Review Article

The Susceptibility of Healthy People to COVID-19 Infection and the Role of ACE2

Mehdi Kushkestani*, Mohsen Parvani, Bakhtyar Tartibian and Rasoul Eslami

Faculty of Physical Education and Sport Sciences, Allameh Tabatabai' University, Tehran, Iran

Abstract

The COVID-19 virus has caused many deaths of people worldwide since the pandemic began. However, no definitive treatment for this infection has been discovered so far. It has been shown that comorbidities such as diabetes, hypertension and cardiovascular diseases are associated with an increased risk of SARS-COV-2 infection. Interestingly, SARS-COV-2, like SARS-COV, uses the ACE2 gene to enter the host cell. Also, changes or imbalance in ACE2.ACE can affect SARS-COV-2 susceptibility, related outcomes and mortality. Regarding the crucial role of ACE2 protein in COVID-19 infection, the effect of different factors such as age, BMI, physical activity levels, nutritional status, altitude, as well as blood group was assessed on the level of this protein. Further, to our knowledge, no study has been conducted to examine factors that increase or decrease the risk of COVID-19 and its related severity and outcome in normal subjects emphasizing the pivotal role of ACE2. Therefore, the primary purpose of this study was to investigate the involved mechanisms of ACE2 protein and other risk factors causing infection in different situations and finally, to introduce a safe, accurate, and cost-effective approach to prevent SARS-COV-2 infection and hard clinical outcomes in normal subjects.

Keywords: Blood group antigens, Body mass index, COVID-19, Nutritional status, SARS-CoV-2

* Corresponding author

Mehdi Kushkestani, MSc
Faculty of physical Education and Sport Sciences, Allameh Tabatabai University, Tehran, Iran
Tel: +98 21 7786 3362
Fax: +98 21 7786 3362
Email: mehdi.kushk@gmail.com

Introduction

The 2019 novel coronavirus (2019-nCoV) was recently named SARS-CoV-2 by the World Health Organization (WHO). The disease caused by SARS-CoV-2 has been named COVID-19 (1). Recent studies have shown that the Renin-Angiotensin System (RAS) plays major physiological roles in the respiratory system and two axes of ACE2/ANG1-7/MAS Receptor and ACE/ANG2/AT1 are the main parts of this system and the balance between the function of these two axes is very crucial (2), because ACE2 is expressed in various human tissues including the lungs, serving as the doorway by which the virus can enter and spread (3). However, it should be noted that there are two kinds of ACE2, the full-length and the soluble. The soluble type of ACE2 does not have the membrane anchor and circulates in small amounts in the blood (4). The full-length type, expressed in various tissues like the lungs, affects the connection between SARS-COV-2 and the RAS system, because it includes a structural transmembrane domain that operates as the receptor for the SARS-COV-2 spike protein which simplifies the entry of the virus into host cells, viral replication and cell-to-cell transmission (4,5). The interaction with the SARS-CoV-2 would result in a diminished ACE 2 enzymatic activity, an imbalance favoring the ANG II and AT1R axis and virus-induced lung injury (6). Among cases infected with SARS-CoV-2, various conditions have been associated with increased virus susceptibility and the burden of COVID-19.

Recently, it has been reported that there is a robust association between obesity, age, sex, physical fitness status, vitamin D levels, living at high altitude and specific blood group with the risks, clinical consequences [Hospitalization or needing treatment in Intensive Care Units (ICUs)] and mortality of COVID-19 infection (7-16). Interestingly, the expression of the ACE2 protein (SARS-COV-2 receptor) is very different in the mentioned groups. For example, the level of ACE2 in the normal elderly is lower than younger people (17,18) or physical training and hypoxia may increase ACE2 levels in people (19,20). Moreover, some differences in this protein are related to biological inheritance. It has well established that ACE2 levels are higher in men than in women (17,21). Besides, type A blood was a risk factor for getting COVID-19 while O blood type had a protective effect (22,23).

Regarding the recent evidence about COVID-19 susceptibility and outcomes in mentioned subjects, the crucial role of ACE2 protein in SARS-COV-2 infection and the variety of ACE2 expression levels in these people, it can be assumed that changes or imbalance in ACE2/ACE levels can affect COVID-19 susceptibility and outcomes in these subjects. Therefore, the primary purpose of this study was to investigate the relationship between ACE2 protein and other risk factors of the disease in different conditions and finally introduce a safe, accurate and cost effective approach to prevent SARS-COV-2 infection and hard clinical outcomes in normal subjects.

Materials and Methods

Data collection

Three electronic data bases of google scholar, Pub Med/MEDLINE and EMBASE were comprehensively evaluated (From its earliest inception to November 20,2020) using keywords including combination of "SARS-COVID-2", "COVID-19 and ACE2", "RAAS system and COVID-19", "SARS-COVID-2 risk factors", "High risk COVID-19 patients and "COVID-19 susceptibility". All articles published in English were evaluated and references of selected papers were scrutinized to find other relevant papers.

Inclusion and exclusion criteria

In this narrative review, studies reporting the following items were included: (1) epidemiological research about COVID-19 in normal subjects, (2) ACE2 alterations in COVID-19 patients, (3) high and low risk subjects with COVID-19 and (4) severity and mortality rate of COVID-19 in mentioned groups. Our exclusion criteria were: (1) case reports, (2) articles published in languages except English, (4) pieces of correspondence, (5) local studies and (6) retracted papers. Further, an attempt was made to minimize the possibility of including patients from the same population twice when exploring one outcome.

