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Molecular and pro-inflammatory aspects of COVID-19: The impact on cardiometabolic health

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ABSTRACT

Obesity, type 2 diabetes (T2DM), hypertension (HTN), and Cardiovascular Disease (CVD) often cluster together as "Cardiometabolic Disease" (CMD). Just under 50% of patients with CMD increased the risk of morbidity and

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mortality right from the beginning of the COVID-19 pandemic as it has been reported in most countries affected by the SARS-CoV2 virus.

One of the pathophysiological hallmarks of COVID-19 is the overactivation of the immune system with a prominent IL-6 response, resulting in severe and systemic damage involving also cytokines such as IL2, IL4, IL8, IL10, and interferon-gamma were considered strong predictors of COVID-19 severity. Thus, in this mini-review, we try to describe the inflammatory state, the alteration of the adipokine profile, and cytokine production in the obese state of infected and not infected patients by SARS-CoV2 with the final aim to find possible influences of COVID-19 on CMD and CVD.

The immunological-based discussion of the molecular processes could inspire the study of promising targets for managing CMD patients and its complications during COVID-19.

1. Introduction

Infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pathogen that causes coronavirus disease 2019 (COVID-19) illness in humans, is often characterized by a systemic inflammatory host response. Pre-existing cardiovascular comorbidities are known risk factors that increase the severity of COVID-19. They are usually present alone or in combination in COVID-19 patients and include chronic respiratory, cardiovascular, and kidney disease, type 2 diabetes (T2DM), and nonalcoholic Fatty liver disease (NAFLD) [1,2]. These conditions are identified as independent risk factors for poor prognosis in COVID-19, each playing a role in its pathophysiology through a number of different mechanisms [3,4]. The presence of hypertension (HTN), diabetes, obesity, and atherosclerosis predispose to disease severity and are correlated with higher mortality in hospitalized patients with COVID-19 [5–8]. In more advanced cases, disease severity is characterized by hyperactivation of the immune system causing a "cytokine storm" responsible for cytokine release syndrome (CRS) [9]. The aggressive inflammatory response begins with a local release of cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which can spread systemically, evolving to acute respiratory distress syndrome (ARDS) and multiple organ injury such as brain damage [10,11].

To bind COVID-19 and CMD are also the expression of genes related to inflammation (eleven genes) found overlapping among hypertension, DM, coronary artery disease (CAD) and that are considered predictors of susceptibility and severity of COVID-19 [12]. The core gene was IL6 that interconnect the phenomena associated to inflammatory responses by CMD and infection by SARS-CoV-2. These data explain why some individuals become more severely affected by SARS-CoV2 exacerbating symptoms for the expression of a regulator of the immune response, cytokine activity, and viral infection. The identification of key genes among genes associated with COVID-19 and comorbidities, have suggested combinatory therapies based on dexamethasone and vitamin D. Dexamethasone treatment, a corticosteroid with effectiveness immunosuppressive role, in moderate to severe COVID-19 patients was correlated with improving clinical outcome, while Vitamin D shown antimicrobial effects regulating the expression of TLR2 and TLR4 and reducing IL6 levels [13]. Moreover, Vitamin D is an effective renin inhibitor leading the reduction ARDS risk, myocarditis, or heart injury in patients with COVID-19 [14].

The interplay of risk factors that determine the course of COVID-19 is not fully understood. In this review, we focus our attention on the effect of COVID-19 disease in patients with cardiometabolic disease (CMD), with particular attention to the molecular aspects and proinflammatory processes that are prevalent in these conditions. We detail the features of the immune system in the context of CMD in patients without and with SARS-CoV2 infection and review current knowledge regarding their impact on clinical outcomes as summarized in Table 1.

2. Cardiometabolic disease and COVID-19

Obesity, T2DM, HTN, and Cardiovascular Disease (CVD) often cluster together as the "Metabolic Syndrome" (MeS) and increase the risk of morbidity and mortality. CMD is multidimensional and involves genetic, behavioral, and environmental factors. There is growing evidence that healthy lifestyle and patient education can greatly reduce the risk of adverse outcomes in CMD [15]. While it is not clear whether MeS and CMD have an underlying pathophysiology or are merely an assemblage of risk factors, the identification of its elements is important for appropriate management.

