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MINIREVIEWS

Advanced-glycation end-products axis: A contributor to the risk of severe illness from COVID-19 in diabetes patients

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Abstract

Compelling pieces of evidence derived from both clinical and experimental research has demonstrated the crucial role of the receptor for advanced-glycation end-products (RAGE) in orchestrating a plethora of proinflammatory cellular responses leading to many of the complications and end-organ damages reported in patients with diabetes mellitus (DM). During the coronavirus disease 2019 (COVID-19) pandemic, many clinical reports have pointed out that DM increases the risk of COVID-19 complications, hospitalization requirements, as well as the overall severe acute respiratory syndrome coronavirus 2 case-fatality rate. In the present review, we intend to focus on how the basal activation state of the RAGE axis in common preexisting conditions in DM patients such as endothelial dysfunction and hyperglycemia-related prothrombotic phenotype, as well as the contribution of RAGE signaling in lung inflammation, may then lead to the increased mortality risk of COVID-19 in these patients. Additionally, the cross-talk between the RAGE axis with either another severe acute respiratory syndrome coronavirus 2 receptor molecule different of angiotensin-converting enzyme 2 or the renin-angiotensin system imbalance produced by viral infection, as well as the role of this multi-ligand receptor on the obesity-associated low-grade inflammation in the higher risk for severe illness reported in diabetes patients with COVID-19, are also discussed.

Key Words: COVID-19; Diabetes mellitus; Advanced glycation; Alarmins; Advanced-glycation end-products axis; Inflammation

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Core Tip: Compelling evidence support that diabetes mellitus increases the risk of coronavirus disease 2019 (COVID-19) complications, as well as the overall syndrome coronavirus 2 case-fatality. Different reports have suggested the putative involvement of several molecular mechanisms underlying this increased risk. We herein discuss the contribution of the activation of the receptor for advanced-glycation end-products axis to the higher risk for severe illness reported in diabetes patients with COVID-19.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease, where the etiological agent is a novel coronavirus, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). This disease was initially detected and reported in December 2019 in Wuhan, China and then spread rapidly all over the world. This situation forced the World Health Organization to declare on January 30, 2020, the COVID-19 as a global pandemic, and thus leading humanity to face up an extraordinary challenge of a new viral disease.

Lung inflammation is the main cause of life-threatening respiratory disorders at the COVID-19 severe stage[1,2], and where lower respiratory tract symptoms and low oxygen saturation in the blood resembling acute respiratory distress syndrome (ARDS) as well as the requirement of invasive mechanical ventilation.

In addition to the lungs, SARS-CoV-2 may also infect the gastrointestinal tract, cardiovascular system, as well as central nervous system[3-5].

SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) molecule as the receptor for viral cell entry[6]. ACE2 plays an important role in renin-angiotensin system (RAS), and the imbalance between ACE/angiotensin II (Ang II)/angiotensin II receptor type 1 (AT1R) pathway and ACE2/Ang (1–7)/Mas receptor pathway in the RAS system will lead to multisystem inflammation[7]. The activation of the AT1R by Ang II may trigger the activation of proinflammatory signals such as oxidative and nitrosative stresses, the induction of cytokines, cell adhesion molecules, as well as the activation transcription factors such nuclear factor kappa B[8-11]. Therefore, ACE2/Ang-(1-7)/Mas receptor, has been pointed out as a counter-regulator of the deleterious effects of Ang II[12].

During the pandemic, it has been shown that DM increases the risk of COVID-19 complications. Data from different studies have pointed out that increased hospitalizations, longer and repeated hospital stays as well as the overall SARS-CoV-2 case-fatality rate are significantly higher in diabetes patients who have poorly controlled glycemia when compared to patients without DM[13-16]. Although the huge amount of compelling clinical data supporting COVID-19 complications in people with diabetes, the molecular mechanisms underlying this association are not fully understood.

The receptor for advanced-glycation end-products (RAGE) was discovered as a receptor for advanced glycation endproducts (AGEs), which are accelerated formed in hyperglycemia. Afterward, RAGE emerged as a multi-ligand receptor able to interact with a diverse myriad of non-AGE ligands and being implicated in diverse chronic inflammatory states[17,18].

