Different continuous glucose monitors provide different personalized meal recommendations to minimize postprandial glucose in subjects without diabetes

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Summary

Precision nutrition often seeks to personalize diets to minimize glycemic responses measured by continuous glucose monitors (CGMs), but do meal recommendations depend on the CGM? We collected 27489 simultaneous measurements from Dexcom G4 Platinum and Abbott Freestyle Libre Pro CGMs in 16 inpatient adults without diabetes and compared glycemic responses to 760 *ad libitum* meals. Overall, Abbott measurements were (mean $\pm$ SE) 12.9 $\pm$ 0.1 mg/dl lower than Dexcom ($p<0.0001$). During 22 oral glucose tolerance tests, Abbott measurements were 12.3 $\pm$ 5.5 mg/dl lower than venous measurements ($p=0.03$) which were not significantly different from Dexcom ($p=0.34$) and the incremental average glucose responses were not significantly different ($p>0.19$). Within-subject meal rankings for incremental glycemic responses were relatively discordant between CGMs such that meals in the bottom versus top half of glycemic responses ranked by Abbott resulted in 50 $\pm$ 10% ($p=0.0002$) less glycemic reduction compared to Dexcom, and vice versa. Therefore, personalized meal recommendations are CGM dependent.

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Introduction

Postprandial glucose is believed to play an important role in health and disease (Blaak et al., 2012; Hall et al., 2018) and precision nutrition approaches are being developed to personalize an individual's diet to minimize postprandial glycemic responses measured using continuous glucose monitors (CGMs) (Mendes-Soares et al., 2019; Zeevi et al., 2015). However, it is unclear to what extent different CGMs provide discordant meal rankings in terms of glycemic response and therefore whether personalized diets might be CGM dependent.

To address this question, we explored CGM data in adults without diabetes who simultaneously wore Dexcom G4 Platinum and the Abbott Freestyle Libre Pro CGM systems during a 28-day inpatient study at the NIH Clinical Center. We previously reported the primary outcome of the study which was the difference in *ad libitum* energy intake between two experimental diets provided in random order for two weeks each (Hall et al., 2019). Here, we explored the simultaneous CGM measurements to investigate whether within-subject meal rankings according to their post-prandial glycemic response were CGM dependent and whether meals chosen to minimize glycemic response using one CGM also minimized the glycemic response as determined by the other CGM.

Methods

We previously reported the primary aim of the present study which was to investigate *ad libitum* energy intake differences between an ultra-processed and unprocessed diet, for 2 weeks each (Hall et al., 2019). The study protocol was approved by the Institutional Review Board of the National Institute of Diabetes & Digestive & Kidney Diseases (NCT03407053). Eligible subjects were between 18-50 years old with a body mass index (BMI) > 18.5 kg/m² and were weight-stable (< ± 5% over the past 6 months) with no history of illness or psychiatric disease, dietary restrictions, and could not be taking prescription medications that could influence metabolism.

The subjects were admitted as inpatients to the Metabolic Clinical Research Unit at the NIH Clinical Center for 28 days. Each subject had two 75 gram oral glucose tolerance tests (OGTTs) performed at the end of each diet period, on study days 14 and 28. After fasting overnight, subjects consumed 75 grams of oral glucose and we compared the CGM measurements to the glucose measurements from venous blood samples at 0, 10, 20, 30, 60, 90, and 120 minutes post consumption.

Twenty subjects wore the Dexcom G4 Platinum, and 16 subjects also simultaneously wore the Abbott Freestyle Libre Pro. Each device consisted of a small sensor, a transmitter, and a hand-held receiver. The sensor was inserted subcutaneously to measure interstitial glucose concentrations which the transmitter would send wirelessly to the receiver. Subjects were blinded to their glucose readings obtained by the monitors. The Dexcom sensor was inserted in the lower abdomen, and sampled glucose levels every 5 minutes. Per manufacturer specifications, the device was calibrated after insertion and each morning and night, using capillary blood finger stick measurements. The sensor was changed every 7 days, following the manufacturer specified lifetime. The Abbott Freestyle Libre Pro was inserted in the back of the upper arm and sampled glucose levels every 15 minutes with a minimum glucose reading of 40 mg/dl. No finger stick calibrations were required, and the sensor was changed after 14 days. Both CGM systems were removed during MRI procedures and the Dexcom was removed for DXA scans once a week. The data for each monitor were downloaded at the end of each inpatient stay.

