

DIABETES AND RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM: IMPLICATIONS FOR COVID-19 PATIENTS WITH DIABETES TREATMENT MANAGEMENT

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Abstract

In the context of the COVID-19 continuous spreading, this paper focuses on the increased risk of diabetic patients regarding the metabolic control and the uncertainties related to SARS-CoV-2 infection. Chronic hyperglycaemia negatively affects the immune system, which triggers an increase of morbidity and mortality for viral infections. A key aspect of COVID-19 resides in the involvement of renin-angiotensin-aldosterone (RAAS) system that causes a cascade of reactions mediated by vasoactive peptides with implications in vasoconstriction, vascular permeability, oxidative stress remodelling and tissue injuries. Activation of RAAS at pulmonary level, is responsible for the local damage. Many questions regarding the treatment with ACE inhibitors and angiotensin receptor blockers were raised considering the correlation between RAAS and viral infection in diabetic patients.

Rezumat

În contextul răspândirii continue a COVID-19, această lucrare se concentrează asupra riscului crescut al pacienților diabetici referitor la controlul metabolic și incertitudinile legate de infecția cu SARS-CoV-2. Hiperglicemia cronică afectează negativ sistemul imunitar, ceea ce determină o creștere a morbidității și a mortalității pentru infecțiile virale. Un aspect cheie al COVID-19 rezidă în implicarea sistemului renină-angiotensină-aldosteron (SRAA) care determină o cascadă de reacții mediate de peptide vasoactive, cu implicații în vasoconstricție, permeabilitate vasculară, stres oxidativ și leziuni tisulare. Activarea SRAA la nivel pulmonar este responsabilă de leziunile locale. Multe întrebări legate de tratamentul cu inhibitori ai enzimei de conversie și blocații ai receptorilor de angiotensină au apărut, având în vedere corelația dintre SRAA și infecția virală la pacienții diabetici.

Keywords: COVID-19, SARS-CoV-2, diabetes, of renin-angiotensin-aldosterone system, RAAS, ACEi, ARBs

Introduction

It's been over 4 months now since the entire globe has been tried by the COVID-genocide that affected more than 187 countries [1]. From China to Europe, America and Africa, all medical and scientific community researches intensely for a potential treatment for SARS-CoV-2 as well as potential vaccine. Until the beginning of May, 3,483,194 cases have been confirmed, out of which 1,114,454 resolved and over 246,000 deaths [1]. Diabetes mellitus, according to the statistics in force, is one of the conditions that determine vulnerability to COVID-19 disease and increase mortality.

The question arises, however, if all patients with diabetes have this risk or only those with chronic metabolic imbalance [2]. Another question concerns the increased risk of people with diabetes and cardiovascular or microvascular disease. Metabolic syndrome is recognized as a conglomerate of diseases that increase the risk of vascular disease, but can it increase the risk of a viral infection with an unfavourable evolution?

Chronic hyperglycaemia and viral infection

Chronic hyperglycaemia affects negative immune function, which may implicitly increase morbidity

and mortality for infections in general. The association of diabetes mellitus - hypertension has been shown to increase the risk of a viral infection by 10 times, as is the case in severe respiratory syndrome (SARS) or severe respiratory syndrome in the Middle East (MERS-COV) [3]. The disease itself may increase insulin resistance and increase blood sugar levels.

Hyperglycaemia and diabetes are independent predictors of mortality and morbidity for the infection with corona virus. This assertion is based on the pro-inflammatory effect of chronic hyperglycaemia, the condition that causes the release of cytokines, which can be defined as “metabolic inflammation”. It can compromise the body's defence capacity mainly by decreasing the number of leukocytes. Aggressive viral infection in turn causes a “storm” of inflammatory cytokines that impacts evolution and survival.

The renin-angiotensin-aldosterone system and viral infection

In the body's defence system, the renin-angiotensin-aldosterone system (RAAS) occupies a very important place.

Is there a possibility that this RAAS system to be involved in viral aggression?

This question arose after the previous coronaviruses infections that caused two epidemics that could be also valid for the current pandemic.

The renin-angiotensin-aldosterone system (Figure 1) is a cascade of reactions caused by vasoactive peptides with implications in physiological processes in the body such as tissue injury, fibrosis in chronic diseases, etc. [3, 4].

The main pawn is angiotensin II (Ang II) which acts on the target organs through specific surface receptors, AT1 and AT2 [5].

