

REVIEW

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Endocrine and metabolic aspects of COVID-19

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Abstract

The paper presents the theoretical considerations on the role of endocrine and metabolic alterations accompanying COVID-19 infection. These alterations may be presumed on the basis of the following two observations. Firstly, the virus SARS-CoV-2 responsible for the COVID-19 infection uses an important renin-angiotensin system (RAS) element — angiotensin-converting enzyme 2 (ACE2) — as a receptor protein for entry into target cells and, in consequence, disturbs the function of the main (circulating) renin-angiotensin-aldosterone system (RAAS) and of the local renin-angiotensin system localized in different tissues and organs. The binding of SARS-CoV-2 to ACE2 leads to the downregulation of this enzyme and, in the aftermath, to the excess of angiotensin II and aldosterone. Thus, in the later stage of COVID-19 infection, the beneficial effects of ACEI and ARB could be presumed. It is hypothesized that the local RAS dysregulation in the adipose tissue is the main cause of the negative role of obesity as a risk factor of severe outcome of the COVID-19 infection. Secondly, the outcome of COVID-19 strongly depends on the age of the patient. Age-related hormonal deficiencies, especially those of melatonin and dehydroepiandrosterone, may contribute to morbidity/mortality in older people. The usefulness of melatonin and angiotensin converting enzyme inhibitors/angiotensin receptor 1 blockers (the latter only in later phases of the infection) as adjuvant drugs is probable but needs thorough clinical trials. (*Endokrynol Pol* 2021; 72 (3): 256–260)

Key words: SARS-CoV-2; COVID-19; renin-angiotensin-aldosterone system; local renin-angiotensin systems; obesity, aging; melatonin; dehydroepiandrosterone

Introduction

There are at least two reasons to presume that the novel viral pandemic infection COVID-19 presents important relations with the endocrine system. Firstly, the virus SARS-CoV-2 responsible for the COVID-19 infection uses an important renin-angiotensin system element — angiotensin-converting enzyme 2 (ACE2) — as a receptor protein for entry into target cells and, in consequence, disturbs the function of the renin-angiotensin-aldosterone system (RAAS) [1–3]. The same mechanism of entry was previously shown for earlier recognized coronaviruses [4, 5]. Moreover, the poor outcome of COVID-19 is linked with advanced age and metabolic comorbidities, e.g. obesity, metabolic syndrome, and 2 type diabetes [6].

The role of the renin-angiotensin-aldosterone system

Angiotensins form the tissular hormonal cascade involved in several vital processes, of which the best known is blood pressure regulation. This regulation depends, in part, on the direct stimulation of the vasoconstriction by angiotensin II (AII). On the other hand, AII stimulates

the secretion of aldosterone from adrenal cortical zona glomerulosa, increasing the sodium retention together with potassium excretion. In relation to COVID-19, the most important finding is that SARS-CoV-2, the virus responsible for this infection, uses angiotensin-converting enzyme 2 (ACE2) as its tissue receptor [4, 5, 7]. Thus, it was hypothesized that higher amounts of ACE2 increased the risk of the infection with SARS-CoV-2 [for review see 8]. However, bound with the viral particles, ACE2 becomes less active, which results in the decreased breakdown and increased accumulation of AII [7, 8]. The low ACE2 activity leads to higher levels of AII and lower levels of angiotensin 1–7 (A1-7), the product of AII conversion by ACE2 [9]. Thus, COVID-19 may itself contribute to arterial hypertension, which is one of the comorbidities linked with severe outcomes of COVID-19. In addition, the oversecretion of aldosterone under the influence of AII not only causes high blood pressure but also exerts a proinflammatory effect in various tissues [for review see: 10]. Aldosterone not only stimulates sodium retention, but also enhances potassium excretion. It is worth recalling that 54.28% of COVID-19 patients studied by Chen et al. [11] showed hypokalaemia. Besides the main circulating RAS, there are numerous local RAS localized in different organs and tissues; among