Several reports have examined the components of CMD and their relationship to COVID-19 patients from an epidemiological, risk factor, prognostic or management perspective [16]. A common limitation of the studies was that they reported the recurrence of symptoms compared with normal conditions, likely underestimating the true prevalence of COVID-19 patients, and limiting the capacity to really estimate the risk of SARS-CoV-2 infection in CMD. It was evident at the onset of the pandemic that just under 50 % of patients had at least one of the major comorbidities mentioned previously [17]. The high prevalence of comorbidities related to CMD has been reported in most countries affected by the pandemic. Another common observation was the higher disease severity and fatality rate in COVID-19 patients with these comorbidities [18]. Conversely, HTN, CVD, T2DM, and obesity were all associated with increased susceptibility to SARS-CoV-2 infection [19,20]. Furthermore, there has been a link of SARS-CoV-2 infection and its subsequent inflammation can lead to the development of new onset prediabetes and diabetes [21,22].

Previous researchers have demonstrated that patients with CMD have enhanced levels of proinflammatory factors suggesting an immune dysregulation, resulting in an altered immune response. Components of CMD such as excess fat mass are known to upregulate the levels of key immune factors such as C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6) and numerous other adipokines involving in chronic inflammation. One of the pathophysiological hallmarks of COVID-19 is overactivation of the immune system with a prominent IL-6 response [23], resulting in severe inflammation, chemokine storm, and systemic damage. Other cytokines are considered biomarkers and strong predictors of COVID-19 severity such as IL2, IL4, IL8, IL10, and interferon-gamma [24]. Thus, the levels of proinflammatory cytokines and other inflammatory factors are already high in patients with CMD and COVID-19 increases their expression, inducing the phenomenon of "cytokine storm". There seems to be compelling reasons to argue that to guide the Future Management of Diabetes patients, we can search for relevant notions from recent experiences of COVID-19 pandemia [25]. Both obesity and CVD are the predominant comorbidities in the CMD spectrum that are present in COVID-19 patients and are discussed in more detail in the ensuing sections.

3. Pathophysiologic mechanisms of immune dysregulation in obesity

Obesity is characterized by adipose tissue remodeling; the latter being classified as white (WAT) and brown adipose tissue (BAT). Adipose tissue is considered an endocrine organ producing several bioactive molecules that act in a pleiotropic manner. Adipocytokines ("adipokines") are WAT-derived compounds that exert variegate functions, one of them being immune system regulation. There is an alteration of the

Table 1
Short description of the roles of main mediators in the outcomes of COVID-19 infection.

Mediators	Clinical outcome of COVID-19 patients
Cytokines storm: IL-6, TNF-α, IL-1β, ferritin and CRP, CXCL10, MCP-1	High serum concentrations were correlated with severe COVID-19
IL-2, IL-4, IL-8, IL-10, and IFN-γ	Considered strong predictors of COVID-19 severity
Leptin	Contribution to acute respiratory distress syndrome (ARDS) in patients with COVID-19
Anti-inflammatory adipokines: chemerin, omentin and vaspin	Considered significantly decreased in COVID-19 patients and are related with pathogenesis.
Angiotensin II (Ang II)	Increased level was associated with severe COVID-19
Angiotensin (1-7)	Decreased level were associated with severe COVID-19

adipokine profile and cytokine production in the obese state, with an increased propensity to develop insulin resistance, T2DM, HTN, and CVD. Inflammation in obesity is characterized by the secretion of proinflammatory cytokines induced by adipocytes and produced by adipose tissue-resident activated macrophages.

The severity of inflammation is not only dependent on the quantum of body weight but more on the location and distribution of body fat [26]. Higher inflammation has been reported in individuals with high body fat despite normal weight, a phenotype that is commonly seen in the south Asian region [27,28].

