-repetition maximum (RM) to four sets at 6-RM, did not improve femoral neck, trochanter or Ward's triangle aBMD in 10 men (mean age; 70 years) currently treated with ADT (mean duration; 3.1 years). Similarly, the findings from a 16-week PRT program in 28 men (mean age; 66 years) currently treated with ADT (mean duration; 9 months) demonstrated no significant differences in femoral neck, trochanter, total hip and lumbar spine (L1–4) aBMD when compared with men undergoing usual care ($n = 30$).⁷⁶ In this study, the training program included three sessions per week, with each session including 9 exercises that progressed from two sets of 10 repetitions at 40–50% 1-RM to 1–3 sets at 6–10-RM in a daily undulating periodisation model.⁷⁸ Consistent with these results, Cormie *et al.*⁷⁷ observed no significant change in femoral neck or lumbar spine (L2–4) aBMD, as well as tibia volumetric BMD following a 12-week combined PRT and AT program in 32 men (mean age; 70 years) initiating ADT when compared with usual care ($n = 31$). The PRT component of the exercise program was administered during two sessions per week and included eight exercises progressing from 1–4 sets of 6–12RM.⁷⁷ In all these studies, the sample sizes were relatively modest and the lack of any beneficial skeletal effects was not unexpected given that the typical bone remodelling cycle takes 6–8 months to complete, and to demonstrate clinically relevant and observable physiological changes, longer-term trials with appropriate sample sizes are needed.

To date, only one trial of adequate duration has assessed the role of exercise training on bone health in men treated with ADT.⁷⁶ Winters-Stone *et al.*⁷⁶ reported that a 12-month targeted PRT and weight-bearing impact loading program did not

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significantly improve femoral neck, total hip, greater trochanter or lumbar spine (L1-4) aBMD in 29 men (mean age; 70 years) currently treated with ADT (mean duration; 39 months) when compared with an exercise placebo group consisting of stretching ($n=22$). It was suggested that due to concerns with treatment-induced muscle weakness, frailty and incontinence, a cautious approach was taken towards exercise prescription and this may have not provided an adequate stimulus to elicit improvements in aBMD.⁷⁶ For example, the program only included one impact exercise (two-footed jumps), performed three times per week, which progressed from 10–50 repetitions and 0–10% body weight (via weighted vests).⁷⁶ Previous research in 180 healthy and osteopenic older men (age range; 50–79 years) showed that a combination of moderate-to-high-intensity PRT (60–85% 1-RM) with weight-bearing impact exercises (90–180 impact loads) performed three times per week that varied in the type, magnitude and direction of loads was effective at improving femoral neck (1.7%) and lumbar spine (L1-4; 2.1%) aBMD over 12 months compared with non-exercising controls.⁷⁹ Similarly, a meta-analysis of randomised controlled trials in older adults also found that multi-component exercise programs incorporating moderate-to-high-intensity PRT and weight-bearing impact exercises were most effective for maintaining (or improving) hip and spine aBMD.⁸⁰ Although further studies are warranted to evaluate the safety and efficacy of targeted, multi-component exercise program on bone health in this susceptible population group, based on the available evidence in healthy and osteopenic older men, it is advised that men treated with ADT be prescribed a similar exercise program under the supervision of an appropriately qualified exercise physiologist or trainer (Table 4).

Lean tissue mass. The guidelines for managing metabolic health during ADT briefly discuss the link between lean tissue mass and insulin resistance, yet do not recommend any interventions specifically intended to preserve or improve muscle health.^{37,40,61,63} Regular exercise training and/or physical activity are recommended, but greater emphasis is placed on weight management as an outcome, rather than lean tissue mass.^{37,40,61,63} In healthy older men, there is consistent and compelling evidence demonstrating that PRT is safe and effective for improving muscle mass and strength, with the greatest benefits typically observed with high-intensity training.⁸¹ However, in men with PCa treated with ADT, a recent systematic review⁸⁴ concluded that there was inadequate evidence to produce specific exercise prescription guidelines for this population group, and therefore suggested that these men adopt general guidelines for cancer patients.^{82–85} For example, Exercise and Sport Science Australia⁸³ recommend 1–3 PRT sessions per week that include 6–10 exercises targeting different muscle groups, completed at an intensity of 50–80% 1-RM or 6–12-RM in sets of 1–4. A growing body of evidence examining the role of exercise training in men treated with ADT has shown that interventions including at least two PRT sessions per week for 12 weeks or greater can maintain^{77,78,86} or improve⁸⁷ (0.5–0.7 kg) total body and/or appendicular lean tissue mass. In contrast, no improvement in lean tissue mass was demonstrated following a 24-week AT program, including three sessions per week progressing from 15–45 min at an intensity of 50–75% VO_{2peak} in 25 men (mean age; 66 years) treated with ADT (mean duration; 106 days).⁸⁶ Therefore, it is advised that all men treated with ADT be prescribed a moderate-to-high-intensity PRT program, with a specific focus on muscles attached to or near the hip, spine and forearm, as these are the most common fracture sites (Table 4).

