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Vitamin D, renin-angiotensin system, and COVID-19 — their importance in diabetes

ABSTRACT

The SARS-CoV-2 is responsible for the coronavirus disease 2019 (COVID-19) pandemic and has created much interest in the mechanisms of its infection and expression of this disease. To date, the majority of aspects remain to be investigated in the pathophysiology of SARS-CoV2 infection, especially in diabetic patients. One of these aspects is the correlation between angiotensin-converting enzyme 2 (ACE2), a part of the renin-angiotensin system (RAS), and SARS-CoV-2 infection. ACE2 has been recognized as a potential entry receptor for SARS-CoV-2. This review discusses the role of RAS and ACE2 in the pathophysiology of COVID-19 in patients with diabetes. Moreover, we will explain the role of vitamin D in regulating the RAS in COVID-19. (Clin Diabetol 2022, 11; 1: 45–51)

Keywords: SARS-CoV-2, COVID-19, renin-angiotensin system, angiotensin-converting enzyme 2, vitamin D, diabetes

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Introduction

Coronavirus (COV) is a genus of the Coronaviridae family, which are enveloped viruses with a single strand RNA virus genome and a diameter of about 80–120 nm [1, 2]. Their RNA genome has 27–32 kb size, capped, and polyadenylated [3]. COVs have been identified in many species, such as rats, chickens, turkeys, dogs, cats, rabbits, horses, bats, and humans. They can cause a variety of severe diseases consisting of gastroenteritis and respiratory tract diseases [4–6]. COVs were previously famous for causing human diseases from a simple common cold to severe acute respiratory syndrome (SARS) with an outbreak in 2003 [7, 8]. The recently characterized novel coronavirus (2019, nCoV), named SARS-CoV2 by World Health Organization (WHO) and called COVID-19, causes life-threatening pneumonia and becomes the most pathogenic human COV that has been identified so far [9, 10]. Its outbreak started in December 2019 in Wuhan, Hubei province in China, and has spread rapidly throughout the world and become pandemic in March 2020 [11, 12]. Compared with the SARS-CoV, COVID-19 has a stronger transmission capacity, and its control and prevention are essential.

The renin–angiotensin system

The renin-angiotensin system (RAS) and its regulatory cascade play a key role in regulating blood pressure, electrolyte, and fluid volume maintenance within the human body [13]. RAS stimulation is accompanied by hypertension. Renin belongs to the family of aspartyl protease and is the rate-limiting component of the RAS. Renin functions by cleavage of 10 amino acid peptides at the N-terminus of angiotensinogen to produce inactive decameric peptide angiotensin I (Ang I) [14]. Then, by angiotensin-converting enzyme (ACE) action, Ang I