The 27489 simultaneous CGM measurements were identified by pairing time stamps of two devices with the closest match. The maximum gap within a pair was set to 150 seconds. Not all subjects had simultaneous CGM data during the entire study to scheduling of procedures and sensor lifetime of each monitor. We restricted our analysis to the 16 subjects and time periods with simultaneous data from both CGMs and with post-meal data of at least 105 minutes with a minimum of 7 data points for the

Abbott system and 20 data points for the Dexcom system. We analyzed 760 *ad libitum* meals in 16 subjects and 22 OGTTs from 15 subjects who had simultaneous CGM measurements meeting these criteria. Average postprandial glucose was either the absolute or incremental area under the glucose curves, calculated using the trapezoid rule, divided by the postprandial duration.

Statistical analyses were performed using SAS (version 9.4; SAS Institute Inc, Cary, NC, USA). Kendall rank correlation coefficients were calculated using PROC CORR KENDALL. The data are presented as mean $\pm$ SE. Paired t-tests were used to compare the CGM results and significance was declared at the threshold $p < 0.05$.

Results

We collected CGM data from 7 male and 9 female adult subjects without diabetes aged (mean $\pm$ SE) 31 ± 2 years with body mass index of 26 ± 1.4 kg/m² who simultaneously monitored glucose using the Dexcom G4 Platinum and the Abbott Freestyle Libre Pro systems while they resided for 28 continuous days as inpatients at the NIH Clinical Center. In 15 subjects, we collected simultaneous CGM data during 22 OGTTs and compared their results with venous glucose measurements. We also compared 27489 simultaneous CGM glucose measurements and analyzed the measured glucose responses to 760 *ad libitum* meals.

CGM Measurements Compared with Venous Glucose during OGTTs

Figure 1A shows the mean venous glucose during 22 OGTTs in 15 subjects along with the simultaneous CGM glucose measurements that exhibited a delayed rise, likely due to the physiological delay required for increased blood glucose to elevate interstitial glucose at the site of the CGM sensor. Across all subjects, the average glucose during the OGTTs was (mean $\pm$ SE) 131 ± 4 mg/dl with the Dexcom system which was not significantly different from 126 ± 4 mg/dl using the venous measurements ($p = 0.34$). Compared to the venous measurements, the Abbott CGM resulted in significantly lower average glucose during the OGTTs (113 ± 4 mg/dl; $p = 0.03$) which was also significantly lower than the Dexcom measurements ($p = 0.003$).

The average venous glucose measurements during the OGTTs were significantly correlated with both the Abbott ($r = 0.53$; $p = 0.01$) and the Dexcom ($r = 0.68$; $p = 0.0005$) measurements. However, the CGM measurements during the OGTTs were not significantly correlated with each other ($r = 0.34$; $p = 0.13$).

The average increment above baseline glucose during the OGGTs was 38 ± 3 mg/dl as determined by the venous measurements which was not significantly different from the Abbott (38 ± 3 mg/dl; $p=0.98$) or Dexcom (43 ± 3 mg/dl; $p=0.19$) measurements. Incremental average glucose during the OGTTs were significantly correlated between venous measurements and both Abbott ($r=0.69$; $p=0.0004$) and Dexcom ($r=0.76$; $p<0.0001$) systems which were significantly correlated with each other ($r=0.59$; $p=0.004$).

Comparison of CGM Glucose Measurements during 28 days of Inpatient Ad Libitum Feeding

Figure 1B shows the comparison of the average post-prandial glucose measurements for 2 hours following 760 *ad libitum* meals in 16 subjects, with the Abbott system resulting in lower average glucose after the meals (93.6 ± 0.7 mg/dl) compared to the simultaneously worn Dexcom system (99.8 ± 0.6 mg/dl; $p<0.0001$). However, the average incremental glucose response above baseline following each meal was 1.9 ± 0.4 mg/dl greater using the Abbott as compared to the Dexcom system ($p<0.0001$). Across all 16 subjects, the CGMs provided moderately correlated measurements in terms of both absolute ($r=0.62$, $p<0.0001$) and incremental ($r=0.68$, $p<0.0001$) average glucose following the meals.