Emerging evidence in older adults has also provided a rationale for the potential use of protein supplementation alongside PRT in clinical populations susceptible to muscle loss, such as those treated with ADT.⁸⁸ Although yet to be examined within this population group, a recent meta-analysis of randomised

controlled trials conducted in healthy older adults concluded that protein supplementation combined with PRT may elicit further gains in muscle mass than PRT alone.⁸⁸ However, the responses appeared to vary according to the type, amount, spread and/or change in protein intake, timing, pattern or distribution of intake and the potential influence of co-ingestion with other nutrients.⁸⁹ There is a growing body of evidence to suggest that high-quality, rapidly digested, leucine-rich protein sources (for example, whey protein), when compared with other types of protein supplementation (for example, casein and soy), can produce additive or synergistic benefits on post-exercise skeletal muscle protein synthesis and promote increases in muscle mass in older adults.⁹⁰ Similarly, emerging evidence suggests that 20–40 g of high-quality protein may be required to elicit maximal gains in muscle mass in older adults.⁹¹ Moreover, the timing of protein ingestion in relation to the exercise session is also important with early (within 1–4 h) post-PRT consumption of protein reported to be most effective for optimising muscle protein synthesis.^{91,92} Due to the lack of randomised controlled trials examining the role of protein supplementation in men treated with ADT, the potential disease-specific risks are unknown, however increased protein intake is commonly shown to be well tolerated and accompanied by no serious adverse events in older population groups.^{93,94} Therefore, further evaluation is still required in men treated with ADT to elucidate both the risks and benefits of protein supplementation when used in combination with exercise training as a strategy to optimise muscle health (Table 4).

Fat mass. Most guidelines for managing adverse effects of ADT have placed greater emphasis on weight management, and do not specifically focus on monitoring and preventing the accumulation of fat mass via robust measures such as DXA.^{37,40} Although not specifically stated within the current guidelines,^{37,40} exercise training is one potential intervention to address the accumulation of fat mass during ADT. However, evidence regarding the efficacy of exercise training in reducing fat mass during ADT is currently mixed.^{77,78,87,95,96} In a sample of 32 men (mean age; 70 years) commencing ADT, fat mass was shown to decrease by 0.6 kg following a 12-week combined PRT and AT program when compared with usual care ($n=31$).⁷⁷ Exercise training was conducted twice weekly and involved 20–30 min AT at 70–85% of estimated heart rate maximum and PRT prescribed at 6–12-RM in sets of 1–4.⁷⁷ Similarly, a 24-week PRT program performed three times per week (1–2 sets of 8–12 repetitions at 60–70% 1-RM) decreased the accumulation of body fat percentage when compared with usual care (+0.4% vs +3.2%), whereas a concurrent AT program also performed three times per week (progressing from 15–45 min at 50–75% of maximal heart rate) of the trial showed no change to fat mass when compared with usual care.⁸⁶ No change in fat mass was also observed following interventions including PRT performed two or more times per week for 12–52 weeks.^{78,87,96} Despite these negative findings, the lack of change in fat mass may be viewed as beneficial due to the expected accumulation of fat mass during ADT. Although it is clear that further studies are needed to evaluate the effect of various types and dose of exercise training on total body and regional fat in men with PCa treated with ADT, it is recommended that AT be included as part of a multi-component exercise program for men with PCa treated with ADT (Table 4).

CONCLUSION

Despite ADT improving overall survival in appropriately selected patients, it is accompanied with a range of adverse effects, including negative alterations to BMD, structure and strength, lean tissue mass and fat mass, which may contribute to the increased risk of osteoporosis, falls, fractures and cardiometabolic-related events observed in this population group. Although various

guidelines exist for men with PCa treated with ADT, there is a need to implement and evaluate the growing body of evidence supporting the use of lifestyle interventions to ameliorate and manage the adverse effects of ADT. Clinicians should consider referring suitable men to practitioners within the allied health profession (for example, exercise physiologists and dietitians) to ensure these men receive the greatest quality of evidence-based care. Our proposed recommendations are outlined in Table 4. Future trials are required to assess both the risk and benefits of adhering to these guidelines and only then may these be fully incorporated into standard practice for men treated with ADT.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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PLAIN LANGUAGE STATEMENT AND CONSENT FORM

TO: Participant

Plain Language Statement

Date: 12/01/16

Full Project Title: The efficacy of exercise training and nutritional supplementation on musculo-skeletal and cardio-metabolic health in men living with prostate cancer treated with androgen deprivation therapy

Chief Investigator: Dr Steve Fraser

Principal Researcher(s): Prof Robin Daly, Prof Patricia Livingston, A/Prof Jeremy Millar