It has been observed that in the obese state, normal immune cells like M1 macrophages, Th1, Th17, and CD8+ T cells secrete proinflammatory cytokines such as IL-1β, IL-6, IL-17, and IFN-γ replacing regulatory T cells (Treg), M2-type macrophages, type 2 innate lymphoid cells (ILC2) and T-helper (Th)2 populating non fatty tissue [29]. In parallel, there are circulating systemic immune adaptations such as elevated levels of proinflammatory cytokines, increased numbers of monocytes, neutrophils, Th1, Th17, Th22 and, in contrast, decreased circulating Treg with anti-inflammatory effects. The resulting imbalance between pro and anti-inflammatory adipokines is an important risk factor for acute lung injury [30]. Proinflammatory cytokines such as TNF-α, IL-1β and IL-6, IL-8 and C-reactive protein (CRP), and monocyte chemotactic protein-1 (MCP-1) in patients with obesity and in various animal models of obesity have been shown to impact the immune response to infections. In addition, adiponectin has a relevant role in the suppression IFN-γ production in macrophages upon LPS-stimulation leading to inadequate antiviral immunity. The release of IL-1β is considered responsible for the enhanced myelopoiesis in the bone marrow. In fact, obesity is linked to the activation of myelopoiesis, demonstrated by the enhanced numbers of myeloid progenitor cells and the resulting neutrophilia and monocytosis in animal models.

It is generally accepted that metabolic stress induces both local and systemic immune alterations in adipose tissue [29]. Locally, there is a decrease in diffusion/exchange of gas (O2/CO2) with progressive local hypoxia and, consequently, stimulation of hypoxia-inducible factor 1alpha (HIF-1α) and NF-κB expression. The HIF-1a activities include the expression of the leptin gene that in turn, induces Th1, Th17 cell differentiation and inhibits T regulatory cells (Treg cells). Leptin can directly stimulate Dendritic Cells, macrophages, and Natural Killer cells to secrete inflammatory cytokines such as IL-6, IL-1, and TNF-α and, through autocrine signaling, induces adipocytes to produce the same pattern of cytokines [31]. In light of these observations, it is reasonable to assume that obesity predisposes to an increased risk of pneumonia, and COVID-19 could worsen the outcome. The following sections summarize the consequences of COVID-19 in patients with obesity.

4. Impact of COVID-19 on the immune response of patients with obesity

Individuals with COVID-19 and obesity have a 6-fold higher risk of hospitalization compared with adults of normal weight [32,33]. Although individuals with obesity might not be more susceptible to infections, obesity still confers an element of risk for more serious diseases and for increased lung complications due to respiratory viruses such as coronavirus, influenza, parainfluenza, meta-pneumovirus and rhinovirus. Interestingly, the 'obesity paradox' refers to the phenomenon in which critical ill patients with obesity may have worse morbidity outcomes, but their mortality rates are not increased. To date, the mechanism remains unclear even though it has been affirmed in several clinical studies and meta-analyses. Unexpectedly, both during the 2009 H1N1 and the current COVID-19 pandemic, this phenomenon has not been observed. Obese Intensive Care Unit (ICU) patients with coronavirus infection lose the survival advantage when they are infected by the virus, except for only two studies [34,35]. A well-studied aspect of SARS-CoV2 infection is the dysregulated immune response that impairs T-cell-mediated immunity and produces abnormal levels of proinflammatory cytokines. Both children with obesity [36] and adult patients [37] are exposed to an increased risk of pneumonia and worse outcomes in COVID-19 [38] due to the enhanced secretion of proinflammatory cytokines that are involved in chronic low-grade inflammation [39]. Chronic inflammation and impaired T-cell immunity could be considered the key processes linking obesity and COVID-19. Thus, increased mortality in SARS-CoV2 infected patients with obesity is caused by a potential increase in the inflammatory response to COVID-19 infection ("cytokine storm") and disturbances in T-cell-mediated immunity [37].

Leptin and adiponectin modulate lung inflammation [40]. Many studies have analyzed adipokines activities suggesting their possible influence in pathogenesis and SARS-CoV2-infection course [41]. In a study of 70 COVID-19 patients demonstrated that serum concentrations of chemerin and omentin were significantly decreased compared to healthy volunteers, but there were no correlations between these levels and frequency of symptoms and disease severity [42]. Adiponectin is an anti-inflammatory adipokine usually reduced in obesity. It is regulated in an opposite manner to leptin, which has been found in higher concentrations in COVID-19 patients admitted to the ICU [43]. However, a nonsignificant increase in adiponectin levels in patients with severe COVID-19 was reported [44]. Another study demonstrated that the ratio of adiponectin/leptin could be related to the pathogenesis of COVID-19 [45]. Indeed, a group of patients with mild disease showed a lower adiponectin/leptin ratio reflecting milder inflammation, while moderate COVID-19 patients had the highest ratio associated with an adequate response and better outcome. Surprisingly, severe ill patients showed a similar ratio as the mild patients [45]. The reason for this apparent discrepancy could be due to the dysregulated immune response in severe COVID-19 patients with obesity.