In the present review, we will discuss the possible contribution of the activation of the RAGE axis to the higher risk for severe illness in diabetes patients infected with COVID-19.

RAGE AXIS

RAGE was initially reported in 1992, as a membrane-associated molecule that can bind

AGEs[19]. AGEs are a heterogeneous group of molecules formed from the non-enzymatic reaction of reducing sugars with free amino groups of proteins, lipids, and nucleic acids to form a freely reversible Schiff base, which spontaneously rearranges itself into an Amadori product, as is the case of the well-known hemoglobin A1c[20]. Hemoglobin A1c is an important indicator of long-term glycemic control with the ability to reflect the cumulative glycemic history of the preceding two to three months[21].

The formation of AGEs is thought to be the major cause of different diabetic complications in large part through their interactions with RAGE. Of note, AGEs may also contribute to diabetic complications through the formation of cross-links between key molecules in the basement membrane of the extracellular matrix, and thus altering the constitution of the matrix and increases stiffness[22-25].

RAGE is a single-pass transmembrane protein, which belongs to the immunoglobulin superfamily of cell surface receptors, which is now considered as a pattern recognition receptor[26]. This multi-ligand receptor is regarded as a central mediator in chronic inflammatory and immune responses[27,28].

RAGE is found in human airways with high basal levels of RAGE expressed in pulmonary tissue[29]. It is also found on vascular cells, neurons, cardiomyocytes, adipocytes, glomerular epithelial cells, or podocytes[30], as well as on pro-inflammatory and immuno-competent cells such as neutrophils, monocytes, macrophages, and T and B lymphocytes[31].

Besides AGEs, RAGE can recognize many other ligands including the alarmin high mobility group box 1 protein (HMGB1), members of the S100 protein family, glycosaminoglycans, and amyloid β peptides[32].

As a consequence of RAGE engagement by its ligands, multiple signaling pathways are triggered, including reactive oxygen species, p21ras, erk1/2 (p44/p42) MAP kinases, p38 and SAPK/JNK MAP kinases, rhoGTPases, phosphoinositol-3 kinase, and the JAK/STAT pathway, having crucial downstream inflammatory consequences such as activation of nuclear factor kappa B, AP-1 and Stat-3[33].

RAGE AXIS ACTIVATION AND DIABETES COMPLICATIONS

Endogenous formation of AGEs is markedly increased in diabetes as the result of hyperglycemia and increased oxidative stress. At present, an increasing prevalence of diabetes and its complications is reported worldwide. Elevated levels of circulating AGEs are believed to play a major role in the pathogenesis of macrovascular and microvascular disease in diabetes mellitus.

Additionally, it has been demonstrated that dietary AGEs also play a major role in maintaining a high body pool of AGEs in diabetes[34].

The diabetic condition is a chronic systemic low-grade inflammation[18], and consequently, other RAGE ligands are bioavailable as is the case of some members of the S100 family and HMGB1, which can be either passively released from damaged cells or actively secreted by immune cells. A compelling body of evidence demonstrates that both AGEs and non-AGEs ligands accumulate in the plasma/serum of human subjects with diabetes[35,36].

Compelling data derived from both clinical and experimental studies support the crucial contribution of RAGE activation in vascular complications in diabetes[37].

Endothelial cells actively regulate cellular adhesion, thromboresistance, smooth muscle cell proliferation, and vessel wall inflammation. Therefore, dysfunction of the vascular endothelium is considered as an important factor in the pathogenesis of the micro-and macro-angiopathies observed in diabetes patients, and where the activation of the RAGE axis is an important contributor to this dysfunctional state[38-40].

DM has been associated with platelet hyper-reactivity, which plays a central role in the hyperglycemia-related pro-thrombotic phenotype[41,42]. In this sense, the activation of the RAGE axis has been pointed out as an important contributor to the development of a pro-thrombotic state, by its capacity to activate platelets[43,44].

COVID-19, DIABETES, RAGE AXIS, AND LUNG INJURY

DM is associated with increased disease severity and a higher risk of mortality in patients with COVID-19, who can rapidly progress to ARDS, septic shock, and multiple organ dysfunction syndrome[13-16].