Student Researcher(s): Mr Patrick Owen, Ms Niamh Mundell

1. Introduction:

You are invited to take part in this research project. This is because you have been either diagnosed with prostate cancer or are of similar age as men who are commonly diagnosed with prostate cancer in Australia. The primary aim of this research is to determine if an exercise program and nutritional supplementation can improve muscular, skeletal, cardiovascular and metabolic health among men who are currently treated with androgen deprivation therapy for prostate cancer. Overall, we will be recruiting 102 participants that are currently treated with androgen deprivation therapy for this study (group A). A sub-study embedded within will compare the effects of androgen deprivation therapy in men diagnosed with prostate cancer on the above measures to 50 men previously diagnosed with prostate cancer who have not been treated with androgen deprivation therapy (group B) and a group of 50 healthy men of similar age who have not been diagnosed with prostate cancer (group C). Participants in group A will be randomly allocated into either an intervention group (exercise program and nutritional supplementation) or usual care group (no exercise program and a vitamin D and calcium supplement). Participants in group B and C will not be allocated to an intervention or usual care group and will only complete the initial assessment discussed in section 3 below. If you fall into either group B or C, please disregard any additional information and focus on the requirements of the initial assessment.

This research is currently funded by Deakin University. This participant information and consent form will inform you about the research project. It explains what is involved to help you decide if you want to take part.

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Please read this information carefully. Ask questions about anything you do not understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local health worker.

Participation in this research is voluntary. If you do not wish to take part, you do not have to.

If you decide you want to take part in the research project, you may be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read;
- Consent to take part in the research project;
- Consent to be involved in the procedures described;
- Consent to the use of your personal and health information as described.

You will be given a copy of this participant information and consent form to keep.

2. What is the purpose of this research project?

The primary aim of this research project is to determine if an exercise program and nutritional supplementation can improve muscular, skeletal, cardiovascular and metabolic health among men who are currently or have recently been treated with androgen deprivation therapy for prostate cancer. This project is also aiming to determine if this intervention can improve functionality (one's ability to perform activities of daily living), quality of life, cognitive function and fatigue. This research will contribute to our understanding of health and well-being among men who have been treated for prostate cancer with androgen deprivation therapy. A secondary aim of this study is to compare the effects of prostate cancer, with and without treatment with androgen deprivation therapy, and relative to healthy men of a similar age without prostate cancer, on the above measures.

3. What does participation in this research project involve?

With your permission, your doctor will be asked to provide the following information to ensure your safety throughout the study; ADT status, medication history and brief medical history.

Additionally, you will be asked to complete a questionnaire before your initial assessment that has questions about your condition (if applicable; i.e., your diagnosis and stage of disease), age, education history, marital status, employment status, cultural background, sun exposure habits and practices, alcohol consumption, past and current medical conditions, use of prescription and non-prescription medications and falls history. This questionnaire will be mailed to you and you will be required to bring it to your initial testing session or mail it back to Deakin University in a reply paid envelope.

We will also ask you to complete a questionnaire on how you manage aspects of your treatment for prostate cancer (if applicable), how you have been feeling lately and your current exercise habits.

For participants in group A, these questionnaires will occur five times over 2-years (baseline [i.e., after you consent to be involved in the study], 6, 12, 18 and 24 months) and will take approximately 45-60 minutes to complete. At these five time points you will also be asked to undergo a 2.5-3 hour testing session at Deakin University, Burwood. Participants in group B and C will only receive the questionnaire once and only undergo one 2.5-3 hour testing session at Deakin University, Burwood.

Several tests will be performed, including:

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- Your total body composition (amount of muscle and fat) and bone density of your total body, hip and spine will be measured using a non-invasive method referred to as dual-energy x-ray absorptiometry (DXA). The assessment of body composition and bone density by DXA involves lying on a bed for approximately 20 minutes whilst a scanning arm moves along the length of the bed above you.
- Your arm and leg muscle and fat size composition will also be measured using peripheral computed tomography (pQCT). pQCT is a non-invasive method that will involve you inserting your arm into the opening of a gantry (ring with x-ray source and detectors) for scanning. This will involve remaining still for three to five minutes during the measurement. You will then repeat this process with your leg. The pQCT scans will cause no pain or discomfort other than having to remain still.
- Your height, weight and chest, hip and waist circumference
- Your blood pressure and heart rate will be assessed using an automated machine. This will involve you sitting in a quiet room with minimal movement for five minutes. You will then have a cuff placed around your left arm and this will automatically be inflated and then slowly deflated whilst your blood pressure is measured. This measurement will occur three times with a one minute interval between each measure.
- Your balance and muscle function will be assessed using simple balance and walking tests. Your maximal and grip strength will also be assessed using specific resistance (strength) training equipment. This will involve lifting weights until you can only lift a weight three times.
- Your cognition will be assessed via a series of simple tests that involve reading, writing, listening and using a computer. These may include assessment of your short term memory and problem solving skills.
- Your diet will also be assessed. This will involve a food recall where you will list all the food and drink you have consumed in the past 24 hours.