Screening and data extraction

Two researchers independently screened titles, abstracts and full-text articles and selected potentially eligible studies. Data extraction was duplicated for all articles by an independent researcher (CN). Totally, 101 articles (original and review) were eligible regarding

the aforementioned criteria. Eventually, after review of full-texts and results and based on the objectives of the research, 93 articles were selected as shown in figure 1.

addition, 8 articles were excluded following full-text review (Not matched with the purpose of study) and finally 93 papers were selected as the final sample.

Results

Experimental components of the papers are shown in figure 1; in general, 162 articles were initially identified from the databases. After removing case studies (1), duplicates (2) and conference papers (7), 152 papers were selected for this review. Then, 37 articles were excluded after the title review and 14 articles were excluded after the abstract review. In

Discussion

Regarding the criteria and the selected articles in this review paper, at first, susceptibility of COVID-19 in various normal subjects was evaluated. Then, the involved mechanisms in progression or inhibition as well as severity and mortality of this infection in mentioned groups were described. Table 1 demonstrates all the procedures.
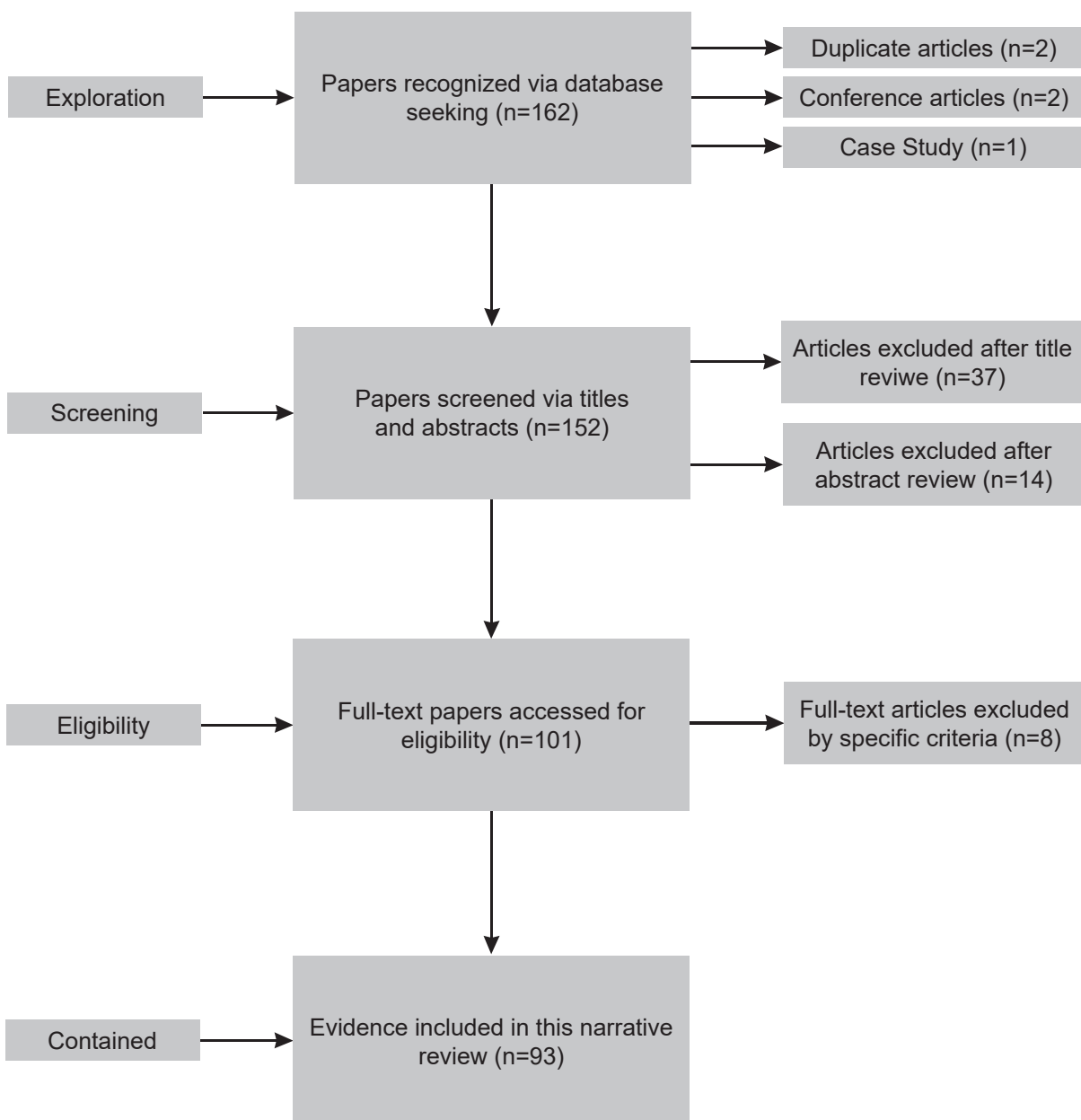

Figure 1. Steps of article check and selection.