AT1 is ubiquitously present in the human body. The ligand binding to this receptor causes: vasoconstriction, water and sodium retention, activation of the sympathetic system, but also cell proliferation and endothelial dysfunction of the vascular environment, which means that it promotes atherothrombosis and atherosclerosis [3].

AT2 receptors are better represented in the brain with important effect on cognitive function and memory [6]. While the proinflammatory characteristics of the angiotensin AT1 receptor are well established, most current evidence supports an anti-inflammatory role of the AT2 receptor. However, data on this receptor and its role in inflammation are somewhat controversial. Adjusting the balance between the activity of angiotensin II receptors, given that their function is antagonistic (AT1 and AT2), is an essential process in the management of inflammation and the healing process. The imbalance in the expression of these receptors can cause the disease.

Manipulation of the angiotensin system using anti-hypertensive therapy could provide a new approach to the treatment of chronic conditions.

The conversion enzyme of angiotensin (angiotensin-convertase, ACE) catalyses the transformation of angiotensin I (Ang I) into angiotensin II (Ang II), a potent vasoconstrictor. ACE is mainly expressed in lung capillaries, vascular endothelial cells in the heart and kidney [7].

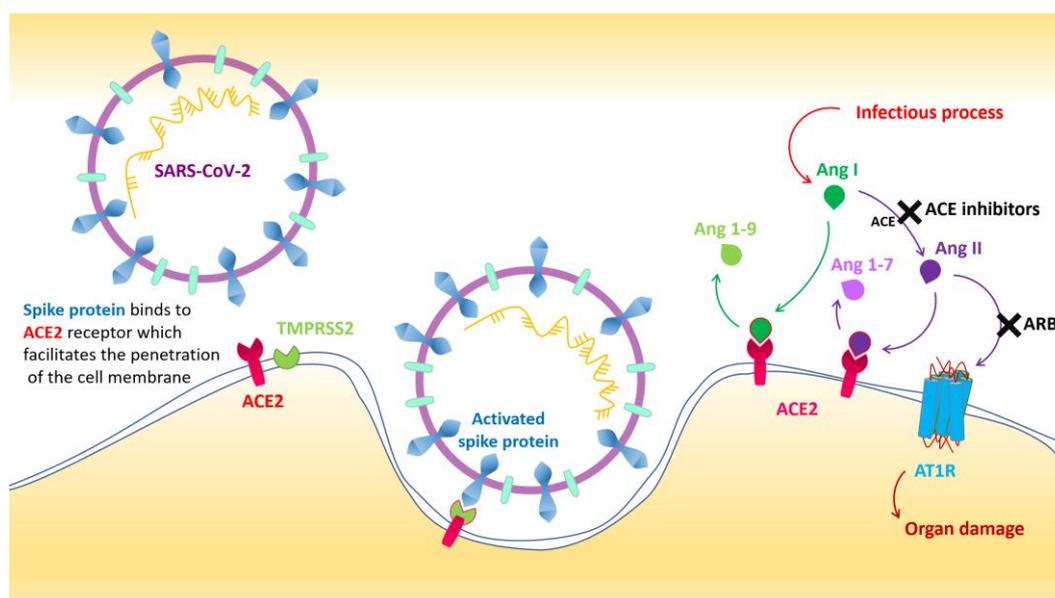


Figure 1.

The SARS-COV-2 infection and the Renin-Angiotensin-Aldosterone System (RAAS)
 ACE2 – Angiotensin-convertase 2; TMPRSS2 – Transmembrane serine protease 2; Ang – Angiotensin;
 AT1R – Angiotensin II Receptor type 1, ARBs – Angiotensin receptors blockers [19]

Another enzyme, angiotensin converting 2 (ACE2) degrades Ang II into Ang I, acting as a regulator of angiotensin level. ACE2 is a membrane protein mainly expressed in lungs, heart, kidneys and intestine. This enzyme can also function as a receptor for promoting COVID-9 infection and therefore, the interaction between SARS and this receptor is the most important factor regarding the virus infectiveness. A particular viral membrane glycoprotein (spike protein) of SARS-COV2 binds the ACE2 receptor found on pneumocytes surface facilitating the viral entry inside the body. The mechanism of viral complex endocytosis follows with a down-regulation of surface ACE2, resulting in accumulation of Ang II [8]. Activation of the renin-angiotensin system at the lung level is responsible for local injury (Figure 1).