Several mechanisms have been claimed for explaining the exacerbating effect of diabetes on COVID-19. These mechanisms include those directly related to hyperglycemia and the associated imbalances in pathways involved in virus entry into the cell as well as in the immune and inflammatory response. At present, the role of RAGE axis activation has been demonstrated in different animal models of ARDS and where RAGE inhibition attenuated lung injury (LI) and restored alveolar fluid clearance[45,46].

In this context, it is important to highlight that the release of the RAGE ligand HMGB1 is increased under hyperglycemic conditions[47,48], as well as the crucial role of HMGB1 in lung inflammation in diabetes[49-51].

Additionally, the contribution to LI by HMGB1-mediated RAGE signaling is well-documented in other viral diseases of the respiratory tract, as reported for the influenza virus[52].

Considering the abundance of RAGE in the lungs, the robust proinflammatory signaling triggering after the engagement, as well the relatively high expression levels in RAGE in diabetes patients[53], the activation of the RAGE axis may be an important contributor in exacerbating clinical complications in COVID-19 patients with diabetes. In this sense, it is important to highlight the contribution of RAGE axis activation in preexisting conditions such as endothelial dysfunction as well as the hyperglycemia-related prothrombotic phenotype, which increases the mortality risk of COVID-19 in DM patients.

Noteworthy, the RAGE ligand S100A12 is overexpressed in COVID-19, as recently reported[54]. This molecule is also closely related to the pathogenesis of sepsis-induced ARDS[55].

THE IMBALANCE OF RENIN-ANGIOTENSIN SYSTEM IN DIABETES

The association of the RAS with the endocrine system is particularly illustrated by the prominent role of Ang II in diabetes and metabolic syndrome. RAS has been extensively described to be involved in the onset and progress of hypertension, retinopathy, nephropathy, and cardiovascular disease in DM patients. RAS is considered an important pharmacological target in the management of micro-and macrovascular complications for these patients[56-59].

Of particular importance, individuals with diabetes have a reduced ACE2 expression. This enzyme is found in multiple organs including the lungs. ACE2 plays an important role in the RAS, and the imbalance between ACE/Ang II/AT1R pathway and ACE2/Ang (1–7)/ Mas receptor pathway in the RAS system will lead to multisystem inflammation. This reduced expression confers to individuals with diabetes an increased risk of severe LI as well as ARDS if infected by COVID-19[60].

SARS-CoV-2 INFECTION, RENIN-ANGIOTENSIN SYSTEM IMBALANCE, AND THE RAGE AXIS

As already mentioned SARS-CoV-2 uses ACE2 molecule as the receptor for viral cell entry[6]. ACE2 is a key counter-regulatory element in the pathway of the renin-angiotensin system, which acts to opposite the actions of Ang II by generating Ang-(1–7), and thus reducing inflammation and fibrosis and mitigate end-organ damage[61].

Strikingly, SARS-CoV-2 hijacks ACE2 to invade and damage cells, downregulating ACE2, reducing its protective effects, and exacerbating injurious Ang II effects[62].

Considering the facts that diabetes patients have a reduced expression of ACE-2, as well as the capacity of SARS-CoV-2 to hijacks ACE2, ACE2 exhaustion will be produced in patients with diabetes during infection and, thus reducing its capacity to fully function as a counterbalancing element of RAS through the ACE2/Ang-(1-7)/mas receptor pathway.

Decades of research have demonstrated that the activation of ATR1 by Ang II, triggers a robust inflammatory response involving the recruitment and activation of inflammatory cells, as well as apoptosis of both alveolar epithelial cells and pulmonary microvascular endothelial cells, and consequently, a marked increased microvascular permeability and loss of epithelial and endothelial integrity[63].

RAGE axis is an important contributor to the pathophysiology of lung inflammation because the use of different inhibition strategies can increase arterial oxygenation,

reduce alveolar inflammation, and improve lung damage in acute lung inflammation[46,64].

Strikingly, a novel ligand-independent mechanism for RAGE transactivation has been recently reported to occur following activation of the AT1R by Ang II and thus leading to nuclear factor kappa B dependent expression of pro-inflammatory mediators[65]. This novel mechanism is expected to continuously fuel the lung inflammatory environment in diabetes patients during SARS-CoV-2 infection, considering both the high expression of RAGE and the reduced levels of ACE-2 in the lungs[66].