At each assessment you will also be asked to attend a pathology collection centre, local to you, to provide an overnight fasted blood sample, which will be used to assess a number of markers for muscle and bone metabolism, cardiovascular, metabolic and neurological health and disease progression (prostate specific antigen [PSA]; if applicable). The blood sample of 30 mls (1.5 tablespoon) will be taken from a vein in your arm using a needle. The blood sample will be collected by trained staff at the pathology clinics in the morning when you have had nothing to eat or drink from the night before.

Group A participants randomised to the intervention arm will also be involved in a 12-month exercise program and provided with a yearly fitness centre membership (supplied via YMCA). If you are allocated to this arm you will be required to attend two supervised exercise training sessions per week (approximately one hour each). Within these supervised exercise sessions, the exercise program will be adapted to suit your individual abilities. In addition, you will also be advised to undertake a home-based program on a separate day per week. Supervised exercise training sessions will take place at a fitness centre that is convenient for you or at Deakin Clinical Exercise Learning Centre. You will also be asked to maintain a log of your exercise participation throughout the intervention.

Group A participants randomised to the intervention arm will also be provided with a nutritional supplement that you will be required to consume daily for 12 months. This will include a sachet of powder (produced via Omniblend) containing approximately 25g whey protein, 480mg elemental calcium and 1000IU vitamin D that will be mixed with water. You

will also be asked to take one vitamin D capsule (produced via Ostelin) per day which will provide you with an additional 1000IU of vitamin D per day. Compliance to the supplement will be monitored using a simple calendar that you will be required to fill out on a daily basis (this will be provided to you). Any supplementation that you do not consume must be returned to Deakin University.

Group A participants randomised to the control arm will receive usual care from their doctor(s) and be provided with a vitamin D and calcium supplement. If you are allocated to this group you will be asked to take one vitamin D capsule (produced via Ostelin) per day which will provide you with 1000IU of vitamin D.

At the end of the initial 12 months, group A participants in the intervention arm will be asked to participate in a 'step-down' less intensive maintenance program for another 6 months. During this phase, you will not be provided with a gym membership or the supplements but will be asked to continue to exercise (at your expense) at a health and fitness centre of your choice. During this time, you will receive a monthly 1-hour exercise session with an accredited exercise physiologist to monitor your progress. At the end of this period, we will no longer provide you with weekly support but will ask you to return for one final testing session 6 months after the end of the program to establish if there are any long-term benefits to regular exercise. Group A participants in the control group will also be invited back to Deakin University for additional testing after 18 and 24 months.

Reimbursement:

You will not be paid for participation in this research. However, all expenses related to parking at Deakin University (Burwood) for testing sessions will be reimbursed. Group A participants who are randomised into the control arm will also receive vitamin D supplementation free of charge. Group A participants who are randomised into the intervention arm will also receive a nutritional supplement and vitamin D free of charge as well as a yearly gym membership at a YMCA health and fitness centre free of charge. If you are unable to attend a YMCA centre, you will be eligible to receive a reimbursement up to the value of \$500 which will be paid to you at the end of the study. Prior to receiving this reimbursement, you are required to pay for the gym membership upfront.

4. What are the possible benefits?

We cannot guarantee or promise that you will receive any benefits from this project. For some people, there are potentially significant health benefits in terms of improvements in bone and muscle mass and strength as well as reduced body fat, improved blood lipids and blood pressure and cognitive function. The program may also improve your inflammatory, hormonal and biochemical profile, as well as your mood and health-related quality of life. We also expect that the findings from this study will make an important contribution to the development of safe, practical and widely-accessible exercise and nutrition guidelines for improving both bone and muscle health and function and cognitive health and well-being in men with prostate cancer.

5. What are the possible risks?

Medical treatments often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects. There may be side effects that the researchers do not expect or do not

know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

This research study involves exposure to a very small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisieverts (mSv) each year. The effective dose from this study is less than 0.05 mSv. At this dose level, no harmful effects of radiation have been demonstrated as any effect is too small to measure. The risk is believed to be minimal.

Have you been involved in any other research studies that involve radiation? If so, please tell us. Please keep information contained within the Patient Information and Consent Form about your exposure to radiation in this study, including the radiation dose, for at least five years. You will be required to provide this information to researchers of any future research projects involving exposure to radiation. The assessment of muscle strength and muscle function via performance based tests are potentially hazardous in that they may cause some initial muscle soreness and there is a small risk of muscular injury, skeletal injury or cardiovascular complications. However, this will be minimised as all testing will be conducted by experienced and qualified staff.

Group A participants randomised to the intervention group who receive resistance training may also experience some minor muscle soreness. To minimise the risk, you will be provided with ongoing personal supervision and an individually tailored exercise training program.

Collection of blood samples (by qualified employees of a commercial pathology) collection centre may be perceived as unpleasant by some participants, and may cause minor pain and bruising at the site of the needle entry.