A very interesting idea is about androgen involvement in ACE2 regulation. The X chromosome contains loci for the receptor of androgen and the ACE-2 genes. Several studies have shown that SARS-CoV-2 uses the receptor of ACE2 as gate to penetrate the cell as it links to the viral spike (S) proteins to cellular receptors and also uses the transmembrane serine protease 2 (TMPRSS2) for S protein priming (Figure 2) [11].

The activity of the androgen receptor is considered necessary for the transcription of the TMPRSS2 gene, and TMPRSS2 cleaves angiotensin converting enzyme 2 (ACE2) for augmented viral entry (Figure 2) [12].

Also, TMPRSS2 cleaves and activates the spike S protein of the severe acute respiratory syndrome coronavirus (SARS-CoV) for membrane fusion [13, 31]. Testosterone is the main androgen hormone with an already known suppressive activity on immunity, while the oestrogen stimulates it, especially through the regulation of the immune response by impairing negative selection of high affinity auto-reactive B cells, modulating B cell function and leading to Th2 response [9]. Testosterone activates lymphocytes T CD8+, down-regulates NK cells response, increasing some anti-inflammatory cytokines (e.g. IL-10) and the production of Th1 to the detriment of Th2 lymphocytes in men [10, 32, 33].

In SARS, the experiments on mice show that males are more susceptible to the viral infection than females. This difference seems to be influenced by age as well. The male mice that are exposed to less virus give a lower immune response and clear the virus much more slowly. Male rats whose lungs are more damaged die at higher rates [13].

A recent study demonstrated the direct role of oestrogen in limiting the viral replication of the flu virus at the level of the nasal epithelial cells by modulating genes that regulate the metabolic functions of cells [13]. It seems that the protective role of oestrogen asserts itself. Maybe this sexual difference is a possible explanation as to why children or young adults develop only mild forms of SARS-Cov-2.

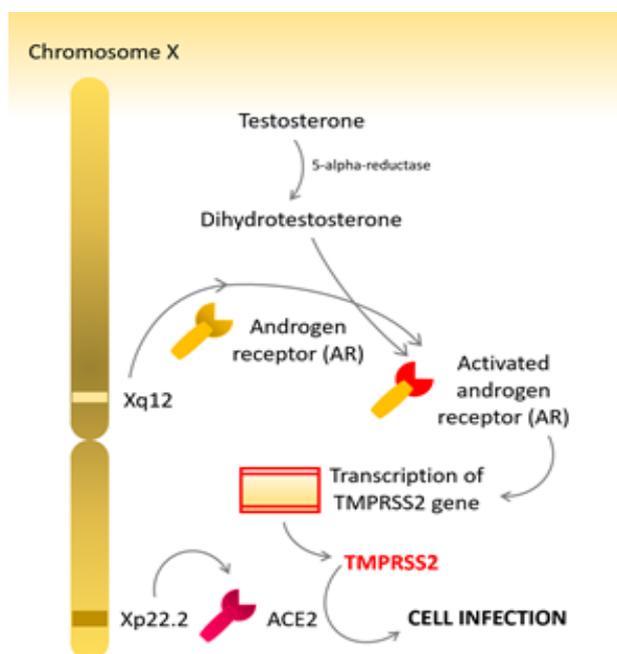


Figure 2.

The role of androgen hormones in ACE2 regulation, a mechanism with potential role on the SARS-COV-2 infection

Testosterone activates the androgen receptor followed by the stimulation of TMPRSS2 expression and the cleavage of angiotensin converting enzyme 2 (ACE2) facilitating the virus entry in the human cells.

ACE2 – Angiotensin Converting Enzyme 2; TMPRSS2 – Transmembrane serine proteases 2; AR – Androgen Receptor [39]

ACE inhibitors, Angiotensin Receptor blockers and viral infection

Many questions regarding the treatment with ACE inhibitors (ACEi) and angiotensin receptor blockers (ARBs) were raised considering the correlation between RAAS and viral infection.

We should mention from the beginning that there are significant differences between the mechanism and place of action of ACE2 and ACE, in spite of a very similar structure. For this reason, ACE therapy does not appear to have a direct effect on ACE2. There are animal studies that have analysed the effects of ARBs on ACE2, which have shown increased messenger RNA expression with an elevated ACE2 level in tissues, but the results have been inconsistent [14].