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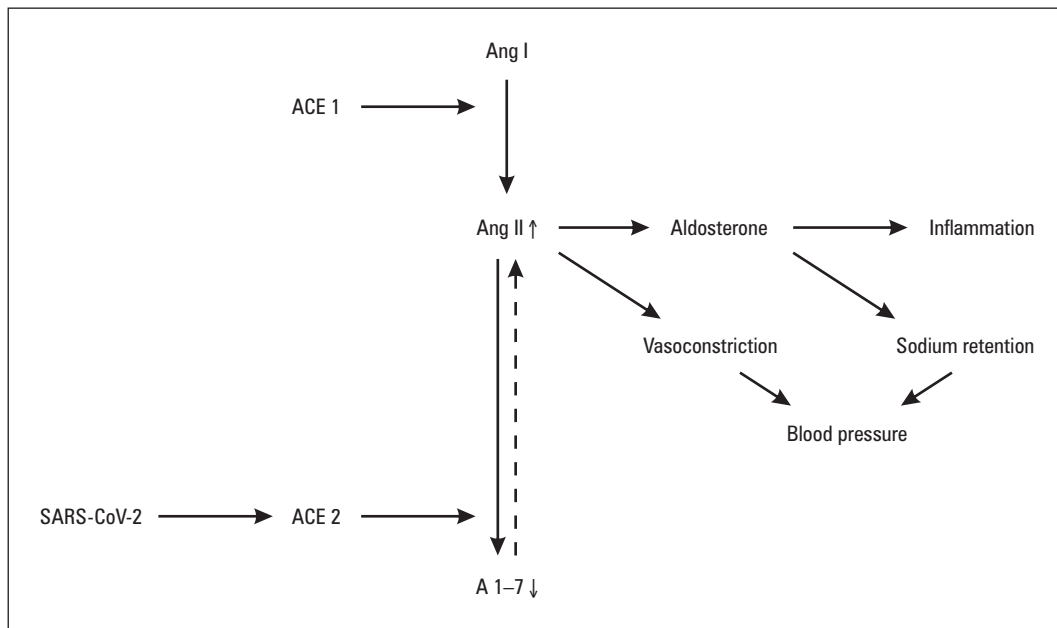


Figure 1. Dysregulation of the renin-angiotensin-aldosterone system in COVID-19. Continuous lines — stimulatory pathways; broken line — inhibitory pathways; arrow up — upregulation; arrow down — downregulation

others, in certain classical endocrine organs, such as the anterior and posterior pituitary [12–15], adrenal gland [16], pancreatic islets [17, 18], and testis and ovary [19, 20]. The role of the above-mentioned local RAS in these endocrine glands is only partially explored, and their dysregulation in COVID-19 may have important but as yet partially unknown consequences. Because the increase of AII seems to be the most important result of COVID-19, available angiotensin receptor 1 blockers (ARB), like valsartan, are proposed as adjuvant drugs in this infection [21]. On the other hand, the application of angiotensin converting enzyme inhibitors (ACEI) and ARB increases the biosynthesis of ACE2 [22], and it was hypothesized that the administration of these drugs might enhance the risk of COVID-19 infectivity. However, it has not been proven that treatment with ACEI or ARB constitutes an independent risk factor of SARS-CoV-2 infection. American and European Societies of Cardiology expressed the view that ACEI and ARB are safe and should be continued in patients according to the established guidelines [AMSC]. It was also suggested that irrespective of their effect on COVID-19 infectivity, in patients once infected, the treatment with ACEI or ABR turns out to be beneficial [23]. Alterations of the RAAS system due to SARS-CoV-2 infection are presented in Figure 1.

The role of obesity and diabetes

Morbidity and mortality in COVID-19 is increased not only by advanced age, but also by several comor-