Group A participants randomised to the intervention group will be asked to consume approximately 25g of protein, 2000IU of vitamin D and 480mg elemental calcium. The amount of protein and calcium is within the recommended range for a healthy diet. Although unlikely with the doses provided, excessive protein can be harmful to the kidneys. For reassurance, we will monitor your kidney function throughout the study via blood tests at baseline, 6 and 12 months. If we (or your general practitioner during a routine checkup) detect any problems we will ask you to withdraw from the study for your safety. Treatment with vitamin D is also very safe. There is a very small risk of hypercalcaemia (high calcium levels in the blood) and hypercalciuria (high calcium levels in the urine) with calcium and vitamin D therapy. If you have been previously told you have high levels of blood calcium or are found to have hypercalcaemia at the beginning of the study, you will not be permitted to participate in this study. We will also monitor your risk of hypercalcaemia throughout the study. The amount of calcium and vitamin D in the supplements is at the level recommended for health benefits. Possible side effects include constipation, flatulence (gas), vomiting and abdominal (stomach) pain. Thus, normal health will not be adversely affected by consumption of the supplement to be used in this study. We advise you against taking any additional calcium and/or vitamin D supplementation during this study for your own safety. If you are concerned about your dietary intake of either calcium or vitamin D or any other supplement that may contain these compounds please discuss this with one of the researchers.

Group A participants randomised to the control group, will also consume a vitamin D supplement. Similar low risks as mentioned above apply.

There is also a small chance that some participants may find it distressing to answer some of the survey questions. If you do find answering the questions distressing you may like to take

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a temporary break. If you feel you would like to speak to someone about your experience, we can refer you to services that are available at your treating health provider or in your local community. Alternatively, you may like to contact the Cancer Helpline, 131 120, a telephone helpline staffed by cancer nurses who can assist you with information and support.

6. What if new information arises during this research project?

During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information and the researchers will discuss whether this new information affects you.

7. Can you have other treatment during this research project?

It is important that you tell your doctor and research staff about any treatment or medication that you may be taking, including over-the-counter medication, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your doctor about any changes to these during your participation in this research.

8. Are there alternatives to participation?

Participation in this project is voluntary and will not affect your care in any way.

9. Do participants have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and then later change your mind, you are free to withdraw from the project at a later stage.

Your decision whether to take part or not, or to take part and then withdraw, will not affect your relationship with the researchers, Deakin University or any parties involved in your medical treatment (if applicable).

10. What if you withdraw from this research project?

If you decide to withdraw, please notify a member of the research team. This notice will allow that person or a fellow researcher to inform you if there are any special requirements linked to withdrawing.

If you decide to leave the project, the researchers would like to keep the personal and/or health information about you that has been collected. This is to help make sure that the results of the research can be measured properly. If you do not want the researchers to do this, you must tell the researchers before you withdraw from the research project.

11. Could this research project be stopped unexpectedly?

The researchers of this project do not anticipate that this project will be terminated before the completion.

12. How will you be informed of the final results of this research project?

You will receive a brief report via email or the post of both the overall study and your individual results approximately six months after the final participant has completed the study (this delay is due to the time it takes to analyse the data). Additionally, if you are interested in getting a copy of the published articles, please email or contact the student researcher, Mr Patrick Owen (details below).

13. What else do you need to know?

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- **What will happen to my test samples?**

Any information obtained in connection with this research project will be made re-identifiable (coded) and will only be used for the purpose of this research project. It will only be disclosed with your permission, except if required by law. Hard copies of your testing results and surveys will be stored in a locked cabinet in the office of the student researcher. The electronic files will be stored on the password-protected computer of the student researcher. The information will be retained for seven years as per the Deakin University policy. At the end of this period, information will be removed physical from the computer storage and any hard copies securely destroyed. Alfred Health retains the right to maintain this information indefinitely as per policy.

Blood samples will be stored securely at Deakin University and only the investigators will have access. Some of the samples will be tested immediately at the end of the study and some will be frozen and stored for 10 years following the publication of study findings. We wish to store these samples to conduct further testing to look for other hormonal, inflammatory and neural related hormones when and if funding for this becomes available in the future. This future testing may be conducted by researchers from the present study or by researchers employed by Deakin University. If any changes to the study are made which affect how these samples will be used, your samples will not be used without your further consent. In this case, you will be contacted once again for informed consent. These samples will be disposed according to standard laboratory practice immediately after testing. Any 'at risk' information will be sent to you in a letter by the chief investigator, advising you to discuss the results with your medical practitioner.

It is anticipated that the results of this research project will be published and or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that the participant cannot be identified, except with your permission. All data from this project will be presented as a group. No information about individuals will be published. The material from the evaluation of the intervention will also be presented in summary form. If your words are used to illustrate a point, all identifying information will be removed from your quotes. At no time will your name or information that could lead to your identification be published.