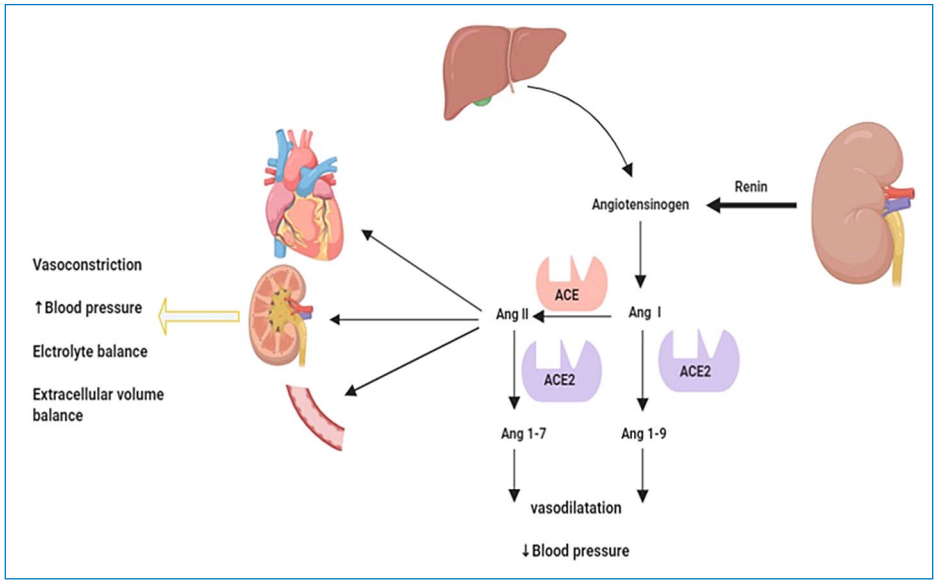

Figure 1. A schematic model of RAS and its functions in the human body
ACE — angiotensin-converting enzyme; Ang — angiotensin; RAS — renin-angiotensin system

is converted to the octapeptide Ang II. Ang II is the critical effector of the RAS [14]. When Ang II interacts with its receptors in different organs such as the heart, kidney, and peripheral vasculature, Ang II exerts different physiological responses and influences blood pressure, electrolyte, and extracellular volume balance [15]. Ang II contributes to hypertension, thorough enhancing vascular smooth muscle vasoconstriction, and renal tubule sodium reabsorption. It has been shown that ACE polymorphism is associated with the impairment of renal and cardiovascular system functions [15].

Today clinician uses pharmacological inhibitor of ACE and Ang II receptors as an effective strategy in lowering blood pressure, preventing kidney disease, and treating heart failure [16]. ACE is produced as a transmembrane protein containing two active domains within the endothelium of many tissues and could be inhibited by ACE inhibitors [16]. ACE needs to be cleaved from the membrane to generate a soluble active enzyme. Another form of ACE, known as ACE2, also exists [17]. ACE2 is a membrane-associated and secreted enzyme through the endothelium and is highly specific to the heart, kidney, and testis [18]. It catalyzes Ang I conversion to Ang 1–9 and cleavage of Ang II to its metabolite Ang 1-7 [18]. The exact physiological function of Ang 1-7 has not yet been discovered, but it generally appears to oppose the blood pressure actions of Ang II [19]. This action may suggest that there are counterbalances between ACE and ACE2 in RAS (Fig. 1) [19]. The amino acid sequence of Ang I, Ang II, and Ang 1-7 are presented in Table 1.

Table 1. The amino acid sequence of three important Ang in the human body

Ang	Amino acid sequence
Ang I	Asp Arg Val Tyr Ile His Pro Phe His Leu
Ang II	Asp Arg Val Tyr Ile His Pro Phe
Ang 1-7	Asp Arg Val Tyr Ile His Pro

Ang — angiotensin

COVID-19 and ACE2

How does COVID-19 invade the cells? Like other coronaviruses, COVID-19 thorough its N-terminal S1 portion of viral spike glycoprotein with a high-affinity binding capacity to superficial receptors of cells attack cells of different organs [20, 21]. It has been shown that ACE2 acts as a functional receptor for some CVs such as SARS- CoV and COVID-19 [20, 22]. Given that ACE2 is highly expressed in the heart, lungs, and kidneys, we can expect that these tissues are the primary viral infection source in the human body [18]. Here is an important question, why do most patients appear to have pulmonary problems? The answer to this question is that the lungs have a vast surface area that makes them highly susceptible to inhaled viral particles [23, 24]. Also, it has been documented that 83% of ACE2 expressing cells are alveolar epithelial type II cells and suggesting these cells act as a reservoir for coronavirus invasion [25, 26]. Furthermore, we can expect that these symptoms may be more severe in patients with cardiovascular disease (CVD). A good reason for this

