



Mechanism of inflammatory response in associated comorbidities in COVID-19

Thays Maria Costa de Lucena ^{a, b}, Ariane Fernandes da Silva Santos ^{a, b},
Brenda Regina de Lima ^{a, b}, Maria Eduarda de Albuquerque Borborema ^{a, b},
Jaqueline de Azevêdo Silva ^{a, b, *}

^a Department of Genetics, Federal University of Pernambuco, Recife, Pernambuco, Brazil

^b Laboratory of Immunopathology Keizo Asami (LIKA), Federal University of Pernambuco, Recife, Pernambuco, Brazil

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ABSTRACT

Background and aims: The outbreak of the new coronavirus, SARS-CoV-2, causes a respiratory disease and individuals with pre-existing cardiometabolic disorders display worse prognosis through the infection course. The aim of this minireview is to present epidemiological data related to metabolic comorbidities in association with the SARS-CoV-2.

Methods: This is a narrative mini-review with Pubmed search until April 23, 2020 using the keywords COVID-19, SARS-CoV-2, treatment of coronavirus and following terms: diabetes mellitus, obesity, arterial hypertension, ACE-inhibitors, cytokine storm, immune response and vitamin D.

Results: Studies indicate that obese individuals are more likely to develop infections, and that adipose tissue serves as a pathogen reservoir. In diabetic individuals higher rate of inflammatory processes is seen due to constant glucose recognition by C type lectin receptors. Hypertensive individuals, usually grouped with other conditions, are treated with drugs to reduce blood pressure mostly through ACEi and ARB, that leads to increased ACE2 expression, used by SARS-CoV-2 for human's cell entry. Until now, the studies have shown that individuals with those conditions and affected by COVID-19 present an uncontrolled release of pro-inflammatory cytokines and an unbalanced immune response, leading to the cytokine storm phenomenon. Vitamin D is highlighted as a potential therapeutic target, because in addition to acting on the immune system, it plays an important role in the control of cardiometabolic diseases.

Conclusion: Currently, since there is no proven and effective antiviral therapy for SARS-CoV-2, the efforts should focus on controlling inflammatory response and reduce the risks of associated complications.

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1. Introduction

Diabetes, hypertension and other cardiovascular diseases (CVD) are strongly related to a higher risk of mortality or disease's severity among COVID-19 patients. In China, from 44,672 confirmed cases, 4.7% were critical, with a case-fatality rate (CFR) of 49%. Patients without comorbidities had lower CFR (0.9%), while those with CVDs, diabetes and hypertension had higher rates (10.5%, 7.3%, 6.5%, respectively) [1]. Obesity is another comorbidity raising the risk of complications in COVID-19 infection. The immune system acts

upon inflammation that occurs in adipose tissue due to obesity, increasing vulnerability to infections [2]. Increased circulating levels of many cytokines and proteins released by adipocytes are associated with inflammation in obese individuals [3]. Inflammation from adipose tissue generates chronic and systemic metabolic alterations leading to dyslipidemia, hypertension, CVD and diabetes, thus increasing the risk of infection by Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2)². It is thought that SARS-CoV-2, as SARS-CoV and MERS-CoV, suppress anti-viral type IFN- γ responses in the early stage of infection leading to an uncontrolled viral replication. This mechanism later leads to an influx of neutrophils and monocytes/macrophages, resulting in hyperproduction of pro-inflammatory cytokines that can damage lung tissue (i.e. pneumonia, acute respiratory distress syndrome).

* Corresponding author. Av. Prof. Moraes Rego, 1235, CEP 50760-901, Recife, Brazil.

E-mail address: jaqueline.azevedo@ufpe.br (J. de Azevêdo Silva).

Specific Th1/Th17 cells may be activated and contribute to increased inflammation. These facts and the higher mortality by COVID-19 observed in those with underlying diseases indicates that immune response is a determining factor to COVID-19 outcome [4].