- **How can you access your information?**

In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about you. Please contact one of the researchers named at the end of this document if you would like to access your information.

In addition, in accordance with regulatory guidelines, the information collected in this research project will be kept for seven years. Access to information about you after this point will not be possible.

- **What happens if you experience any adverse outcomes as a result of participation in this research project?**

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment

required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

- **Has this research project been approved?**

The ethical aspects of this research project have previously been approved by the Human Research Ethics Committee of Deakin University under project ID 2013-184 and the Alfred Hospital Ethics Committee under project ID 455/15

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research* (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

14. Complaints

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact:

The Manager, Research Integrity, Deakin University, 221 Burwood Highway, Burwood Victoria 3125, Telephone: 9251 7129, research-ethics@deakin.edu.au. Please quote project number 2013-184.

Ms Emily Bingle, Research Governance Officer, Alfred Health, Telephone: 9076 3619, research@alfred.org.au. Please quote Project number 455/15.

15. Further information, queries or any problems

If you require further information, wish to withdraw your participation or if you have any problems concerning this project, you can contact the research team.

The researchers responsible for this project are:

Chief Investigator:

Dr Steve Fraser
Institute for Physical Activity and Nutrition Research
School of Exercise and Nutrition Sciences
Deakin University
221 Burwood Hwy, Burwood, VIC 3125
Telephone: +61392446012
Email: steve.fraser@deakin.edu.au

Principal Researchers:

Prof Robin Daly
Institute for Physical Activity and Nutrition Research
School of Exercise and Nutrition Sciences
Deakin University
221 Burwood Hwy, Burwood, VIC 3125
Telephone: +61392446040
Email: robin.daly@deakin.edu.au

Prof Patricia Livingston
Faculty of Health
Deakin University
221 Burwood Hwy, Burwood, VIC 3125
Telephone: +61392446609
Email: trish.livingston@deakin.edu.au

A/Prof Jeremy Millar
Melbourne South Block
The Alfred
55 Commercial Road, Melbourne, VIC 3004
Telephone: +61390762167
Email: jeremy.millar@monash.edu

Student Researchers:
Mr Patrick Owen
Institute for Physical Activity and Nutrition Research
School of Exercise and Nutrition Sciences
Deakin University
221 Burwood Hwy, Burwood, VIC 3125
Telephone: +61414221902
Email: pow@deakin.edu.au

Ms Niamh Mundell
Institute for Physical Activity and Nutrition Research
School of Exercise and Nutrition Sciences
Deakin University
221 Burwood Hwy, Burwood, VIC 3125
Telephone: +61392443729
Email: niamh.mundell@deakin.edu.au

PLAIN LANGUAGE STATEMENT AND CONSENT FORM

TO: Participant

Consent Form

Date: 12/01/16

Full Project Title: The efficacy of exercise training and nutritional supplementation on musculo-skeletal and cardio-metabolic health in men living with prostate cancer treated with androgen deprivation therapy

Reference Number: 2013-184

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Deakin University and Alfred Health concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Participant's Name (printed)

Signature Date

Please mail this form to:

Dr Steve Fraser

Institute for Physical Activity and Nutrition Research

School of Exercise and Nutrition Sciences

Deakin University

221 Burwood Hwy, Burwood, VIC 3125

Telephone: +61392446012

Email: steve.fraser@deakin.edu.au

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PLAIN LANGUAGE STATEMENT AND CONSENT FORM

TO: Participant

Withdrawal of Consent Form

(To be used for participants who wish to withdraw from the project)

Date: 12/01/16

Full Project Title: The efficacy of exercise training and nutritional supplementation on musculo-skeletal and cardio-metabolic health in men living with prostate cancer treated with androgen deprivation therapy

Reference Number: 2013-184

I hereby wish to WITHDRAW my consent to participate in the above research project and understand that such withdrawal WILL NOT jeopardise my relationship with Deakin University or any parties involved in my medical treatment.

Participant's Name (printed)

Signature Date

Please mail this form to:

Dr Steve Fraser
Institute for Physical Activity and Nutrition Research
School of Exercise and Nutrition Sciences
Deakin University
221 Burwood Hwy, Burwood, VIC 3125
Telephone: +61392446012
Email: steve.fraser@deakin.edu.au
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Appendix E

Participant ID: _____

Date completed: _____

Improving Musculoskeletal Health During Prostate Cancer Androgen Deprivation Therapy [IMPACT]

BASELINE QUESTIONNAIRE

In this questionnaire, we will ask you questions about your general health and lifestyle.

Please allow approximately 45-60 minutes to complete this questionnaire.

Group A

All questionnaires are confidential.

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Participant ID: _____

Section 1 – Personal Details

1. Initials (first name and surname only): _____
2. Date of birth: ____/____/____
3. What country were you born in? *(Tick one box)*

☐ Australia
☐ New Zealand
☐ Other (specify): _____
4. What country were your parents born in?