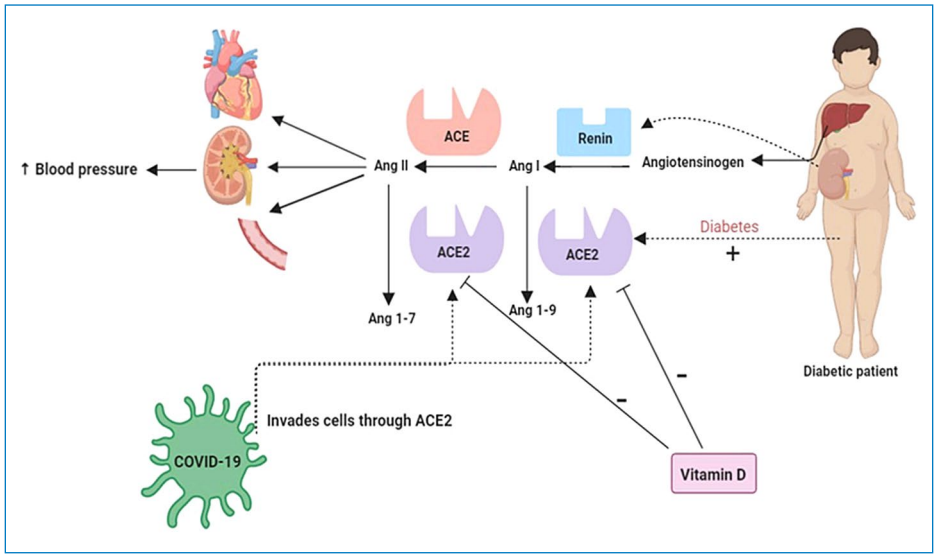

Figure 2. RAS and COVID-19 in patients with diabetes mellitus
ACE — angiotensin-converting enzyme; Ang — angiotensin; COVID-19 — coronavirus disease; RAS — renin-angotensin system

hypothesis is that ACE2 is increased in patients with CVD that use renin-angiotensin-aldosterone system inhibitors compared with healthy people [27]. Because ACE2 is the primary receptor for coronavirus, the safety and use of an anti-hypertension drug such as ACE inhibitors or angiotensin- receptor blockers should be noticed in patients with COVID-19 [27].

ACE2 in diabetic patients

RAS consists of a multistep enzymatic cascade that had potent effects of regulating blood pressure and electrolyte balance [28]. The existence of RAS in several tissues such as the heart, vasculature, retina, liver, and pancreas has highlighted the role of RAS in the organs' metabolic function [14]. Accumulating data from animal and clinical studies indicates that the RAS is dysregulated in many diseases, including diabetes, cardiovascular disease, and malignancy [29]. A meta-analysis study has shown that RAS blockade reduces the incidence of new-onset type 2 diabetes by about 22% in high-risk populations [30].

Another interesting point for scientists and clinicians is to assess a relationship between diabetes and ACE2 expression; however, the findings obtained are not entirely clear and need to be studied in more detail. Clinical and experimental evidence indicates the ACE2 provides protective roles against several pathophysiologic conditions such as lung injury, diabetes, cardiovascular and renal complications related to diabetes [31, 32]. Moreover, the expression of ACE2 in glucose-regulating tissues such as the pancreas and liver indicates its effects on glucose homeostasis [33]. Recent studies indicate that deficiency in ACE2 expression is related to impaired glucose metabolism; ACE2-deficient mice have shown a reduction in insulin secretion and alterations in glucose tolerance [34, 35]. Also, in high-calorie diet-fed mice, deficiency in ACE2 expression is accompanied by an increase in insulin resistance via the reduction of GLUT4 [36]. In line with these findings, Nadarajah et al. [37] indicated that overexpression of ACE2 in the pancreas results in improved glycemic levels and islet function and increases insulin content.