Obesity

The prevalence of overweight or obese individuals in different countries is greater than 20% (24). The association between overweight and obesity with risk of COVID-19 (9,25,26) and related severity, outcomes and mortality was documented (27-30). Obesity is connected in humans and experimental animals with an irregularity in the RAAS system resulting in an overexpression of the ANG II and AT1R axis at the systemic level (31) and in adipose tissue (32). ACE 2 is expressed in adipose tissue and mainly in visceral adipose tissue rather than peripheral subcutaneous tissue (33). Consequently, obese individuals, especially those with increased visceral adipose tissue mass could develop an explosive systemic response with an increased ANG II and AT1R axis and a huge viral load which likely contributes to the development of a more severe form of the disease (2). Also, the underlying metabolic and inflammatory factors in obesity play a noteworthy role in the manifestation of severe lung diseases. Susceptibility to Acute Respiratory Distress Syndrome (ARDS), the primary cause of COVID-19 mortality, is significantly higher among individuals with obesity (29,34). It should be noted that obesity independently boosts the risk of influenza morbidity and death, likely by impairing innate and adaptive immune responses (35). Furthermore, since the adipose tissue is the main source of inflammatory molecules, including IL-6, it can exacerbate the COVID-19 (35).

Aging

According to an initial clinical report including 138 COVID-19 cases in Wuhan (36), patients admitted to the in ICU were older than non-ICU patients. In a study including 52 critically ill patients in Wuhan, the average age of non-survivors was 64.6 years

Table 1. The cases mentioned in this article are summarized

ACE2	Susceptibility to Covid-19	Severe outcomes	Subjects	References
Increase (Compensatory)	Increase	High	Obese	(2,11–16,20,21)
Decrease (compensatory)	Contradictory evidence	High	Elderly	(12,16,36-50)
Increase (physiological adaptation)	Not-established	Not-stablished	Athletes	(19,20,58-65)
Not established	Increase (Stronger references)	High (Most of the references)	Vitamin D deficiency	(66-80)
Higher in men (Physiological)	Higher in men	Higher in men	Gender	(21,50-57)
Decrease (physiological) (Stronger references)	Decrease (Stronger references)	Low (Stronger references)	people living in high altitude	(8,15,81-87)
Decrease in O and increase in A blood group	Decrease in O blood group and increase in A blood group	Higher in A blood group and Lower in O blood group	Blood group (A and O)	(22,23,88-93)

(37). Another recent study also showed that old age is a risk factor for in-hospital mortality (38). All these investigations propose the elderly are more susceptible to COVID-19 and likely to have poor outcomes (16,39,40). Remarkably, while aging is associated with many diseases, including geriatric syndrome, healthy older adults are also more likely to have severe outcomes after COVID-19 infection (12,39,41-43). Also, aging itself has been greatly linked with worse outcomes, because of the pathophysiological alterations that characterize the respiratory system (44). It has been reported that there is an age-related decline in the clearance of inhaled particles in the small airway region, which seems to be a determining factor for the huge pervasiveness of respiratory symptoms amongst the elderly (45). Also, a progressive and relatively linear increase in nasal cavity volume with aging coupled with an age-dependent reduction of nasal resistance might represent the determinants for a higher prevalence of COVID-19 in elderly population (46). Moreover, novel data shows that while younger subjects may be more prone to infection, lower levels of ACE2 in older cases may prompt more severe clinical behavior of COVID-19 (47), so that ARDS was seen in the preponderance of patients (96.8% of cases) dying in hospitals (47). Immunosenescence represents a recognized characteristic of aging (48). Older adults exhibit a perpetual production of inflammatory mediators and cytokines, also known as 'inflamm-aging' (49). Accumulating researches have reported worse outcomes related to the presence of an excessive number of cytokines and inflammation mediators in SARS-CoV-2 infected patients. On the other hand, in early studies, the impact of weakening immune system responses to viral infections in older adults has been widely reviewed. An inverse relationship between CD4/CD8 T-cell ratio and increasing frailty has been summarized and also the amount of circulating 'competent' B cells has significantly declined with aging (50).

Gender

It has been reported that male gender is a risk factor for higher severity and mortality in patients with COVID-19, independent of age and susceptibility (50). Regarding the most extensive body of publicly accessible sex-disaggregated data from international reports, although no apparent sex diversity exists in the number of confirmed cases, more men than women have died of COVID-19 in 41 out of 47 countries (51) and the overall COVID-19 case-fatality ratio is around 2.4 times greater amongst men than women. A paper on 3,200 COVID-19 related deaths from Italy noted higher death rates among men than women irrespective of age groups, with men accounting for more than 70% of deaths (52). In another research, it was shown that men and women had the same susceptibility, but men were more prone to dying. Jin *et al* reported that men with COVID-19 are more at risk for worse outcomes and death regardless of age (53). As mentioned, ACE2 protein is an essential factor for entry of coronaviruses into host cells. It has been shown that circulating ACE2 levels are higher in men than in women (21). This could explain why men might be more susceptible to infection with/as a consequences of COVID-19 (54). On the other hand, men and women vary in both innate and adaptive immune responses, conceivably due to sex-specific inflammatory responses as a result of X-chromosomal inheritance. Hence, women (high density of immune-related genes) commonly mount more robust innate and adaptive immune responses than men which are related to differences in sex chromosome genes and sex hormones such as progesterone and estrogen (52). Moreover, compared with women, men tend to engage in more high-risk behaviors such as psychological and social ones that results in developing COVID-19 (55). For example, risky behaviors in men like tobacco use and alcohol consumption more likely increase the chance of COVID-19 infection (54). Further, men observe preventive measures of handwashing, social distancing, wearing masks, seeking medical care less than women (56,57).