Mother: ☐ Australia
 ☐ New Zealand
 ☐ Other (specify): _____
 Father: ☐ Australia
 ☐ New Zealand
 ☐ Other (specify): _____
5. What is the ethnic origin of your parents? *(The place where most of their ancestors came from) (Tick one box)*

Mother: ☐ North European
 ☐ South European
 ☐ Asian
 ☐ African
 ☐ Other (specify): _____
 Father: ☐ North European
 ☐ South European
 ☐ Asian
 ☐ African
 ☐ Other (specify): _____

Participant ID:

6. What is your highest level of schooling? (Tick one box)

- ☐ Never attended school
- ☐ Primary school
- ☐ Some high school
- ☐ Completed high school
- ☐ Technical/trade certificate
- ☐ University or tertiary level

7. Do you currently work? (Tick one box)

- ☐ Yes (go to question 8)
- ☐ No (go to question 10)

8. What is your current employment status? (Tick one box)

- ☐ Full time employment
- ☐ Part time employment
- ☐ Home duties (example: gardening)
- ☐ Other (specify): _____

9. What type of work are you currently involved with? (Tick one box)

- ☐ Predominantly physical (example: heavy lifting, packing shelves, exercise teacher, heavy gardening, cleaner & heavy housework, maintenance worker, factory worker with heavy physical work, nurse)
- ☐ Standing and some walking (example: office workers, bank workers, light house work, factory work with some walking and some lifting, light gardening, teachers)
- ☐ Predominately sitting (example: desk work, factory but mostly sitting, cashier, student, academic, computer work)
- ☐ Other (specify): _____

Participant ID:

10. What are your current living arrangement? *(Tick one box)*

☐ Living alone

☐ Living with adults without children

☐ Living with adults with children

☐ Living in a retirement village/hostel

☐ Other (specify): _____

11. What is your current marital status? *(Tick one box)*

☐ Married

☐ De facto

☐ Separated

☐ Divorced

☐ Widowed

☐ Never married

Participant ID: _____

Section 2 – General Health And Falls History

1. When were you diagnosed with prostate cancer (month and year)?

2. Provide as much detail as you can regarding your current and/or previous androgen deprivation (hormone) therapy:
 Drug name: _____
 Initial start date: _____
 Projected end date (if applicable): _____
 Last dose: _____
 Any other information (e.g. on and off periods, reasons for stopping/restarting therapy, changes in drugs etc.):

3. Is your prostate cancer currently confined to your prostate (localised) or has it spread to other organs or lymph nodes (advanced)? *(Tick one box)*
☐ Localised
☐ Advanced (provide any details): _____

☐ Don't know

3. Have you received any treatment for prostate cancer other than androgen deprivation (hormone) therapy? *(Tick as many boxes as applicable and provide dates/details if possible – e.g. month and year treated)*
☐ Prostatectomy (surgery): _____
☐ Radiotherapy: _____
☐ Chemotherapy: _____
☐ Other (specify): _____
☐ No
☐ Don't know

Participant ID: _____

4. Have you ever had or has your doctor ever told you that you have: *(Tick as many boxes as applicable and provide as much detail as possible)*

- ☐ Asthma/respiratory problems _____
- ☐ Chronic bronchitis _____
- ☐ Glandular fever _____
- ☐ Muscular/ligament problems _____
- ☐ Back pain _____
- ☐ Hernia _____
- ☐ Epilepsy _____
- ☐ Regular headaches/migraines _____
- ☐ Faintness/light headiness/blackouts _____
- ☐ Angina/stroke/heart condition _____
- ☐ Diabetes _____
- ☐ Recent surgery (last 6 months) _____
- ☐ Hayfever/allergies _____
- ☐ Vision/hearing problems _____
- ☐ Family history of heart disease _____
- ☐ High blood pressure _____
- ☐ High levels of cholesterol _____
- ☐ Cancer (other than prostate) _____

5. Do you have a family history of osteoporosis or low trauma bone fracture? *(Tick one box)*

- ☐ Yes (provide details below)
- ☐ No (go to question 6)
- ☐ Don't know (go to question 6)

If Yes, which relatives? *(Tick as many boxes as applicable)*

- ☐ Mother
- ☐ Father
- ☐ Grandmother
- ☐ Grandfather
- ☐ Sister
- ☐ Brother

Participant ID:

6. Have you broken any bones since the age of 45? (Tick one box)

☐ Yes (provide details below)☐ No (go to question 7)If Yes, provide details below: (Tick as many boxes as applicable)

Site?	Age?	How did it happen?
	<i>Example:</i> 66 years old	<i>Example:</i> Slipped on wet floor and fell on outstretched arm
Toe(s)	☐ Left	
	☐ Right	
Ankle	☐ Left	
	☐ Right	
Leg	☐ Left	
	☐ Right	
Hip	☐ Left	
	☐ Right	
Finger(s)	☐ Left	
	☐ Right	
Hand	☐ Left	
	☐ Right	
Wrist	☐ Left	
	☐ Right	
Forearm	☐ Left	
	☐ Right	
Back	☐ Left	
	☐ Right	
Other	☐ Left	
	☐ Right	