Not all studies have found a significant correlation between adipokine levels with most inflammatory mediators and the severity of the disease [46]. Plasma cytokine levels between patients with or without obesity found significant differences only in the baseline IL-1β levels, which were lower in metabolic syndrome (MeS) than non-MeS patients, with a specific cytokine pattern having been identified that correlated with mechanical ventilation [47]. Thus, the poor prognosis in obese or MeS patients with COVID-19 pneumonia could be influenced by factors other than the "cytokine storm". CXCL10, a Th-1 chemokine and cytokines such as TNF-α, IL-2, IL-1β or IL-6, IFN-γ, protein inducible by interferon 10 (IP-10) and monocyte chemoattractant protein-1 (MCP-1) were found in high concentration in alveolar and plasma of COVID-19 patients [48]. Leptin is a regulator of proinflammatory response by the innate and adaptive immune systems regarding Th1-like differentiation. Leptin receptor was found in lungs both from human and animals directly modulating inflammatory responses that contribute to the

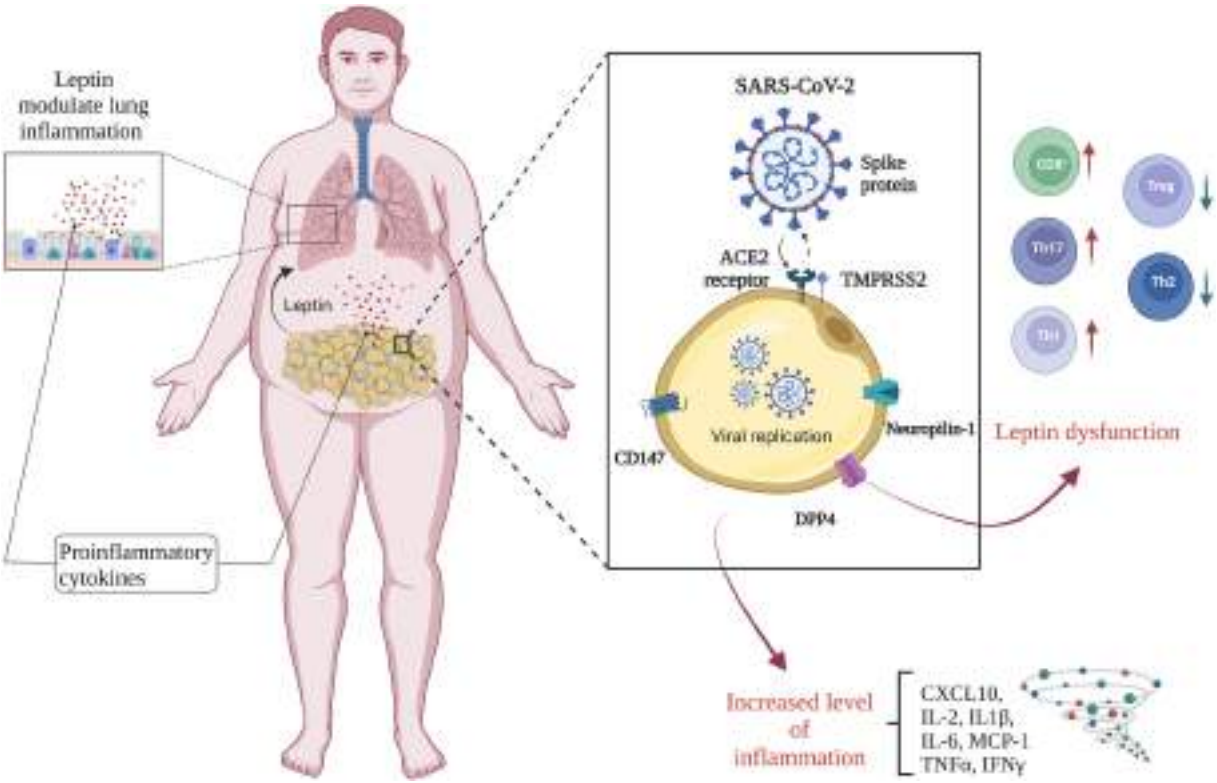

Fig. 1. Molecular mechanisms linking obesity, typified by a state of low-grade inflammation, to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