According to phylogenetic analyses, SARS-CoV-2 is related to other existing respiratory infections, such as SARS-CoV and Middle East respiratory syndrome-Coronavirus (MERS-CoV) [5]. SARS-CoV infection accounted for 8098 cases and 774 deaths in 26 countries [6], meanwhile, MERS-CoV infection was identified in 27 countries, with 2449 confirmed cases and 845 deaths [7]. As is being observed in COVID-19, MERS-CoV infection also caused more severe complications in older and immunocompromised patients with a history of diabetes, renal failure, and lung diseases [8]. According to genome sequencing, SARS-CoV-2 is about 89% identical to bat SARS-like-CoVZXC21, 82% identical to human SARS-CoV and about 50% to MERS-CoV [5,9]. Several phylogenetic analyses suggests the bat as most probable animal reservoir for SARS-CoV-2, and as both SARS-CoV and MERS-CoV were transmitted from bats to palm civets or dromedary camels, and then to humans, it is possible though that another animal plays the role of intermediate host between bat and human in SARS-CoV-2 infection [10]. These viruses have a structural protein, the Spike glycoprotein (S) that is responsible for its binding to host cells [11]. According to Hoffman [12] protein S is primed by human serine protease (TMPRSS2) and recognized by the cell receptor. A recent study described by Liu [11] shows that SARS-CoV entering in the respiratory tract depends on a receptor-binding domain (RBD) to bind to the host, and protein S has two trimers that bind to the heterodimer of angiotensin-converting enzyme II (ACE2). A synthetic SARS-CoV-2 RBD analysis indicated that the virus enters into the host cell through ACE2 binding. However, MERS-CoV binds specifically to another receptor, dipeptidyl peptidase 4 (DPP4) [11,13]. Therefore, since SARS-CoV-2 is analogous to SARS-CoV, it is suggested that both use ACE2 as the main mechanism for cell entry.

The pathophysiology of SARS-CoV-2 is not yet well understood, it is known to cause an acute lung injury and that this condition resembles SARS-CoV, which results in aggressive inflammation initiated by viral replication [14]. In this review, we tried to discuss and report possible mechanisms of inflammatory responses mediated by SARS-CoV-2 in individuals with pre-existing cardiometabolic diseases and to speculate possible therapeutic target that can be applied to obtain a better immune response, reduce pro-inflammatory profile, and consequently reduce critical levels of the disease.

2. Search methodology

We systematically searched the PubMed database up until April 23, 2020 using the keywords COVID-19, SARS-CoV-2, treatment of coronavirus and following terms: diabetes mellitus, obesity, hypertension arterial, ACE-inhibitors, cytokine storms, immune response and vitamin D. Our database research results were accessed and relevant cross references were made to the proposed mini review.

3. Metabolic syndrome

Approximately 25% of the adult population (40–49 years) have Metabolic Syndrome (MS), this percentage increases as the population ages, reaching more than 40% of the population over 60 years of age [15]. The appreciation of the MS presence was due to the finding of its relationship with cardiovascular and chronic diseases. When present, MS increases twice the mortality of patients with type 2 diabetes and by three times the mortality due to CVDs [15,16].

MS can be controlled with the direct action of the renin-angiotensin-aldosterone system (RAAS), in which, in the normal functioning of the body, this system acts in the regulation of blood pressure [17,18]. Angiotensin-converting enzyme I (ACE) and its counterpart, ACE2, are the main enzymes in this system. The main role of ACE is the conversion of angiotensin I (Ang-I) into angiotensin II (Ang-II), allowing vasoconstriction and positive regulation of blood pressure [18,19]. The role of ACE2 is the conversion of angiotensin I into angiotensin 1–9 (Ang 1–9), which is converted by ACE into the angiotensin vasodilator peptide 1–7 (Ang 1–7); ACE2 also regulates the conversion of Ang-II into Ang 1–7, and a negative regulation of blood pressure occurs [19].

Because it is a multifactorial and complex process, affected individual must present 3 or more associated clinical characteristics, and for a better understanding of the processes that trigger metabolic syndrome, the next sections clarify the clinical characteristics involved and how they are related to SARS-CoV-2.

3.1. Obesity

The immune system plays an important role in inflammation that occurs in adipose tissue due to obesity, which increases vulnerability to infections. Inflammation in adipose tissue generates metabolic alterations that can cause comorbidities such as dyslipidemia, hypertension, cardiovascular diseases and diabetes, thus increasing the risk of infection by SARS-CoV-2 [2].

The overexpression of inflammatory adipokines from visceral fat deposits can affect the immune response, impair chemotaxis and alter the differentiation of macrophages. The imbalance between the secretion of anti- and pro-inflammatory adipokines from thoracic visceral fat deposits, such as the epicardium and mediastinal, may also play a role in the cytokine storm described in patients with severe SARS-CoV-2. A study demonstrated the active role of macrophages in morbid obesity and the relationship they have with inflammatory processes, concluding that the disease of chronic inflammation initiated in adipose tissue is a consequence of insulin resistance [20].