There are several studies in human subjects that have examined the effect of RAAS inhibition on ACE2 receptor expression [15]. A pertinent question is whether these medications have a direct effect on ACE2 or not. To answer this question, plasma activity and renal elimination of ACE2 were analysed in patients treated with RAAS inhibitors (RAASi) and the conclusion was that therapy with ACEi and ARBs does not alter ACE 2 action [16].

However, there have been studies showing that in patients on long-term treatment with ACEi, the level of ACE2 was increased in the intestine, but this effect was not observed in those treated with ARBs [17]. There is no data on ACE2 expression in the lung. All these seemingly contradictory results demonstrate the complex and incompletely known effects of the RAAS system and show once again that preclinical patterns do not always overlap with the physiological processes, and ACE2 expression distribution is not uniform in the RAAS system, depending on the tissue and clinical status [18].

Unfortunately, data are lacking to demonstrate the effect of ACE medication or ARBs on the pulmonary level. It is assumed that RAAS inhibitors modifies ACE2 activity and expression level in target tissues, but there are no relevant clinical studies showing the treatment impact on viral entry.

ACE2, in addition to facilitating virus penetration into the cell, down-regulates enzyme expression with a decreasing of the protective effects in tissues [19]. Following the moment of contamination, viral replication continues to induce further down-regulation of ACE2 activity, especially at the lung level, with release of endotoxin, which will initially cause the onset of neutrophil infiltration, and subsequently induce the accumulation of Ang II with local activation of RAAS [19].

Exposure to SARS-CoV-1 spike protein causes severe lung damage, and level of Ang II is greater as the viral load is higher.

Under conditions of viral contamination with severe evolution, there is a hypothesis of the occurrence of subclinical myocarditis, which would explain the unfavourable evolution and the increase of the death rate [17, 19]. For this reason, patients with cardiovascular disease are more vulnerable and in general evolution is unfavourable.

All these phenomena produce dysregulation of ACE2, decreasing the cardioprotective capacity.

Uncertainties regarding the pharmacological regulation of ACE2 to slow down adverse effects related to SARS-COV-2 infections have led to a different approach, ranging from discontinuation of RAASi or ACEi therapy in COVID -19 patients or contacts [20].

The treatment withdrawal has been shown to be harmful and may expose patients at high risk to severe decompensation. Moreover, it has been shown that in patients with COVID-19 and cardiovascular disease therapy with RAASi has brought benefits and determined cardiac and renal protection. It is important to establish the risks and benefits for people treated with RAASi, because this is the optimal therapy after acute myocardial infarction, heart failure, hypertension. Moreover, according to current guidelines, there are many patients on this therapy and stopping this medication, especially in patients with cardiovascular disease, may be more risky than continuing it [20].

If we consider the clinical experience and the fact that the clinical trials are controversial, the most correct attitude is the continuation of RAASi therapy in the critically suspected or positive COVID-19 patients [21]. In Yang X *et al.* study, the most important comorbidities in the 32 patients without COVID-19 were cerebrovascular disease 22% and diabetes mellitus 22% [22]. Another study with a larger group of infected patients sustained that 23% had high blood pressure, 16% diabetes, 5% coronary heart disease and 2.3% cerebrovascular disease [23].

Diabetes and COVID-19

In patients with diabetes, we need to consider that ACE2 receptors are better expressed if treated with ACEi and ARBs.

We know that the coronavirus binds to the target cells through ACE2, well represented in the lung, intestine, kidney and blood vessels. Increased expression of ACE2 receptors makes the patient with diabetes more vulnerable to viral aggression, leading to the conclusion that people with diabetes and hypertension in treatment with ACE2 stimulants will have more severe forms and a high death rate. Pioglitazone and ibuprofen are among the therapies that stimulate these receptors. Perhaps this is the explanation of the unfavourable evolution of COVID-19 in people who have previously taken anti-inflammatory treatment [23].

On the other hand, it is known that ACE2 has anti-inflammatory effect and that is why it is difficult to explain why increased expression of these receptors induces the worsening of viral infection. ACE2 polymorphism associated with diabetes, stroke and hypertension may also be considered.

Calcium channel blockers do not influence ACE2 activity and may therefore be an alternative for hypertension in people with diabetes [21].

Hyperglycaemia is a state of metabolic inflammation with cytokine release that decreases the immune system's ability to react effectively to viral aggression and compromises healing.

There is a direct link to COVID-19 and diabetes explained by the direct binding of the virus to ACE2 receptors, because pancreatic expresses ACE2 induce decreased insulin secretion [24].