bidities, mostly by obesity, metabolic syndrome, and type 2 diabetes [6]. These three conditions are linked together, because obesity, mostly central, leads to insulin resistance, the key factor of metabolic syndrome and type 2 diabetes. Stefan et al. [24] showed that high body mass index (BMI) is an important risk factor for severe course of COVID-19. The pathophysiological mechanisms of these effects are yet not fully elucidated. Obesity, from a purely mechanistic point of view, leads by itself to poor ventilation. On the other hand, we know that adipose tissue contains a local RAS [for review see: 25–28]. This system is responsible for a large proportion of synthesized AII, e.g. in rodents, adipose tissue RAS contributes to approximately one third of circulating AII [25]. Under the SARS-CoV-2 invasion the adipose tissue RAS might undergo the alterations described above for the circulating RAS, resulting in AII and aldosterone excess. We can presume that the expected excessive amount of AII depends on the adipose tissue mass. In obese patients, the fat tissue deposits contain abundant local RAAS, and thus the alterations to angiotensin and aldosterone levels can be more enhanced than in lean subjects. Other metabolic disorders, besides obesity itself, have been suggested to exert a negative effect on COVID-19 outcome. Diabetes (mostly type 2) is a frequent comorbidity accompanying severe outcome of COVID-19 [6, 29, 30]. COVID-19 patients with diabetes mellitus present increased inflammatory markers and more rapid progression of CT lesions in the lungs in comparison with non-diabetics [31].

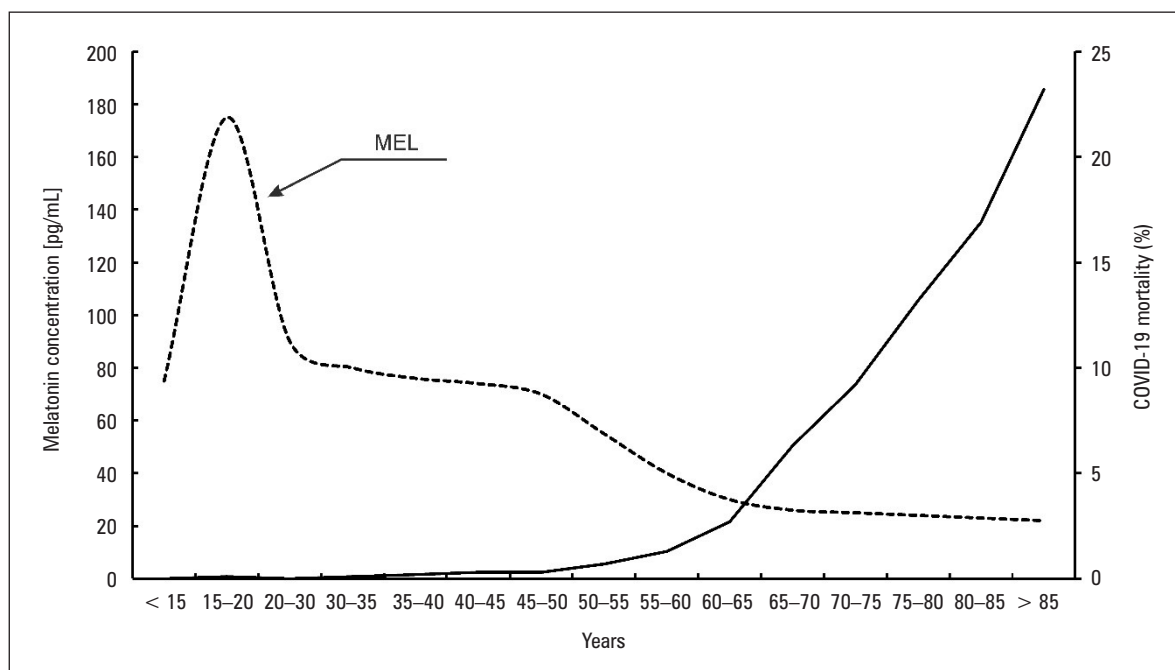


Figure 2. Curves of nocturnal peak of melatonin (MEL) and COVID-19 mortality (broken line) in relation to age

Chronic hyperglycaemia negatively affects immune functions [32]. Because of the occurrence of ACE2 in pancreatic islets, COVID-19 may induce worsening or onset of diabetes [3].