Athletes

It has been well established that exercise can influence the risk of infection by its immunity-enhancing and immunosuppresive effects (58). Also, exercise can modulate the ACE2-ANG (1-7) Mas receptor axis while suppressing the ACE-ANG II-AT1 receptor pathway (19,59). In other words, regular exercise can increase the level of ACE2 and decrease the level of ANG2 in athletes or active people (20,58,60).

Therefore, athletes and people who regularly exercise and do physical activity indicate less complications and severe symptoms of SARS-COV-2 such as dyspnea, hospitalization, heart disease and mortality owing to high concentration of ACE2 and lower levels of angiotensin 2 as the leading cause of adaptation to exercise. Consist with our statement and mentioned evidence, the results of one original study examining the relationship of exercising and COVID-19 infection showed that from 1701 athletes in various fields who participated in study, just 99 (5%) suffered from SARS-COV-2 and interestingly from 99 athletes just 4 (5%) cases experienced hospitalization. More importantly, the rate of hospitalization was less than half of the expected rate (61). On the other hand, based on open window theory, athletes or individuals who do high intensity exercise are more susceptible to infection (12,58,62) because of immune system suppression. In contrast, there are no studies as of today that show the correlation between strenuous exercise and hard clinical events (61,63). Moreover, some studies have shown that athletes have greater anti-inflammatory and immunological response and respiratory infection rate is low among them (64,65). Therefore, regarding the mentioned evidence in this part and single original paper conducted in the field, it can be concluded that athletes are less susceptible to SARS-COV-2 and related hard clinical outcomes.

Vitamin D status

The important role of vitamin D in the immune system and its association with various diseases including systemic infections has already been established (66,67). The results of a meta-analysis revealed that serum 25(OH)D levels below 50 *nmol/l* (*i.e.*<20 *ng/ml*) increases the risk of community-acquired pneumonia up to 64% (68), Thus, a hypothesis has been put forward that vitamin D deficiency can increase the severity of COVID-19 infection as well as the mortality rate in these individuals (69,70). The association between vitamin D levels and the severity of COVID-19 mortality has already been reported in several retrospective studies (71,72). Vitamin D follows different mechanisms in reducing the risk of viral infections including COVID-19 and its resulting mortality; these mechanisms include maintaining cell junctions and gap junctions, increasing cellular

immunity by decreasing the cytokine storm with an influence on interferon γ and tumor necrosis factor α and regulating adaptive immunity through inhibiting T helper cell type 1 responses and stimulating T cells (69). On the other hand, some studies suggest that vitamin D deficiency strengthens the RAS (73), which can in turn increase the severity of COVID-19 outcomes (74). In the meantime, there is strong evidence that vitamin D supplementation can mitigate the risk of acute respiratory tract infection (75,76). In other words, analysis of data collected from COVID-19 patients in 20 European countries showed that although there is no significant correlation between serum 25(OH)D levels and COVID-19 mortality rate, the incidence of COVID-19 is significantly correlated with serum 25 (OH) D levels (77). Nevertheless, some reports in this regard are mostly contradictory. The results of other studies revealed that the severity of COVID-19 is not correlated with serum 25 (OH) D levels (78,79).

Also, the results of a recent study carried out using the data collected from various regions of the world showed a 15% reduction in severe outcomes of COVID-19 in people with normal serum 25 (OH) D levels (71). Finally, despite uncertainties in this regard, researchers have recommended the use of vitamin D supplementation to prevent the incidence and severe outcomes of this infection. This is particularly crucial during winter and for people who are less exposed to sunlight. It has generally been reported that vitamin D supplementation should be taken into account to maintain a normal circulating levels of 25 (OH) D (75-125 *nmol/L*) (80). However, it should be noted that consuming vitamin D is dependent on geographical area and the health status of individuals.

High altitude

Over 140 million people worldwide live at high altitudes (>2500 *m*) (81,82); the physiological adaptations that are generated in these people can affect the risk of various diseases, including respiratory infections. Noteworthy, the results of an epidemiological study showed that people who live at high altitudes are less susceptible to developing COVID-19 (8). Xi *et al* reported the prevalence of COVID-19 in people dwelling at high altitudes is low probably because of hypoxia-induced physiological adaptations. Besides other factors such as ethnic and

genetic population differences, environmental factors about viral transmission, social structure and norms contribute to infection with COVID-19 (83). Further, the change in ACE2 expression in various tissues that are affected by hypoxia is one of the most momentous elements that can affect individuals' susceptibility to COVD-19 at high altitudes. There are considerable controversies and differences in the results of conducted studies in this field. Some researchers suggested an increase and decrease in ACE1 and ACE2 expression, respectively, as a result of residence at high altitudes after a few days, while other researchers have reported conflicting results (15). Although long-term exposure to hypoxia can theoretically reduce ACE2 expression in various tissues, changes in ACE2 expression in the airway epithelium of individuals living (born and raised) at high altitudes have not been established in any study so far (15). Interestingly, Dang *et al* have recently stated that exposure to an altitude of 2800 *m* for 28 days can lead to decrease of ACE2 expression in the heart tissue of male rats (84). Following the finding of this study, several researchers also reported that this problem can affect the expression of ACE2 in pulmonary epithelial cells and the susceptibility to and risk of COVID-19 infection among people dwelling at high altitudes would be reduced (85-87). Finally, it should be noted that considering the wide range of factors that can affect the susceptibility of individuals to COVID-19, more extensive researches should be carried out with a focus just on the role of altitude-induced physiological adaptations among people living in these areas as well as among people who regularly come to these areas.