We measured 27489 simultaneous CGM glucose values in 16 subjects with both the Abbott and Dexcom systems excluding the OGTT periods. The glucose values were significantly correlated between the CGMs ($r=0.57$; $p<0.0001$) but mean glucose was significantly higher with the Dexcom (93.4 ± 0.12 mg/dl) as compared to the Abbott system (80.5 ± 0.12 mg/dl; $p<0.0001$). Figure 1C shows the Bland-Altman plot comparing the CGM glucose measurements which were 12.9 ± 0.1 mg/dl ($p<0.0001$) lower with the Abbott as compared to the Dexcom system. A small, but significant linear bias was present such that for every 1 mg/dl increment in mean glucose, the Abbott measurements were progressively 0.03 ± 0.006 mg/dl lower than the Dexcom measurements ($p<0.0001$). Interestingly, the mean within-subject discrepancy between the Abbott and Dexcom systems increased significantly with percent body fat ($r=0.56$; $p=0.02$) such that for each 1% increase in body fat the Abbott system resulted in a 0.49 ± 0.19 mg/dl reduction in mean glucose as compared to the Dexcom system.

Variability in postprandial glycemic responses

Postprandial responses to ad libitum meals were highly variable, with the Abbott and Dexcom systems having coefficients of variation of 20.3% and 16.3% for absolute glucose and 89.7% and 95.6% for incremental glucose, respectively. Figure 1D and 1E shows the incremental glucose measurements of an example subject in response to 64

ad libitum meals using the Abbott and Dexcom systems with coefficients of variation of 77.3% and 68.8%, respectively.

Ranking Ad Libitum Meals by CGM glycemic responses

Within-subject concordance of meal rankings according to the glycemic responses measured by the Abbott and Dexcom systems was quantified using the Kendall rank correlation coefficient, where a value of 1 indicates identical meal rankings between CGMs, a value of -1 indicates completely discordant rankings, and a value of 0 indicates an equal number of discordant and concordant rankings. We found a relatively low degree of concordance in the meal rankings between simultaneous CGMs for most subjects with mean Kendall rank correlation coefficients of 0.43 ± 0.05 and 0.31 ± 0.04 for incremental and absolute glucose responses, respectively.

To examine whether the relatively low concordance of meal rankings between CGMs resulted in meaningful glycemic differences as measured by the discordant CGM, we calculated within-subject differences in the average incremental glucose responses to the top versus bottom half of meals ranked by one CGM as compared to the other.

The left column of Figure 2 presents CGM data when meals were ranked according to the Abbott system and the right column shows the results when the same meals were ranked by the Dexcom system. Figure 2A plots the mean incremental glucose response measured by each CGM to the top versus bottom half of 760 meals ranked according to the Abbott system illustrating an average 17.9 ± 1.1 mg/dl difference in incremental glucose as measured by the Abbott system ($p < 0.0001$). Figure 2B shows that when the same meals were ranked by the Dexcom system then the difference in incremental average glucose as measured by the Abbott system was 10.7 ± 1.6 mg/dl ($p < 0.0001$) which was significantly lower than when the meals were ranked by the Abbott system ($p < 0.0001$).

Conversely, Figure 2C shows that the mean incremental glucose measurements obtained by the Dexcom system in response to the high and low ranked meals according to the Abbott system. The difference in average incremental glucose was 10.7 ± 2.0 mg/dl ($p < 0.0001$). Figure 2D shows the mean Dexcom incremental glucose measurements in response to meals ranked by the Dexcom system and illustrates the 17.9 ± 0.9 mg/dl difference in average glucose between high and low ranked meals ($p < 0.0001$) which was significantly greater than the difference when measured by the Abbott system ($p < 0.0001$).

Figures 2E and 2F show that the mean incremental glucose differences measured by the Abbott system between top and bottom ranked meals according to Abbott were greater than the difference in incremental glucose determined by the Dexcom system, and vice versa. Therefore, personalized meal recommendations determined by one CGM did not result in similar degree of incremental glucose lowering as determined by the other simultaneously worn CGM in the same subjects consuming the same meals.

We quantified the missing fractional reduction in glycemic response missed by ranking meals based on the discordant CGM as follows:

$$Max \left\{ 1 - \frac{(A_{top} - A_{bottom})_{\text{ranked by D}}}{(A_{top} - A_{bottom})_{\text{ranked by A}}}, 1 - \frac{(D_{top} - D_{bottom})_{\text{ranked by A}}}{(D_{top} - D_{bottom})_{\text{ranked by D}}} \right\}$$

where A_{top} and D_{top} are the average within-subject glucose response (either absolute or incremental) measured by the Abbott and Dexcom systems, respectively, to the top half of ranked meals, A_{bottom} and D_{bottom} is the average within-subject glucose response measured by the Abbott and Dexcom systems, respectively, to the bottom half of ranked meals. The subscript “ranked by A, D” refers to whether the Abbott or Dexcom system was used to rank the meals by their glycemic response. The mean fraction of missing glycemic reduction determined by discordant CGMs was $50 \pm 10\%$ ($p=0.0002$) and $61 \pm 6\%$ ($p<0.0001$) with respect to the incremental and absolute glucose responses, respectively. The missing glycemic reduction according to discordant CGM was inversely correlated with each subject’s Kendall rank correlation coefficient for both incremental ($r=-0.95$; $p<0.0001$) and absolute ($r=-0.93$; $p<0.0001$) glucose responses.