pathophysiology of COVID-19. Indeed, macrophages recruited by leptin into adipose tissue secrete an abnormal quantity of IL-6 and TNF-α during SARS-CoV-2 infection in patients with obesity [49]. In this manner, leptin-related adipocyte dysfunction could contribute to acute ARDS in patients with COVID-19 and concomitantly, SARS-CoV2 infection could contribute to enhance systemic hyperinflammation in patients with obesity [50]. The cumulative data suggest that there are potential common mechanisms in obesity and COVID-19 disease [51] such as 1) efflux of proinflammatory cytokines contributing to the "cytokine storm" of COVID-19; 2) altered immune function; 3) diminished pulmonary function with a low expiratory reserve volume and respiratory system compliance and 4) higher expression of ACE2 receptors in fatty tissue that can favor infection in patients with obesity [52,53]. These latter show high levels of expression of several molecules for host cell entry of SARS-CoV-2 into visceral adipose tissue, such as the spike protein processing enzyme (FURIN) and CD147, DPP4, neuropilin-1 [54], suggesting that adipose tissue could act as a reservoir for the virus. In conclusion, COVID-19 enhances the secretion of inflammatory cytokines that together with leptin dysfunction, determine the severity of COVID-19 illness as explained in Fig. 1.

The pathophysiology of SARS-CoV-2 primarily includes cell tropism with respect to adipocytes showing increased expression of ACE2, TMPRSS2, and CD147. SARS-CoV-2 determines the dysregulation of the immune response that is characterized by the so-called "cytokine storm" with high levels of IL-6, TNF-α, IL-1β, ferritin and CRP, CXCL10, MCP-1, macrophages Th1-like and, low level of lymphocytes differentiated as Treg and Th2. In turn, patients with obesity infected by SARS-CoV2 have shown leptin dysfunction with amplification of cytokine production and immune system unbalance at the systemic level. Angiotensin-Converting Enzyme 2 (ACE2); TransMembrane Serine Protease type 2 (TMPRSS2); transmembrane glycoprotein receptor (CD147). interleukin-6 (IL-6); tumor necrosis factor-α (TNFα); interleukin-1β (IL-1β); C-reactive protein (CRP).

5. Pathophysiology basis of immune dysregulation in cardiovascular disease

CVD is conditioned by fat accumulation. Indeed, obesity amplifies the effects of multiple CV risk factors by 1) accelerating their development; an adverse myocardial effect is known to occur due to obesity-mediated activation of the renin-angiotensin-aldosterone system (RAAS) with the overexpression of angiotensin; 2) increasing the risk of thrombosis caused by chronic inflammation resulting in the down-regulation of the antithrombin, C-protein and TFPI (some of the anti-coagulant regulatory proteins), overexpression of the tissue clotting factors and P-selectin, which increase adhesion, thrombin synthesis, and platelet activation [9].

The immune system plays a critical role in the pathophysiology of CMD, in which chronic inflammatory defects promote the progression of complex abnormalities. Indeed, the high frequency of macrophages within the vascular wall is generally indicative of atherosclerosis. They scavenge lipoprotein particles and oxidize LDL in the subendothelial space, eventually becoming foam cells secreting inflammatory molecules and sustaining the progression of atherosclerosis. In chronic advanced lesions, the clearance of apoptotic macrophages is mediated by slow phagocytes [7]. This last process generates a gradual accumulation of apoptotic debris with necrotic core formation and triggers further inflammation and thrombosis. Macrophage subtypes have been found in atherosclerotic lesions with the following characteristics: 1) M1 macrophages release proinflammatory cytokines TNF-α, IL-6, IL-12; 2) Mox macrophages show an antioxidant gene expression profile; 3) M2 macrophages are not influenced by lipid accumulation, possess iron manipulation capabilities, and show anti-inflammatory functions, 4) M4 macrophages are similar to M1 macrophages in their proinflammatory effects but lack the ability of phagocytosis. Sequential space-time recruitment of M1 and M2 macrophages occurs within the plaque. Plaques of symptomatic patients exhibit macrophages with M1 phenotype, while asymptomatic patients predominantly express markers of M2