Hyperleptinemia, tissue dysfunction, low antioxidant defenses, chronic inflammation, and the generation of postprandial ROS are factors involved in the development of obesity in which oxidative stress participates [21]. As the increase in oxidative stress in accumulated fat is, at least in part, the underlying cause of adipocytokine dysregulation and the development of the metabolic syndrome [22], it is known that obesity induces oxidative stress through various mechanisms such as chronic inflammation, endothelial dysfunction, and mitochondrial dysfunction [23]. Interestingly, it was reported that adiponectin predicted mortality in critically ill patients after admission to the Intensive Care Unit (ICU). The innate inflammatory response of visceral fat deposits can cause a positive regulation and greater release of inflammatory cytokines such as IL-6 [24].

In addition, adipose tissue serves as a reservoir for several viruses, such as influenza A, HIV and cytomegalovirus, and may also be infected by the COVID-19 virus [2], for being an important source of IL-6 and its receptor, IL-6R. Therefore, adipose tissue can serve as a reservoir for the activation of IL-6 and cascade signaling of viral infection. The spread of viruses from organs affected by adjacent adipose tissue can take days, with prolonged viral shedding also contributing to the delay of the cytokine storm and consequent tissue damage in patients with COVID-19 [25,26].

3.2. Diabetes mellitus

Diabetes mellitus (DM) is a major risk factor for severity and mortality in individuals infected by SARS-CoV-2. Similar risk

evidence among people with diabetes has been reported for the previous two CoV infections, SARS in 2002 MERS in 2012 [27]. Studies have associated diabetes with greater weight loss and increased lung inflammation with macrophage infiltrates similar to those observed in the disease [27]. The risk of infections in patients with diabetes can be reduced, although it cannot be completely eliminated, by good glycemic control. For all people with diabetes (over 2 years old) pneumococci and annual vaccination against influenza are recommended. In addition, patients with diabetes have a serious disease when infected with respiratory infections. In fact, diabetes was seen as an important risk factor for mortality in patients infected with pandemic influenza (H1N1) in 2009, SARS-CoV and MERS-SCoV [28]. Glycemic homeostasis requires close quantitative and temporal regulation of glucose flow through different organs. Most of the circulating glucose in the body is in a stable configuration, similar to the biochemical characteristics of the cell wall from commensal bacteria found in the individual [29]. In the immune system, host-pathogen and host-host interactions take place through the recognition and binding of oligosaccharides in so-called C type lectin receptors (CLRs), which will induce a specific immune response. Several C type lectins recognize oligosaccharides rich in sugars such as mannose and fucose, which have a similar chemical structure to glucose [30], as SARS-CoV-2 recognition is through protein S, a glycoprotein, it may as well increase inflammatory processes [12]. In addition, the connection of SARS-CoV-2 with ACE2 in people with uncontrolled hyperglycemia may be important in COVID-19 pathogenesis. Possible changes in ACE2 glycosylation, as well as viral peak protein (S) glycosylation, both possibly induced by uncontrolled hyperglycemia, may alter both virus binding to ACE2 and immune response intensity against the virus [31].

3.3. Hypertension

Thiazide-type diuretics, calcium channel blockers (CCB), β -blockers, angiotensin converting enzyme inhibitors (ACEi) and angiotensin II type I receptor blockers (ARB) are antihypertensive drugs with distinct targets to lower blood pressure. The ACEi and ARB drugs targets the Renin Angiotensin System (RAS) and are also used in diabetes treatment, leading to an increased ACE2 expression that has been suggested by Fang [32] as risk increaser for severity of COVID-19, since SARS-CoV-2 uses ACE2 to enter the cells. In contrast, the study by Meng [33], in a hypertensive Chinese population with COVID-19 under treatment with ACEi/ARB drugs, displayed an attenuated inflammatory response. By inhibiting IL-6 cytokine levels they achieved a better clinical result: higher CD3⁺ and CD8⁺⁺ T cell counts in peripheral blood and lower viral load peak in comparison to other antihypertensive drugs. In addition, during hospitalization, 12 patients from the non-ACEi/ARB group (48%) were considered severe and one patient died *versus* ACEi/ARB group with 4 severe patients (23.5%) and no deaths. Therefore, there is no evidence that increased ACE2 expression by these drugs is indeed harmful, and further studies are needed to clarify their effects on COVID-19 infection. Also, the IL-6 controlled levels leading to better clinical results showed that an equilibrated inflammatory response is determining a better outcome for COVID-19 disease.