SARS-CoV-2, CD-147, AND THE RAGE AXIS

Increased infiltration and accumulation of macrophages is a common process in many of the complications of diabetes patients[67].

CD147, originally described in tumor cells, is a highly glycosylated 58-kDa transmembrane protein belonging to the immunoglobulin superfamily and also known as extracellular matrix metalloproteinase functions as a matrix metalloproteinases (MMPs) inducer, predominantly MMP-2 and MMP-9. Of note, the expression of this protein is markedly increased by AGEs by a RAGE-dependent mechanism[68].

Degradation of protein components in the alveolar epithelial–endothelial unit by both MMP-2 and MMP-9 is considered a central process in the pathogenesis of ALI/ARDS[69-71]. Strikingly, SARS-CoV-2 spike protein may bind also to CD147 glycoprotein[72], and thus mediating viral invasion. Due to the high expression levels of this protein in diabetes, this condition may then increase the accessibility of virus to tissue in patients with diabetes. A recent report demonstrates the Meplazumab, a humanized anti-CD147 antibody efficiently improved the recovery of patients with SARS-CoV-2 pneumonia with a favorable safety profile[73].

SARS-CoV-2, THROMBOTIC MICROANGIOPATHY, AND RAGE AXIS

Thrombotic microangiopathy is reported as a frequent event in COVID-19[74]. In patients with diabetes, endothelial dysfunction is a very common condition, and events such as enhanced vasoconstriction, platelet hyperactivity and thrombus formation are activated due to the metabolic milieu, and where the activation of the RAGE axis is continuously fueled by hyperglycemia, insulin resistance, and the oxidative stress seen in diabetes[75]. Noteworthy, platelets can be activated by a RAGE-dependent mechanism[43].

The dysfunctional state of the endothelium is linked to an impairment of nitric oxide production and activity, which may then affect not only the vasodilator tone and platelet activity but also the recruitment of endothelial progenitor cells, which directly contribute to the homeostasis and repair of the endothelial layer in blood vessels[76-78].

Very recently, clinical findings suggest that SARS-CoV-2 infection facilitates the induction of endotheliitis in several organs as a direct consequence of viral infection[79]. However, these data have generated controversy about the nature of the viral-type particles reported because of endoplasmatic reticulum may mimic SARS-CoV-2 particles on electron microscopy[80,81]. Additionally, other pieces of evidence show the absence of viral ribonucleic acid inside endothelial cells, suggesting that indirect effects rather than direct viral infection might trigger endothelial damage[82]. On the other hand, SARS-CoV-2 spike protein may bind also to CD147 glycoprotein which is upregulated by hyperglycemia and by RAGE activation[68]. CD147 expression is significantly upregulated in activated endothelial cells[83]. Therefore, these findings raise the intriguing possibility that RAGE activation may play a role also in viral invasion to host cells.

The activation of the RAGE axis has been widely documented to be crucial to prime proinflammatory mechanisms and rendering endothelial cells into an activation state and thereby amplifying proinflammatory mechanisms in many chronic inflammatory disorders[84-86]. Thus, preexisting blood vessel damage may put people with COVID-19 at heightened risk of complications from the infection.

A dysfunctional endothelium as observed in diabetes, leading to detrimental shifts in the vascular equilibrium towards vasoconstriction, inflammation, and a procoagulant state resulting in thrombosis, constitute a much more proper condition to fuel inflammation in the blood vessel wall and then putting diabetes patients with COVID-19 at heightened risk of complications from the infection.

SARS-CoV-2, OBESITY, DM-2, AND RAGE AXIS

More than 90% of patients with type 2 diabetes have obesity or overweight[87]. In the context of the COVID-19 outbreak, many reports highlight that obesity and type 2 diabetes as comorbidities of SARS development in COVID-19 patients[88-90].

Both obesity and type 2 diabetes are associated with a chronic low-grade inflammatory state, and this particular basal state could then aggravate the inflammatory response to SARS-CoV-2 infection observed in severe COVID-19 cases.