Participant ID:

7. Have you ever been diagnosed with or treated for osteoporosis? *(Tick one box)*☐ Yes (provide details below)☐ No (go to question 8)☐ Don't know (go to question 8)If Yes, provide details below of diagnosis and/or treatment:

8. Have you ever been diagnosed with or treated for arthritis? *(Tick one box)*☐ Yes (provide details below)☐ No (go to question 9)☐ Don't know (go to question 9)If Yes, what type(s)? *(Tick as many boxes as applicable)*☐ Rheumatoid arthritis☐ Osteoarthritis☐ Other (specify): _____☐ Don't knowIf Yes, what body site(s) are affected?

9. Have you had any falls in the last 12 months? *(Tick one box)*☐ Once (continue with this section)☐ Twice (continue with this section)☐ Three or more (continue with this section)☐ No (go to section 3 – medication)

Participant ID:

10. Where have you fallen? *(Tick one box for each fall)*

Inside	Fall 1	Fall 2	Fall 3
On the one level	☐	☐	☐
Getting out of bed	☐	☐	☐
Getting out of a chair	☐	☐	☐
Using the shower/bath	☐	☐	☐
Using the toilet	☐	☐	☐
Walking up or down stairs	☐	☐	☐
Home entrances or in the garden	Fall 1	Fall 2	Fall 3
Walking up or down a step/stairs	☐	☐	☐
On the one level (example: pathway)	☐	☐	☐
In the garden	☐	☐	☐
Away from home	Fall 1	Fall 2	Fall 3
On the footpath	☐	☐	☐
On a kerb/gutter	☐	☐	☐
Getting out of a vehicle	☐	☐	☐
In another person's home	☐	☐	☐

If none of the above describe where you have fallen, provide further detail about where the fall(s) occurred:

If you have fallen more than three times in the past year, provide further detail below about where the fall(s) occurred:

Participant ID:

11. How did you fall? (Tick as many boxes as applicable)

	Fall 1	Fall 2	Fall 3
Tripped	☐	☐	☐
Slipped	☐	☐	☐
Lost balance	☐	☐	☐
Legs gave way	☐	☐	☐
Felt faint	☐	☐	☐
Felt giddy/dizzy	☐	☐	☐
Don't know	☐	☐	☐

If none of the above describe how you have fallen, provide further detail about how the fall(s) occurred:

If you have fallen more than three times in the past year, provide further detail below about how the fall(s) occurred:

Participant ID:

12. As a result of your fall(s), did you suffer any injuries? *(Tick one box)*☐ Yes (provide details below)☐ No (go to section 3 - medication)If Yes, what injuries did you suffer? *(Tick as many boxes as applicable)*

	Fall 1	Fall 2	Fall 3
Bruises	☐	☐	☐
Broken wrist	☐	☐	☐
Broken ribs	☐	☐	☐
Cuts/grazes	☐	☐	☐
Broken hip	☐	☐	☐
Back pain	☐	☐	☐

If none of the above describe the injuries you suffered, provide further detail about the injuries:

If you have fallen more than three times in the past year, provide further detail below about any injuries you suffered:

Participant ID:

Section 3 – Medication

This section is about the medication you take. If you are unsure how to fill this in, bring a list of all your medication with you to your testing session at Deakin University.

Non-prescription medication:

1. Are you currently taking any non-prescription medication or supplements (vitamin, mineral and herbal type/remedies)? *(Tick one box)*

☐ Yes (provide details below)

☐ No (go to question 2)

If Yes, specify the **NAME** of the medication/supplement, the **DOSE**, the **FREQUENCY**, the **DURATION OF USE** and the **REASON** for using the **NON-PRESCRIPTION** medication(s)/supplement(s).

Name of medication	Dose	Frequency (per day)	Duration of use	Reason for taking medication
<i>Example:</i> Caltrate	<i>Example:</i> 500mg	<i>Example:</i> Once a day	<i>Example:</i> 6 months	<i>Example:</i> Low bone density

Participant ID:

Prescription medication:**2. Are you currently taking any prescription medication? (Tick one box)**☐ Yes (provide details below)☐ No (go to section 4 – sun exposure and habits)

If Yes, specify the **NAME** of the medication, the **DOSE**, the **FREQUENCY**, the **DURATION OF USE** and the **REASON** for using the **PRESCRIPTION** medication(s).

Name of medication	Dose	Frequency (per day)	Duration of use	Reason for taking medication
<i>Example:</i> Lipitor	<i>Example:</i> 20mg	<i>Example:</i> Twice a day	<i>Example:</i> 2 years	<i>Example:</i> High cholesterol