3.4. Cytokine storm

It has been reported that patients with severe symptoms of COVID-19 present the cytokine storm (CS) phenomenon, an uncontrolled release of pro-inflammatory cytokines. CS can be triggered by infectious diseases, rheumatic diseases, and tumor immunotherapy, and it generally presents as systemic inflammation, and multiple organ failure [34]. Among the consequences of CS

on lung viral infections are epithelial and endothelial cell apoptosis, resulting in vascular leakage and alveolar edema ultimately leading to hypoxia; impaired T cell response, accumulation of alternatively activated macrophages, changed tissue homeostasis, and acute respiratory distress syndrome (ARDS), the last being a primary cause of death in SARS-CoV/MERS-CoV patients [35]. The levels of inflammatory factors were measured in a study reported by Huang [36], including 41 COVID-19 patients (13 ICU and 28 non-ICU patients). IL-1B, IL-1RA, IL-7, IL-8, IL-9, IL-10, fibroblast growth factor (FGF), granulocyte-colony stimulating factor (G-CSF), interferon- γ (IFN γ), interferon- γ -inducible protein (IP10), monocyte chemo-attractant protein (MCP1), macrophage inflammatory protein 1 alpha (MIP1A), tumor necrosis factor (TNF α), vascular endothelial growth factor (VEGF) and others inflammatory factors were increased in both ICU and non-ICU patients compared to healthy adults. ICU patients showed higher concentrations of GCSF, IP10, MCP1, MIP1A, and TNF α than non-ICU patients, suggesting that the cytokine storm was associated with higher disease severity. A retrospective cohort study conducted by Zhou [37] reported elevated IL-6 blood levels in non-survivors compared with survivors throughout the clinical course of COVID-19 illness. Other studies also reported IL-6 increased levels in patients with severe COVID-19 [38–40]. In Anhui, China, a clinical trial (ChiCTR2000029765) using the IL-6 receptor-targeted monoclonal antibody (mAb) tocilizumab, reported improvement of respiratory function and rapid fever control in 21 patients with severe COVID-19. All patients recovered and were discharged from hospital, including two who were in critical condition [41]. This indicates the need of targeting anti-inflammatory strategies to the treatment of COVID-19 and demonstrates that a balanced immune host response is crucial to eliminate SARS-CoV-2 infection successfully.

3.5. Vitamin D and immune response

Given the need for a balanced immune response, vitamin D stands out. Its action is mediated by binding its active form 1- α -dihydroxyvitamin D₃ (VD₃) to its receptor, VDR, expressed in several immune cells [42,43]. VD₃ has a genomic binding site (VDR-GP), in which a transcriptional complex is formed modulating the expression of genes such as ACE and the VDR itself [42]. According to Sassi [42], individuals with respiratory infections and sepsis had exacerbated symptoms and reduced VD₃ levels. When using VD₃ as an experimental treatment protocol in patients with respiratory infections, it was observed infection reduction and modulation of pro-inflammatory cytokines, such as IL-1 β and IL-6, which are produced by helper (Th)1 cells [42]. Besides on acting on the immune system, this hormone plays an important role in metabolic disorders such as the pathophysiology of diabetes, modulating the expression of insulin and reducing systemic inflammation; regulating blood pressure by renin-angiotensin-aldosterone system (RAAS); and in obesity, regulating adipogenesis and the production and release of adipokines and cytokines. As VD₃ is connected to various metabolic pathways and immune system response, it becomes important to identify it as a therapeutic target [43].

4. Conclusion

Individuals with cardiometabolic diseases are more prone to SARS-CoV-2 infection due to immune response dysregulation, as the inflammatory response does not occur immediately. The role of medications generally used by individuals affected with diabetes, hypertension or other cardiovascular diseases, especially ACE inhibitors is debatable since those drugs lead to ACE2 receptor overexpression, associated to SARS-CoV-2 cell's entry. After virus entry into the cell, it multiplies until reaches many copies,

generating a more acute and late inflammatory response. Thus, a storm of cytokines occurs that end up harming healthy cells. In order to regulate inflammation and reduce damage to healthy cells, VD can modulate a favorable immune response and could hypothetically reduce levels of associated complications.

Author's contributions

Ms. Thays Maria Costa de Lucena (TMCL) conceived this mini-review and along with Ms. Ariane Fernandes da Silva Santos (AFSS) and Ms. Brenda Regina de Lima (BRL) carried out all the necessary scientific literature research and wrote the entire body of the text. Subsequently to MsC. Maria Eduarda de Albuquerque Borborema (MEAB) and PhD. Jaqueline de Azevêdo Silva (JAS), discussed the content, revised and adjusted the written material.

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