Blood group
The relationship between blood group and the risk of infectious diseases such as Norwalk virus and Helicobacter pylori infection has been proven (23). Interestingly, some studies have found an association between ABO blood group and the risk COVID-19 and severe outcomes (88,89). Pourali *et al* in 2020 reported that A blood type was a risk factor for getting COVID-19 while O blood type had a protective role and B and AB didn't show any significant relationship with COVID-19 (23). Guillon *et al* reported that S protein expressed by A-positive infected cells shares epitopes of A histo-blood group, and so adhesion of S

protein and ACE2 can be suppressed *via* anti-A normal antibody. The anti-B and anti-A natural antibodies being generated in subjects with O blood type could potentially suppress viral adhesion to cells leading to decreased risk of COVID-19 infection (90); also, since SARS-CoV and SARS-CoV-2 are from the same genus, the similar mechanism might show less susceptibility of O blood type to this disease (23). Also, individuals with O blood type have a lower level of ACE unlike A blood type (91) and the positive relationship between ACE level with hypertension (one of the risk factor of COVID-19) (92) can justify the lower rate of COVID-19 among individuals with O blood type and higher rate of COVID-19 among individuals with A blood type. On the other hand, it has been shown that SARS-CoV-2 attaches to the carbohydrates that specify the ABO blood groups, which are extensively expressed in mucous membrane of respiratory tract; therefore, AB blood group has maximum connection and O blood group the minimum connection with the pathogen (22,93). Furthermore, a research conducted by Dai manifested A blood group antigens have more adhesion molecules that are attached on the vascular wall and they protect P-selectin and Intercellular Cell Adhesion Molecule 1 (ICAM-1) from cleavage which enhance inflammation and adhesion and consequently cause severe SARS-COV-2 infection (91).

Conclusion
Regarding the increased risk of COVID-19 disease and its consequences in the elderly, obese individuals, and men, recommending special and unique preventive measures such as social distancing, maintaining good personal hygiene, as well as doing sufficient physical activity or regular exercise are very important to prevent and reduce the severity of COVID-19 and related mortality. Besides, in order to control this infection and increase immune functions in mentioned groups, doing regular moderate-intensity exercise seems to be the most beneficial solution.

Acknowledgements

Conflict of Interest
The authors declare no conflict of interest, financial or otherwise.

References

1. Ashour HM, Elkhatib WF, Rahman M, Elshabrawy HA. Insights into the recent 2019 novel coronavirus (SARS-CoV-2) in light of past human coronavirus outbreaks. Pathogens 2020;9(3):186.

2. Iannelli A, Favre G, Frey S, Esnault V, Gugenheim J, Bouam S, et al. Obesity and COVID-19: ACE 2, the missing tile. Obes Surg 2020 Nov;30(11):4615-7.

3. Al-Benna S. Association of high level gene expression of ACE2 in adipose tissue with mortality of COVID-19 infection in obese patients. Obes Med 2020;19:100283.

4. Li G, He X, Zhang L, Ran Q, Wang J, Xiong A, et al. Assessing ACE2 expression patterns in lung tissues in the pathogenesis of COVID-19. J Autoimmun 2020;112:102463.

5. Wysocki J, Ye M, Rodriguez E, González-Pacheco FR, Barrios C, Evora K, et al. Targeting the degradation of angiotensin II with recombinant angiotensin-converting enzyme 2: prevention of angiotensin II–dependent hypertension. Hypertension 2010;55(1):90-8.

6. Vaduganathan M, Vardeny O, Michel T, McMurray JJ, Pfeffer MA, Solomon SD. Renin–angiotensin–aldosterone system inhibitors in patients with Covid-19. N Engl J Med 2020;382(17):1653-9.

7. Apicella M, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Del Prato S. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. Lancet Diabetes Endocrinol 2020;8(9):782-92.

8. Arias-Reyes C, Zubieta-DeUrioste N, Poma-Machicao L, Aliaga-Raudan F, Carvajal-Rodriguez F, Dutschmann M, et al. Does the pathogenesis of SAR-CoV-2 virus decrease at high-altitude? Respir Physiol Neurobiol 2020;277:103443.

9. Belančić A, Kresović A, Rački V. Potential pathophysiological mechanisms leading to increased COVID-19 susceptibility and severity in obesity. Obes Med 2020;19:100259.

10. Ebadi M, Montano-Loza AJ. Perspective: improving vitamin D status in the management of COVID-19. Eur J Clin Nutr 2020;74(6):856-9.

11. Filgueira TO, Castoldi A, Santos LER, de Amorim GJ, de Sousa Fernandes MS, de Lima do W, et al. The relevance of a physical active lifestyle and physical fitness on immune defense: mitigating disease burden, with focus on COVID-19 consequences. Front Immunol 2021;12:150.

12. Kushkestani M, Parvani M, Teixeira AM. Physical activity is a preventive factor against SARSCOV-2 in healthy subjects (possible cellular and molecular mechanisms). Biomed J Sci Tech Res 2020;29(3):22429-36.

13. Lanham-New SA, Webb AR, Cashman KD, Buttriss JL, Fallowfield JL, Masud T, et al. Vitamin D and SARS-CoV-2 virus/COVID-19 disease. BMJ Nutr Prev Health 2020;3(1):106-10.