The vulnerability also comes from the fact that ACE2 receptors are better expressed in people with diabetes [25].

Metabolic control is essential for minimizing the risk of unfavourable evolution and can reduce the risk of disease.

There are multiple therapies that can help patients maintain glycaemic control without risk of hypoglycaemia and without weight gain.

GLP-1 agonists therapy has the advantage of glycemic control, offers cardiovascular protection, but at the same time seems to offer protection against the SARS-CoV-2 virus through competitive binding to the ACE2 receptor [26]. Animal studies showed a GLP-1 agonists upregulation effect upon ACE2 expressed at alveolar microlevel and a negative effect on inflammation through the inhibition of cytokine release, mechanisms that may be of benefit during COVID-19 infection [38]. However, there are few evidence-based extrapolations in humans and clinical studies to clearly sustain the correlation between these drugs and SARS-CoV-2 infection evolution. Up to the present publication (May 2020) there are no official recommendations regarding the use of GLP-1 agonists in COVID-19 diabetic patients.

Still, the early association with AngII receptor blockers (telmisartan, losartan) has a favorable effect [14] acting on blood sugar and inflammation, but at the same time having an antiviral action.

Regarding DPP-4i (dipeptidyl-peptidase-4 inhibitors) therapy, we should consider that DPP-4 is found in many tissues and has a T cell activation effect, which is why we could say that it promotes inflammation. It would be logical for DPP-4 inhibition to have inflammation-lowering effects. Also, its hypoglycemic effect is accompanied by an immunomodulatory effect, which proved beneficial in autoimmune pathologies [35] and MERS [36]. Furthermore, DPP-4 was described as a receptor for the coronavirus that developed MERS, which is highly similar to the novel coronavirus. These findings raised theories regarding the possible

therapeutic effect of DPP-4i inhibitors in SARS-CoV-2 infection, but *in silico* and *in vitro* experiments proved controversial results [37].

In some studies, suspicion has been raised about the increased risk of naso-pharyngeal infections. Hence the fears related to this therapy in people with diabetes and viral infection with COVID, taking into account the appearance of respiratory distress. However, studies have not shown impaired respiratory function in patients treated with DPP-4i [26].

In the management of the patient with diabetes and cardiovascular disease, the treatment with SGLT2i (sodium-glucose cotransporter 2 inhibitors) occupies an important place, due to the cardiovascular and renal protection benefits.

In the case of COVID-19 infection, therapy should be discontinued because it increases the risk of ketoacidosis [27]. Treatment will be resumed after quenching the infectious process [25].

It will also stop treatment with metformin because of the risk of lactic acidosis.

It is important if we make changes in therapy to take care of metabolic control, which is essential in controlling infection and hastening healing, eventually the decision to temporarily introduce insulin will be made [28].

Corticotherapy, frequently given to those with respiratory distress, has limited indications in people with diabetes, determining, besides hyperglycemia, decreased Ang1-7 expression and MAS receptor expression. Ang1-7, which acts by binding to the MAS receptor, exerts inhibitory effects on inflammation, has vasoactive effects and cell growth [29].

There is also controversy regarding treatment with hydroxychloroquine.

The best approach in the context of the COVID-19 pandemic is to ensure good metabolic control in people with diabetes, control of lipids and blood pressure.

There are still many unknowns about this virus and there are many questions waiting to be answered, according to the WHO report from 2019 [30].

Conclusions

Overall, the best approach in the context of the COVID-19 pandemic is to ensure good metabolic control in people with diabetes, as well as to control their lipids and blood pressure, and ultimately their entire cardiometabolic risk. There are still too many uncertainties about this new coronavirus, as also highlighted by the WHO. They mainly refer to the source of infection, the pathogenesis and virulence evolution of the virus, transmission dynamics, risk factors for infection, surveillance and monitoring, clinical management of severe and critically ill patients, prevention and control measures and so on. Until clear answers on COVID-19 is available, we have to continue to take care of patients with diabetes based

on all the available (and increasing) evidence, without performing unusual therapeutic approaches not validated by rigorous scientific methodology.

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Conflict of interest

This article has been written independently. The authors have given talks, attended conferences, and participated in advisory boards and clinical trials sponsored by various pharmaceutical companies; yet, no financial or professional help was received for the preparation of this manuscript. MR is currently Director, Clinical Medical & Regulatory Department, Novo Nordisk Europe East. APS is currently Vice-President of National Committee of Diabetes. The authors declare no conflict of interest.

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