The Abbott system measured 3.4 ± 0.6 mg/dl higher average incremental glucose in response to meals ranked low by the Dexcom system as compared to the meals ranked low by the Abbott system ($p<0.0001$). Similarly, the Dexcom system measured 3.4 ± 0.8 mg/dl higher incremental glucose in response to the lower half of meals ranked by the Abbott system as compared to the meals ranked lowest by the Dexcom system ($p=0.001$). The average absolute glucose response measured by the Dexcom system to the lower half of meals ranked by the Dexcom system was 5.0 ± 0.4 mg/dl lower than when the meals were ranked by the Abbott system ($p<0.0001$). When measured with the Abbott system, the average absolute glucose response to the lower half of meals ranked by the Abbott system was 4.3 ± 0.5 mg/dl lower than when the meals were ranked by the Dexcom system ($p<0.0001$).

Discussion

The Abbott CGM system provided absolute glucose measurements that were systematically lower than simultaneous measurements obtained from the Dexcom system and the discrepancy was correlated positively with the percent body fat of the participants. This may have been due to the different anatomical locations of the CGM sensors and the role of subcutaneous fat influencing interstitial glucose. The average glucose responses during OGTTs measured by the Dexcom system were not significantly different from the venous blood measurements, but the Abbott system measurements were significantly lower. However, the mean incremental glucose response to meals and OGTTs were generally comparable between the devices.

Different ad libitum meals resulted in a wide range of postprandial glucose responses regardless of the CGM. However, the within-subject rankings of the same meals according to one CGM did not necessarily correspond to the rankings measured simultaneously by the other CGM. We found substantial differences in glycemic response that depended on the CGM used to make the meal rankings. The difference in glycemic response between the top half of meals compared to the bottom half of meals ranked by one CGM was significantly greater than the glycemic differences measured simultaneously by the other CGM.

Precision nutrition approaches are being developed to personalize an individual's diet to minimize CGM measured glycemic responses to meals (Mendes-Soares et al., 2019; Zeevi et al., 2015). An implicit assumption that has not previously been investigated is that the ranking of an individual's meals by glycemic response is relatively independent of the CGM used to make the measurements. Our results suggest that this assumption may be incorrect and therefore precision nutrition approaches seeking to personalize meals to minimize glycemic responses via one CGM do not necessarily recommend the same meals according to another CGM in adults without diabetes.

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Declaration of Interests

The authors have no conflicts of interest.

Figure Legends

Figure 1. Comparison of simultaneous measurements using the Abbott and Dexcom continuous glucose monitors. A) Mean glucose responses in 15 subjects during 22 oral glucose tolerance tests obtained from simultaneously worn Abbott and Dexcom devices along with venous glucose measurements. B) Mean glucose responses obtained from simultaneously worn Abbott and Dexcom devices to 760 ad libitum meals in 16 subjects. C) Bland Altman plot of 27489 simultaneous CGM measurements using the Abbott and Dexcom devices during 28 days of inpatient ad libitum feeding in 16 subjects. The solid line indicates the mean difference and the dashed lines indicate the limits of agreement ($1.96 \times$ standard deviation of the residuals). D) Abbott glucose measurements in an example subject consuming 64 ad libitum meals. E) Dexcom glucose measurements simultaneously obtained in the same subject.

Figure 2. Abbott and Dexcom systems result in differing personalized meal recommendations and differing glycemic reductions. A) Mean Abbott glucose responses to the high versus low ranked half of 760 personalized meals ranked by the Abbott system. B) Mean Abbott glucose responses to the high versus low glycemic meals ranked by the Dexcom system. C) Mean Dexcom glucose responses to the high versus low glycemic meals ranked by the Abbott system. D) Mean Dexcom glucose responses to the high versus low glycemic meals ranked by the Dexcom system. E) Difference between the Abbott and Dexcom measured glucose responses between personalized high versus low glycemic meals ranked by the Abbott system. F) Difference between the Abbott and Dexcom measured glucose responses between personalized high versus low glycemic meals ranked by the Dexcom system.

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Figure 1

Figure 2