14. Popkin BM, Du S, Green WD, Beck MA, Algaith T, Herbst CH, et al. Individuals with obesity and COVID-19: A global perspective on the epidemiology and biological relationships. Obes Rev 2020;21(11):e13128.

15. Pun M, Turner R, Strapazzon G, Brugger H, Swenson ER. Lower incidence of Covid-19 at high altitude: facts and confounders. High Alt Med Biol 2020;21(3):217-22.

16. Zheng Y, Liu X, Le W, Xie L, Li H, Wen W, et al. A human circulating immune cell landscape in aging and COVID-19. Protein Cell 2020;11(10):740-70.

17. Chen J, Jiang Q, Xia X, Liu K, Yu Z, Tao W, et al. Individual variation of the SARS-CoV-2 receptor ACE2 gene expression and regulation. Aging Cell 2020;19(7):e13168.

18. Xudong X, Junzhu C, Xingxiang W, Furong Z, Yanrong L. Age-and gender-related difference of ACE2 expression in rat lung. Life Sci 2006;78(19):2166-71.

19. Heffernan KS, Jae SY. Exercise as medicine for COVID-19: An ACE in the hole? Med Hypotheses 2020;142:109835.

20. Nunes-Silva A, Rocha GC, Magalhaes DM, Vaz LN, Salviano de Faria MH, Simoes e Silva AC. Physical exercise and ACE2-Angiotensin-(1-7)-Mas receptor axis of the Renin Angiotensin System. Protein Pept Lett 2017;24(9):809-16.

21. Patel SK, Velkoska E, Burrell LM. Emerging markers in cardiovascular disease: Where does angiotensin-converting enzyme 2 fit in? Clin Exp Pharmacol Physiol 2013;40(8):551-9.

22. Arend P. Why blood group A individuals are at risk whereas blood group O individuals are protected from SARS-CoV-2 (COVID-19) infection: A hypothesis regarding how the virus invades the human body via ABO(H) blood group-determining carbohydrates. Immunobiology 2020 Nov 4;226(3):152027.

23. Pourali F, Afshari M, Alizadeh-Navaei R, Javidnia J, Moosazadeh M, Hessami A. Relationship between blood group and risk of infection and death in COVID-19: a live meta-analysis. New Microbes New Infect 2020 Sep;37:100743.

24. NCD Risk Factor Collaboration (NCD-RisC). Rising rural body-mass index is the main driver of the global obesity epidemic in adults. Nature 2019;569(7755):260-4.

25. Leung NY, Bulterys MA, Bulterys PL. Predictors of COVID-19 incidence, mortality, and epidemic growth rate at the country level. medRxiv 2020.

26. Stoian AP, Pricop-Jeckstadt M, Pana A, Ileanu B-V, Schitea R, Geanta M, et al. Death by SARS-CoV 2-a Romanian COVID-19 multi-centre comorbidity study. Sci Rep 2020 Dec 10;10(1):21613.

27. Ho FK, Celis-Morales CA, Gray SR, Katikireddi SV, Niedzwiedz CL, Hastie C, et al. Modifiable and non-modifiable risk factors for COVID-19: results from UK Biobank prospective cohort study. BMJ Open 2020 Nov 19;10(11):e040402.

28. Wu J, Li W, Shi X, Chen Z, Jiang B, Liu J, et al. Early antiviral treatment contributes to alleviate the severity and improve the prognosis of patients with novel coronavirus disease (COVID-19). J Intern Med 2020 Jul;288(1):128-38.

29. Cai Q, Chen F, Wang T, Luo F, Liu X, Wu Q, et al. Obesity and COVID-19 severity in a designated hospital in Shenzhen, China. Diabetes Care 2020 Jul;43(7):1392-8.

30. Peng YD, Meng K, Guan HQ, Leng L, Zhu RR, Wang BY, et al. Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV. Zhonghua Xin Xue Guan Bing Za Zhi 2020;48:E004–E004.

31. Cassis LA, Police SB, Yiannikouris F, Thatcher SE. Local adipose tissue renin-angiotensin system. Curr Hypertens Rep 2008;10(2):93-8.

32. de Almeida Pinheiro T, Barcala-Jorge AS, Andrade JMO, de Almeida Pinheiro T, Ferreira ECN, Crespo TS, et al. Obesity and malnutrition similarly alter the renin–angiotensin system and inflammation in mice and human adipose. J Nutr Biochem 2017;48:74-82.

33. Zhang Y, Somers KR, Becari C, Polonis K, Pfeifer MA, Allen AM, et al. Comparative expression of renin-angiotensin pathway proteins in visceral versus subcutaneous fat. Front Physiol 2018;9:1370.

34. Gong MN, Bajwa EK, Thompson BT, Christiani DC. Body mass index is associated with the development of acute respiratory distress syndrome. Thorax 2010;65(1):44-50.

35. Karlsson EA, Milner JJ, Green WD, Rebeles J, Schultz-Cherry S, Beck MA. Influence of obesity on the response to influenza infection and vaccination. In: Mechanisms and Manifestations of Obesity in Lung Disease. Elsevier; 2019.p.227-59.

36. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA 2020;323(11):1061-9.

37. Yang X, Yu Y, Xu J, Shu H, Liu H, Wu Y, et al. Clinical course and outcomes of critically ill patients with

SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020 May;8(5):475-81.

38. Palaiodimos L, Kokkinidis DG, Li W, Karamanis D, Ognibene J, Arora S, et al. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. Metabolism 2020;108:154262.

39. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020 Mar 28;395(10229):1054-62.

40. Tian S, Hu N, Lou J, Chen K, Kang X, Xiang Z, et al. Characteristics of COVID-19 infection in Beijing. J Infect 2020;80(4):401-6.

41. Kushkestani M, Parvani M, Nosrani SE, Rezaei S. The physical activity and fall risk among Iranian older male adults. Open Nurs J 2020;14(1).

42. Kushkestani M, ENosrani S, Parvani M, Rezaei S. The relationship between the level of physical activity and dementia in elderly residents of nursing homes in Tehran. Biomed J Sci Tech Res 2020;29(3):22437-43.

43. Kushkestani M, Parvani M, Bathaeezadeh SY, Pour Nosrani SE. The Evaluation of Differenceson Geriatric Syndromesbetween Active and Sedentary Elderly. J Sports Sci 2020;8:56-66.

44. Libertini G, Corbi G, Cellurale M, Ferrara N. Age-related dysfunctions: evidence and relationship with some risk factors and protective drugs. Biochem (Mosc) 2019;84(12–13):1442-50.

45. Svartengren M, Falk R, Philipson K. Long-term clearance from small airways decreases with age. Eur Respir J 2005;26(4):609-15.

46. Xu J, Kang YA, Park SK, Yoon YH, Bai SJ, De Jin Y, et al. Nasality Changes With Age in Normal Korean-Speaking Adults. Clin Exp Otorhinolaryngol 2019;12(1):95-9.

47. AlGhatrif M, Cingolani O, Lakatta EG. The dilemma of coronavirus disease 2019, aging, and cardiovascular disease: insights from cardiovascular aging science. JAMA Cardiol 2020;5(7):747-8.

48. Napoli C, Tritto I, Mansueto G, Coscioni E, Ambrosio G. Immunosenescence exacerbates the COVID-19. Arch Gerontol Geriatr Sep-Oct 2020;90:104174.

49. Xia S, Zhang X, Zheng S, Khanabdali R, Kalionis B, Wu J, et al. An update on inflamm-aging: mechanisms, prevention, and treatment. J Immunol Res 2016;2016:8426874.

50. Perrotta F, Corbi G, Mazzeo G, Boccia M, Aronne L, D'Agnano V, et al. COVID-19 and the elderly: insights into pathogenesis and clinical decision-making. Aging Clin Exp Res 2020;32(8):1599-608.

51. The COVID-19 Sex-Disaggregated Data Tracker [Internet]. globalhealth5050. 2020 [cited 2020 Jun 23]. Available from: https://globalhealth5050.org/the-sex-gender-and-covid-19-project/

52. Sharma G, Volgman AS, Michos ED. Sex differences in mortality from COVID-19 pandemic: are men vulnerable and women protected? JACC Case Rep 2020;2(9):1407-10.

53. Jin JM, Bai P, He W, Wu F, Liu XF, Han DM, et al. Gender differences in patients with COVID-19: Focus on severity and mortality. Front Public Health 2020;8:152.

54. Griffith DM, Sharma G, Holliday CS, Enyia OK, Valliere M, Semlow AR, et al. Men and covid-19: A biopsychosocial approach to understanding sex differences in mortality and recommendations for practice and policy interventions. Prev Chronic Dis 2020;17:E63.

55. Smith J, Griffith D, White A, Baker P, Watkins D, Drummond M, et al. COVID-19, equity and men's health. Int J Mens Soc Community Health 2020;3(1):e48-64.

56. Garcia S, Albaghdadi MS, Meraj PM, Schmidt C, Garberich R, Jaffer FA, et al. Reduction in ST-segment elevation cardiac catheterization laboratory activations in the United States during COVID-19 pandemic. J Am

Coll Cardiol 2020 Jun 9;75(22):2871-2.

57. Vandello JA, Bosson JK, Lawler JR. Precarious manhood and men's health disparities. In: Griffith DM, Bruce MA, Thorpe RJ, editors. Men's Health Equity. (Abingdon: Routledge, 08 May 2019), accessed 30 Jun 2021, Routledge Handbooks Online.

58. Simpson RJ, Campbell JP, Gleeson M, Krüger K, Nieman DC, Pyne DB, et al. Can exercise affect immune function to increase susceptibility to infection? Exerc Immunol Rev 2020;26:8-22.

59. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol 2020;94(7):e00127-20.

60. Goessler K, Polito M, Cornelissen VA. Effect of exercise training on the renin-angiotensin-aldosterone system in healthy individuals: a systematic review and meta-analysis. Hypertens Res 2016 Mar;39(3):119-26.

61. Silva FB da, Fonseca B, Domecg F, Facio MR, Prado C, Toledo L, et al. Athletes health during pandemic times: hospitalization rates and variables related to COVID-19 prevalence among endurance athletes. Int J Cardiovasc Sci 2021;34(3).

62. Kakanis MW, Peake J, Brenu EW, Simmonds M, Gray B, Hooper SL, et al. The open window of susceptibility to infection after acute exercise in healthy young male elite athletes. Exerc Immunol Rev 2010;16:119-37.

63. Orhant E, Carling C, Cox A. A three-year prospective study of illness in professional soccer players. Res Sports Med 2010;18(3):199-204.

64. Minuzzi LG, Rama L, Bishop NC, Rosado F, Martinho A, Paiva A, et al. Lifelong training improves anti-inflammatory environment and maintains the number of regulatory T cells in masters athletes. Eur J Appl Physiol 2017;117(6):1131-40.

