1 COVID-19 complex interplay between ACE2 polymorphisms and the apelinergic peptide
2 system: potential tools for risk stratification and therapy.

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8 Abstract:

9 ACE2 polymorphisms have been previously linked to increased susceptibility to multiple
10 diseases and are currently linked to SARS CoV-2 susceptibility and complications.
11 Notably, ACE2 transcribed or regulated proteins include the activity of metalloproteinase-
12 2 and apelin-13 and 36, might be linked to abnormal immune responses and complications.
13 Furthermore, potential genetic or serological tests might be developed to detect the higher
14 vulnerable groups to SARS CoV-2 complications and/or mortality. Furthermore, we
15 hypothesize that diabetic and obese patients suffer from exhausted and/or abnormally
16 functioning apelinergic peptides that predispose them to a higher severe COVID-19 risk.
17 Moreover, infusion of apelin-13 to treat selected critical cases of COVID-19, especially
18 those complaining of refractory advanced heart failure, might be considered for clinical
19 trials.

20 Keywords:

21 COVID-19, SARS CoV-2, ACE2 polymorphisms, the apelinergic system, apelin-13.

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Introduction: ACE2 polymorphisms involvement in health and disease

Several studies have demonstrated that the expression, polymorphism and/or mutations in the receptor binding domain of ACE2, the cell entry receptor of SARS CoV-2, could influence both the susceptibility of people and populations to SARS CoV-2 infection as well as the potential clinical manifestations and outcomes of COVID-19[1-4]. For instance, a study showed that East Asian populations have a much higher ACE2 allelic fraction in expression quantitative trait loci variants which may suggest different susceptibilities or response to SARS CoV-2 from other populations [5]. Interestingly, ACE2 polymorphisms and their induced mutations have been previously linked to enhanced susceptibility to heart diseases including coronary heart disease and myocardial infarction as have been revealed both clinically and experimentally[6,7]. Importantly, the ACE2 rs4646188 variant was suggested as a potential and optimal genetic susceptibility marker for essential hypertension, dyslipidemia and its related ischemic stroke[8]. Similarly, three other ACE2 variants (rs4240157, rs4646155, and rs4830542) were found to be associated with essential hypertension and hypertension-related atrial fibrillation and left atrial remodeling[9]. Moreover, genetic variants in the ACE2 gene have been suggested to be associated with left ventricular mass, septal wall thickness and left ventricular hypertrophy in hemizygous men[10] and genetic variants in the ACE2 gene were significantly associated with diastolic blood pressure responses to cold stress in the Chinese female population[11]. Interestingly, ACE2 was previously suggested to protect against acute lung injury together with a call to explore related potential therapeutics[12] and ACE2 expression was correlated to an age-dependent decrease, and a highly significant decrease was also shown in type II diabetic patients, and it was also negatively correlated with virus infection pathways that might also reason for its correlation with other viruses that do not use ACE2 as a receptor including HSV1, HIV or HPV [13]. However, it should be always considered that a wide individual variation in ACE2 activities within the different age groups can interfere with the possibility to detect a clinically relevant age-related difference[14]. Thus, thorough exploration of ACE2 polymorphisms in several diseases including our main research subject; COVID-19 might eventually help to save lives, especially those belonging to the minority of idiosyncratic complications and/or mortality encountered in young and otherwise healthy patients, including health care professionals.

ACE2 polymorphisms might determine the immune response and outcomes of COVID-19

Notably, ACE2 was suggested to regulate the immune response in SARS and SARS CoV-2 through several mechanisms [15] and it is currently known that a dysregulated immune response is crucial for COVID-19 development[16]. Interestingly, multiple ACE2 variants and mutations were suggested to be correlated with COVID-19 susceptibility e.g. rs73635825 which is common in the African population and rs4646116 which is common in the European population[17]. Moreover, a study showed that six out of ten eQTL variants in ACE2 have been associated with altered ACE2 tissue expression and linked with the need for hospitalization due to COVID-19, suggesting that ACE2 genotype may inform both COVID-19 risk stratification and the need for more intense therapy[18]. Furthermore, a significant ACE2-mRNA expression was observed in the classical human monocyte subpopulation (CD14⁺⁺CD16⁻ cells)[19], thus, a variable immune response associated with some ACE2 variants might prove beneficial when thoroughly examined. Taken together, it is likely that ACE2 polymorphisms might explain at least some cases of the otherwise unexplained COVID-19 induced mortality encountered in some healthy adults/health care professionals[20].

Potential COVID-19 risk stratification basing on the apelinergic peptide system

Interestingly, several apelin peptides have been shown to inhibit human immunodeficiency virus into cells expressing the G protein coupled apelin receptor to which they act as endogenous ligands [21,22] and upregulation of apelin expression was recently shown to share in complete or partial abolishment of excessive pulmonary inflammation after experimental ARDS[23]. Interestingly, apelin-13 has been shown to act as a positive regulator of ACE2 mRNA transcription[24] and it is well established that downregulation of ACE2 receptors triggers important inflammatory lesions in the respiratory tree and has been suggested to play a central role in the pathogenesis of SARS-CoV-2 infection[25,26]. Moreover, a negative correlation between ACE2 expression and COVID-19 fatality at both the population and molecular levels has been shown [13]. Thus, we recommend exploring our suggested hypothesis to detect potential variant ACE2 alleles and their suggested altered abnormal expression and/or activity of some transcribed/regulated proteins

including metallopeptidase-2 activity[27] and apelin-13 and apelin-36 peptide cleavage and/or degradation [26,28] suggesting that abnormal levels and or activities are likely to be discovered with an ultimate aim to develop genetic tests to detect potential variant ACE2 alleles as well as serological tests to detect these abnormal suggested associated proteins leading to risk stratification of patients (Figure 1). Furthermore, besides the serological tests, testing the bronchial lavage and/or examining specimens obtained from CT guided lung biopsies or autopsies might be also considered to directly examine those potential markers in situ in their milieu to be compared in different groups of COVID-19 patients and we recommend to start first with those considered COVID-19 high risk groups examining their ACE2 apelin interplay. Notably, we hypothesize that obese and diabetic patients suffer from exhausted and/or abnormally functioning apelinergic peptides and this might also partly reason for their higher severe COVID-19 risk [29,30].

Potential apelin-13 therapy for selected critical COVID-19 patients

Interestingly, apelin peptides were suggested to ameliorate acute lung injury by several mechanisms that are also associated with COVID-19 associated acute respiratory distress syndrome[31] and apelin-13 continuous infusion at 1 mg/kg/d by an osmotic pump upregulated ACE2 expression, improved heart functions and reduced heart weight in AT1R-deficient mice under transverse aortic constriction[24] and we recommend testing apelin-13 infusion for selected critical cases of COVID-19, especially for those complaining of refractory advanced heart failure not responding to other drugs; we suggest that those cases considered terminal deserve a final trial as the potential benefit is opposed by no risk considering their situation. Finally, we would like to recommend a continuous exploration of this type of COVID-19 related genetic research even if a valid cure and/or vaccine has been developed for the current pandemic as we should prepare better to the upcoming ones.

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115 **Conflicts of interest/Competing interests**

116 The author declares no competing interests

117 **Availability of data and material**

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Figure (1): Potential diagnostic and therapeutic tools out of the ACE2 polymorphisms
apelinergic peptide system interplay

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