In this context, there are shreds of evidence suggesting a key role of RAGE axis activation in fat tissue inflammation, and thus contributing to the obesity-associated low-grade inflammation, as well as to the reported dysregulation of adipokines[91,92].

Furthermore, many RAGE ligands such as AGEs, HMGB1, and S100/calgranulins, accumulate in adipose tissue in many models of obesity as well as in obese subjects[93-96], where they can trigger a robust proinflammatory secretion profile, which in turn, establishes a vicious loop, and thus rendering more inflammation[97].

The low-grade inflammation in adipose tissue is characterized, in addition to the robust secretion of proinflammatory cytokines, by the recruitment of leukocytes, mainly macrophages in this tissue. The accumulation of macrophage into adipose tissue correlates to both the degree of adiposity as well as the production of monocyte chemoattractant protein-1, which in turn, recruit more macrophages and thereby promote the chronicity of inflammation[98].

Furthermore, macrophages infiltrated in adipose tissue undergo a polarization process towards a spectrum of different phenotypes where two extremes are represented by the classically activated type 1 macrophages and the alternative activated type-2 macrophages[99]. Noteworthy, RAGE ligands accumulation and macrophage type 1 macrophages polarization are much more prevalent in perivascular adipose tissues[100] and thus, adding more inflammation to the vascular system.

During this pandemic, some alerts have been raised on side effects of some widely used drugs on diabetic COVID-19 patients, particularly lactic acidosis and ketoacidosis (DKA) for metformin and sodium-glucose cotransporter 2 inhibitors, respectively[101,102].

The RAGE axis has been recently suggested to be a crucial contributor to the acute inflammatory insult during the medical crisis and treatment of DKA and thus acting as a constant source of subclinical inflammation leading to chronic diabetic vascular complications, including those of the heart[103].

Additionally, 3-deoxyglucosone is significantly elevated before and during the treatment of DKA[104]. 3-Deoxyglucosone is a dicarbonyl species that may lead to the formation of AGEs, and then fueling inflammation by RAGE engagement[105].

One mechanism by which metformin increases plasma lactate levels relates to the inhibition of mitochondrial respiration responsible for lactate removal[106,107], which correlate with the inhibition of mitochondrial oxidative phosphorylation[108].

The activation of the RAGE axis is known to increase cytosolic reactive oxygen species production which, in turn, facilitates mitochondrial superoxide production in hyperglycemic environments, and thus rendering a mitochondrial dysfunctional state[109,110]. This particular dysfunctional state could be a particular life-threatening condition in diabetic COVID-19 patients[111].

CONCLUSION

At present, a compelling body of evidence supports the crucial role of the RAGE axis in the pathophysiology of diabetes, being a key contributor in the onset and sustainment of low-grade and chronic inflammation state observed in patients with diabetes, and consequently, marked impairment of endothelial functions. Thus, this basal hyper-activated state of the RAGE axis, as occurs in diabetes patients may represent a crucial element in many clinical complications in diabetes patients who develop COVID-19 (Figure 1).

Furthermore, the novel ligand-independent transactivation of the RAGE axis by AT1R/Ang II further strengthens the hyperactivation state of the axis and consequently, fueling a robust pro-inflammatory environment particularly in the low respiratory tract, where the high expression of RAGE and AT1R receptors plays an essential role in the pathophysiology of the lung inflammation observed in those diabetic patients.