65. Shephard RJ, Kavanagh T, Mertens DJ, Qureshi S, Clark M. Personal health benefits of Masters athletics competition. Br J Sports Med 1995;29(1):35-40.

66. Dankers W, Colin EM, van Hamburg JP, Lubberts E. Vitamin D in autoimmunity: molecular mechanisms and therapeutic potential. Front Immunol 2017;7:697.

67. Bouillon R, Marcocci C, Carmeliet G, Bikle D, White JH, Dawson-Hughes B, et al. Skeletal and extraskeletal actions of vitamin D: current evidence and outstanding questions. Endocr Rev 2019;40(4):1109-51.

68. Zhou YF, Luo BA, Qin LL. The association between vitamin D deficiency and community-acquired pneumonia: A meta-analysis of observational studies. Medicine (Baltimore) 2019;98(38):e17252.

69. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients 2020;12(4):988.

70. Watkins J. Preventing a covid-19 pandemic. British Medical Journal Publishing Group; 2020.

71. Daneshkhah A, Agrawal V, Eshein A, Subramanian H, Roy HK, Backman V. The possible role of Vitamin D in suppressing cytokine storm and associated mortality in COVID-19 patients. MedRxiv. 2020.

72. Raharusuna P, Priambada S, Budiarti C, Agung E, Budi C. Patterns of COVID-19 Mortality and Vitamin D: An Indonesian Study. Available from: https://www.readcube.com/articles/10.2139%2Fssrn.3585561

73. Shi Y, Liu T, Yao L, Xing Y, Zhao X, Fu J, et al. Chronic vitamin D deficiency induces lung fibrosis through activation of the renin-angiotensin system. Sci Rep 2017;7(1):1-10.

74. Tian Y, Rong L. Letter: Covid-19, and vitamin D. Authors' reply. Aliment Pharmacol Ther 2020;51(10):995-6.

75. Bergman P, Lindh AU, Björkhem-Bergman L, Lindh JD. Vitamin D and respiratory tract infections: a systematic review and meta-analysis of randomized controlled trials. PloS One 2013;8(6):e65835.

76. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data.

BMJ 2017 Feb 15;356:i6583.

77. Ilie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. Aging Clin Exp Res 2020;32(7):1195-8.

78. Glicio EJ. Vitamin D Level of Mild and Severe Elderly Cases of COVID-19: A Preliminary Report. Rochester, NY: Social Science Research Network; (2020).

79. Frank HL, Rinku M, Radbeh T, Saeg F, Hoffman R, Cirillo JD, et al. Vitamin D insufficiency is prevalent in severe COVID-19. MedRxiv[Internet]. 2020.

80. Ali N. Role of vitamin D in preventing of COVID-19 infection, progression and severity. J Infect Public Health 2020;13(10):1373-80.

81. Cohen JE, Small C. Hypsographic demography: the distribution of human population by altitude. Proc Natl Acad Sci USA 1998;95(24):14009-14.

82. Penaloza D, Arias-Stella J. The heart and pulmonary circulation at high altitudes: healthy highlanders and chronic mountain sickness. Circulation 2007;115(9):1132-46.

83. Xi A, Zhuo M, Dai J, Ding Y, Ma X, Ma X, et al. Epidemiological and clinical characteristics of discharged patients infected with SARS-CoV-2 on the Qinghai plateau. J Med Virol 2020;92(11):2528-2535.

84. Dang Z, Su S, Jin G, Nan X, Ma L, Li Z, et al. Tsantan Sumtang attenuated chronic hypoxia-induced right ventricular structure remodeling and fibrosis by equilibrating local ACE-AngII-AT1R/ACE2-Ang1-7-Mas axis in rat. J Ethnopharmacol 2020;250:112470.

85. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. The Lancet 2020;395(10224):565-74.

86. Ren LL, Wang YM, Wu ZQ, Xiang ZC, Guo L, Xu T, et al. Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. Chin Med J (Engl) 2020;133(9):1015-24.

87. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun 2020;102433.

88. Fan H, Zhang L, Huang B, Zhu M, Zhou Y, Zhang H, et al. Retrospective analysis of clinical features in 101 death cases with COVID-19. medRxiv 2020 Mar 17;2020.03.09.20033068.

89. Zhao J, Yang Y, Huang H, Li D, Gu D, Lu X, et al. Relationship between the ABO Blood Group and the COVID-19 Susceptibility. Clin Infect Dis 2020 Aug 4;ciaa1150.

90. Guillon P, Clément M, Sébille V, Rivain JG, Chou CF, Ruvoën-Clouet N, et al. Inhibition of the interaction between the SARS-CoV spike protein and its cellular receptor by anti-histo-blood group antibodies. Glycobiology 2008 Dec;18(12):1085-93.

91. Dai X. ABO blood group predisposes to COVID-19 severity and cardiovascular diseases. Eur J Prev Cardiol 2020 Sep;27(13):1436-7.

92. Hessami A, Shamshirian A, Heydari K, Pourali F, Alizadeh-Navaei R, Moosazadeh M, et al. Cardiovascular diseases burden in COVID-19: Systematic review and meta-analysis. Am J Emerg Med 2020 Oct 16;S0735-6757(20)30908-6.

93. Mattos LC de, Moreira HW. Genetic of the ABO blood system and its link with the immune system. Rev Bras Hematol E Hemoter 2004 Mar;26:60-3.