Age-related hormone alterations and COVID-19

As was indicated in the Introduction, the mortality rate of COVID-19 is sharply dependent on advanced age. For instance, in France the mortality varied from 0.001% in subjects < 20 years old to 10.1% in persons aged over 80 years [33]. Similar data are reported by Majewska [34] from Poland: the mortality > 15 years of age was absent and rose with advancing age to 23.2% over 85 years of age. Aging in humans, like in other mammalian species, is associated with deep alterations in hormonal secretion. In turn, hormone deficiencies, mostly of gonadal steroids, dehydroepiandrosterone (DHEA), growth hormone, and melatonin and excess of gonadotropins actively contribute to the aging processes, including age-related dysfunction of the immune system (immunosenescence). For instance, the drop of adrenocortical steroid DHEA may be linked with the failure of its immunoenhancing effect exerted in opposition to glucocorticoids [for review see: 35]. Moreover, in rodents, DHEA was found to exert an anti-obesity effect and induce the enhancement of insulin sensitivity [36]. In mice DHEA was shown to protect against acute lethal viral infection [37]. However, the application of exogenous DHEA is suspected to evoke a possible ex-

acerbation of COVID-19. This negative action of DHEA can be exerted by glucose-phosphate dehydrogenase inhibition [38]. Moreover, DHEA may antagonize the anti-inflammatory action of glucocorticoids used in the treatment of severe complications of COVID-19. One of the remarkable alterations connected with age is melatonin deficiency. If we consider the variations of melatonin secretion in relation to age, we can see that the highest nocturnal peak of melatonin secretion occurs during early childhood, begins to decrease at the first pubertal years, and then slowly drops to minimal values at over 80 years of age [39, 40]. Interestingly, the curves of mortality of COVID-19 and that of melatonin nocturnal secretion in dependence on age have almost the reverse shape (see Fig. 2). A question arises whether the changes in melatonin secretion may explain (at least in part) the age-related differences of COVID-19 morbidity/mortality. Numerous papers concern the relations between melatonin and COVID-19 [41–46]. The quoted authors, on the basis of previous findings of anti-inflammatory, immunomodulatory, antioxidant, and antiviral (demonstrated in other viral infections) actions, suggest the application of melatonin as an adjuvant drug in COVID-19. It should be underlined that recent studies *in silico* showed that melatonin has the properties of an inhibitor of SARS-CoV-2 main protease [47]. Melatonin was also shown to inhibit the protein CD147, which is involved in the cytokine storm [48]. Some clinical trials evaluating the efficacy and safety of melatonin are currently in progress [49–51]. In contrast to melatonin, the changes of DHEA levels

during the lifespan are correlated with COVID-19 mortality only in older age, when the low DHEA levels are accompanied by high COVID-19 mortality. However, the same is not true for childhood, when minimal mortality [33,34] is accompanied by very low DHEA secretion [35].

Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) excess, in contrast to hormonal deficiencies, was considered meaningless for a long time. However, the latest data indicate that gonadotropins, by their direct extra-gonadal action, can contribute to the aging process [for review see: 52, 53]. Although the effect of gonadotropins on immunosenescence was still poorly recognized, it is known that interleukin-6 (IL-6) levels are elevated in elderly humans and aged mice, and the involvement of this cytokine in the aging process is assumed [54, 55]. On the other hand, Komorowski and Stepień [56] demonstrated that both FSH and LH stimulate IL-6 secretion from human monocytes *in vitro*. IL-6 levels are also elevated in COVID-19, mostly in cases of severe outcome, and they are an important element of the so-called cytokine release syndrome. Moreover, the blockade of IL-6 is suggested as a strategy in COVID-19 severe infection [57]. Interestingly, the secretion of FSH and LH during the lifespan is approximately parallel to the age-related COVID-19 mortality. It is known that gonadotropin levels are low in both sexes during childhood before puberty, become moderate in adulthood, and continuously rise in older people.

Conclusions

The SARS-CoV-2 binding to ACE2 evokes dysregulation of the main RAAS, resulting in an excess of AII and aldosterone. The dysregulation concerns also the local RAS, including that localized in the adipose tissue. It is hypothesized that local RAS dysregulation is the main cause of the negative role of obesity as a risk factor for severe outcome of COVID-19 infection. The deficiencies of melatonin and DHEA and the excess of FSH and LH, which occur in older people, may contribute to be the risk factor of morbidity/mortality in COVID-19. The usefulness of melatonin and ACEI/ARB (the latter only in later phases of the infection) is probable but needs thorough clinical trials. The considerations presented above may also be useful in the future in the case of other infections evoked by coronaviruses that use ACE2 as a means of entry to host cells.

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