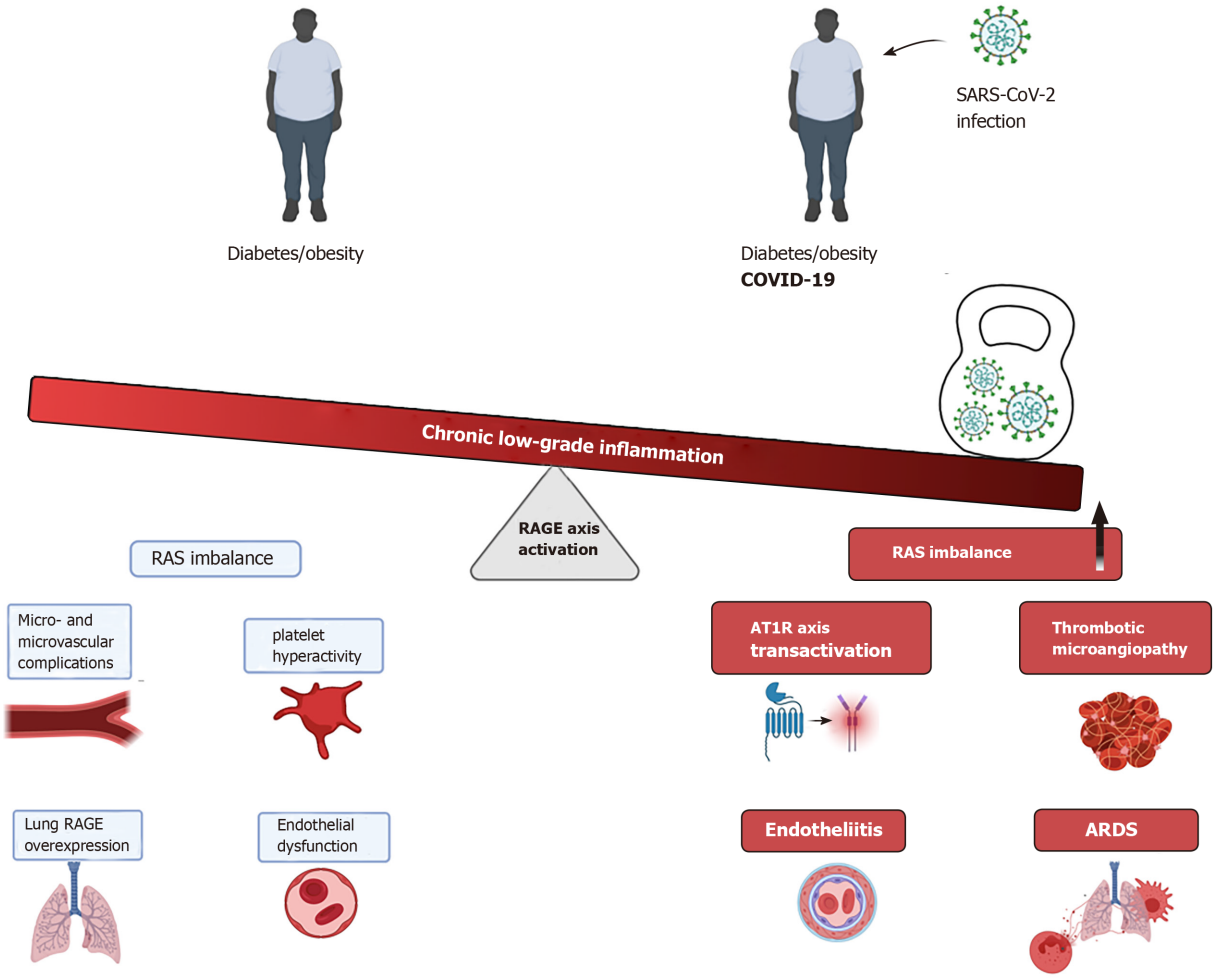

Figure 1 The chronic and low-grade inflammatory state preexisting in diabetes patients as well as in one of the most frequent co-morbidities observed in diabetes seems to be particularly exacerbated in coronavirus disease 2019 patients with diabetes. The receptor for advanced-glycation end-products axis hyper- activation, either by ligand-dependent or cognate-ligand independent mechanisms, is emerging as crucial contributor to this huge inflammatory response leading to acute respiratory distress syndrome, endotheliitis and thrombotic complications. ARDS: Acute respiratory distress syndrome; AT1R: Angiotensin II receptor type 1; COVID-19: Coronavirus disease 2019; RAGE: Receptor for advanced-glycation end-products; RAS: Renin-angiotensin system.

In summary, in light of what is known about the poor clinical outcomes of diabetic patients who develop COVID-19, the RAGE axis seems to be one of the key players in the enhanced inflammatory response and the high mortality rates of these patients. While the precise mechanisms by which the RAGE axis activation contributes to the higher risk of severe illness in diabetes patients infected with SARS-CoV-2 remain to be fully understood, it is important to strengthen future clinical research in this area.

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