Interestingly, experimental models of diabetes have shown that changes in the ACE2 expression levels in renal tissues and pancreatic tissues correlate with the disease stage [38]. In renal tubules from *db/db* mice, as a type 2 diabetes model, ACE2 mRNA, and protein levels, as well as enzymatic activity, are increased at the early stage of diabetes. The ACE2 expression levels in lung tissue seem to be lower than renal and pancreatic tissues [31, 39]. Similarly, it has been shown that non-obese diabetic mice have higher ACE2 activity in serum, pancreas, and liver, but not in the lung [40]. In contrast, in the glomeruli from *db/db* mice, ACE2 expression was down-regulated [39]. Subsequent studies in the *db/db* mice confirmed these findings, which showed decreased ACE2 in glomeruli and increased ACE2 in tubules [41, 42]. In streptozotocin-treated mice, as a type 1 diabetes model, ACE2 mRNA and protein levels are increased in the early stage, followed by a decreased expression (approximately 50%) in the late phase [43].

In concordance with animal models' findings, human renal biopsy research has demonstrated decreased ACE2 in glomeruli from patients with type 2 diabetes and nephropathy [44, 45]. Mizuiri et al. [44] have

performed a cross-sectional study in 20 patients with type 2 diabetes who had diabetic nephropathy and 20 healthy kidneys to determine the expression pattern of ACE2 in diabetic nephropathy patients. They found that the expression of ACE2 was decreased in glomeruli of patients with diabetic nephropathy. In agreement, Reich et al. [45] reported a decrease in ACE2 mRNA levels in the glomeruli of patients with diabetic nephropathy compared to healthy control subjects. Taken together, human biopsy studies have finally demonstrated down-regulation in ACE2 expression levels at both the glomerular and tubular levels in diabetic nephropathy [46]. In comparison, most animal studies have shown a decrease in ACE2 expression in the glomeruli and an increase in ACE2 expression in the tubule. The differences between the results obtained in humans and animals may be due to the different stages of diabetes, as no human studies have been conducted in patients with early-stage diabetes [46].

In contrast, Soro-Paavonen et al. [47] performed a prospective study in 859 patients with Type 1 diabetes mellitus (T1DM) and 204 healthy controls to search alternation in ACE2 activity in patients with T1DM. They noticed increased serum ACE2 activity in T1DM patients with vascular complications but not in those without complications. Liang et al. [48] conducted a study on 132 T2DM patients with different albuminuria degrees and 34 healthy controls to identify the relation between urinary ACE2 levels with metabolic parameters. They observed that patients with T2DM had significantly higher ACE2 levels in their urine than healthy controls, and urinary ACE2 levels were correlated with fasting blood sugar (FBS), hemoglobin A1c (HbA1c), total cholesterol (TC), triglyceride (TG), and RAS inhibitors. These findings suggested that urinary ACE2 levels might be a non-invasive marker for monitoring RAS inhibitors' metabolic status and therapeutic response in diabetes [48]. Similarly, the results from the study of Park et al. [49] revealed that urinary ACE2 levels are significantly higher in insulin-resistant subjects with impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and T2DM than in controls with normal glucose tolerance test (NGT). Also, a cross-sectional study of 66 non-diabetic and eight diabetic patients reported no significant difference in ACE2 expression levels in renal tissue between the two groups. However, diabetic subjects consisted of only a small subset of the study subjects [50].

It has been documented that inhibition of ACE2 in STZ-induced diabetic mice leads to increased albuminuria and glomerular matrix expansion. Using the Akita mice, a model of type 1 diabetes, generated ACE2KO, Wong et al. [49] performed a study to determine the effect of ACE2 gene loss on diabetic mice. They have found albuminuria, mesangial matrix expansion, glomerular basement membrane thickening, and alpha-smooth muscle actin (α-SMA) overexpression associated with diabetes. Interestingly, ACE2 overexpression or administration of recombinant ACE2 to diabetic Akita mice has been shown to attenuate kidney injury and significantly reduce albuminuria [50]. However, these studies need further confirmation. Taken together, ACE2 may play a significant role in diabetes. ACE2 deficiency might contribute to decreased insulin secretion via impaired degradation of Ang II, leading to Ang II accumulation and an increased expression in the transforming growth factor-beta (TGF-β). Moreover, ACE2 deficiency in the kidney glomeruli may amplify proteinuria. Although, ACE2, through fostering the degradation of Ang II and the formation of Ang 1-7, may exert beneficial effects on both the kidneys and the pancreas [32].

Interplay between vitamin D, RAS system, diabetes, and COVID-19

As a fat-soluble vitamin, vitamin D has been recognized to play a critical role in the immune system and exerts its biological effects via vitamin D receptors (VDRs) [51, 52]. The presence of VDRs and enzymes associated with vitamin D metabolism in airway epithelial cells and immune cells indicate that vitamin D can modulate the immune response to respiratory virus infections [53, 54]. Furthermore, the association between vitamin D deficiency and increased risk of respiratory tract infection has been demonstrated by several studies [55, 56]. In line with these studies, other studies also showed that vitamin D deficiency is a risk factor for obesity (BMI > 30 kg/m^2), diabetes mellitus, and hypertension [57, 58]. The regulatory role of vitamin D in the function of pancreatic β-cells and the level of insulin sensitivity have been reported previously [59]. The interplay between viral infections, vitamin D, and diabetics remains an ambiguous matter, and plausible interactions between them do not appear to be simple.

Vitamin D can affect tissue in the following ways: Ang II, as a natural peptide hormone in the RAS system, is associated with increased blood pressure and vasoconstriction [60]. ACE2 catalyzes Ang II to angiotensin 1-7 [60]. During infection with COVID-19, ACE2 expression may be down-regulated, leading to Ang II accumulation [61]. Several studies have demonstrated that vitamin D is a negative regulator of RAS [62–64]. Indeed, vitamin D may down-regulate renin expression and generation by suppressing transcriptional activity within the renin gene promoter [62, 65]. On the other hand, renin is a positive regulator of Ang II [62]. In

a study, subjects with sufficient 25(OH) vitamin D levels, exhibited lower circulating Ang II concentrations than vitamin D insufficient and deficient subjects [63]. Xu et al. [66] also reported that vitamin D suppresses renin, Ang II, and ACE expression. Supplementation with vitamin D has been reported to prevent Ang II accumulation and decrease the pro-inflammatory activity of Ang II [67]. The majority of clinical and experimental studies reported increased ACE2 expression in diabetes [31, 39, 47]. Moreover, vitamin D treatment has inhibited the expression of ACE2 in the kidney [68]. Vitamin D has a reno-protective effect in streptozotocin-induced diabetic rats by increasing the ACE1/ACE2 ratio [69]. In other words, vitamin D supplementation can inhibit the expression of ACE2 in kidney tubule cells, and prevent COVID-19 entry into the cells in patients with diabetes, thereby protecting the kidney [56]. Vitamin D can decrease the production of T helper type 1 (Th1) cells, and suppress the inflammation progression via reducing the expression of pro-inflammatory cytokines [e.g., Interleukin 6 (IL-6), IL-8, IL-12, and IL-17], tumor necrosis factor-alpha (TNF-α) and nuclear factor-κB (NFκB) [70, 71]. Vitamin D deficiency was linked to overexpression of Th1 cytokines, which leads to cytokine storm in patients with severe COVID-19 infection [56, 72–74]. Considering the critical role of vitamin D in diabetes, ACE2 expression, and its possible role in COVID-19, vitamin D may have protective effects and could be considered a therapeutic option for COVID-19 treatment (Fig. 2).

Conclusions

RAS plays an essential role in regulating blood pressure, electrolyte, and fluid volume maintenance within the human body. ACE2, as a negative regulator of RAS, plays a crucial role in the entry of SARS-CoV-2 into the human cells. As patients with diabetes express more ACE2 on their cells, they may have a higher risk of COVID-19 infection. Furthermore, vitamin D could inhibit the expression of ACE2 and prevent COVID-19 entry into the cells in patients with diabetes. More studies are required to understand the role of ACE2 and the potential therapeutic effects of ACE2 inhibitors on the susceptibility to the COVID-19 infection.

Conflict of interest

None declared.

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