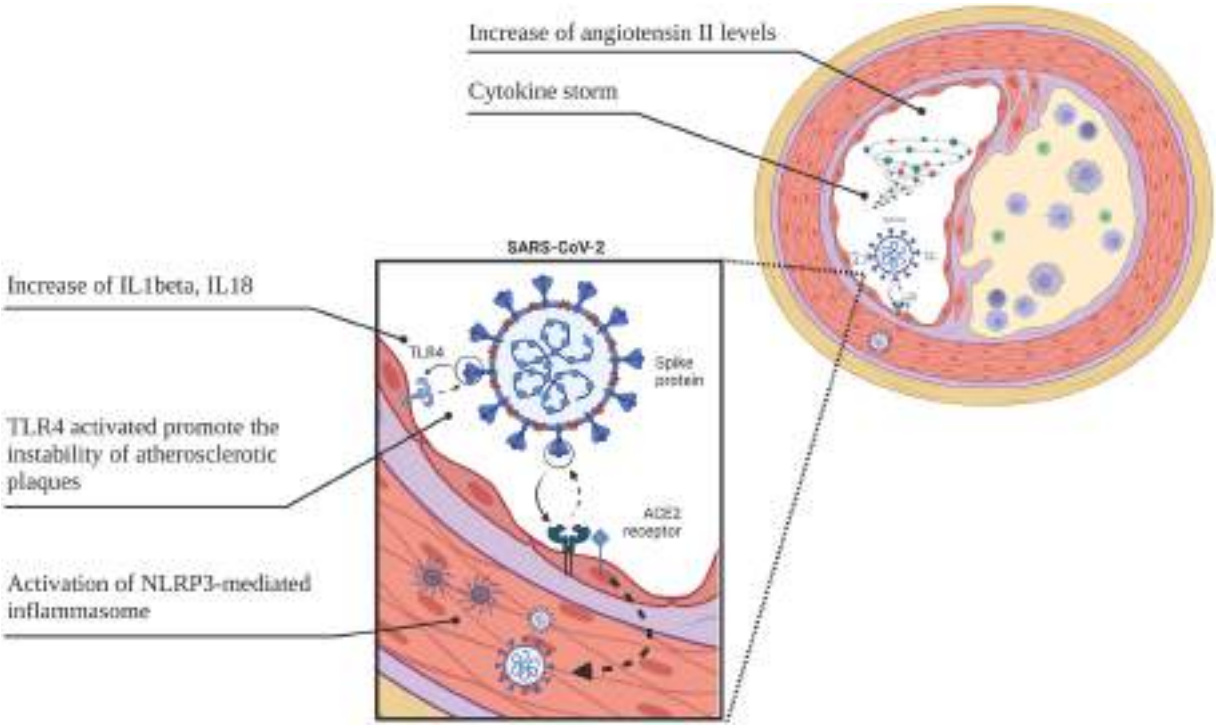

Fig. 2. Cardiovascular complication in SARS-CoV-2 infection.

polarization [18]. Moreover, M1 macrophages are predominant in plaques with an unstable phenotype that could be the mirror of an imbalance between M1 and M2 phenotypes. Reduced numbers and function of Treg cells may be present in a variety of cardiovascular diseases, although the precise molecular mechanisms underlying the cardioprotective effects of them have yet to be clarified [23].

Interestingly, patients with CMD and animal models with induction of CMD showed a high number of mast cells with enhanced activity in the involved tissues. Mast cell mediators impede vascular cell function, affecting extracellular matrix integrity as well as the functions of other inflammatory cells, thus determining the pathobiology of multilayered conditions [4].

6. Impact of COVID-19 on the immune response of patients with cardiovascular disease

The presence of CVD predisposes to serious infections and has a greater risk of morbidity when infected with SARS-CoV-2 [55]. Heart failure (23 %) detected in hospitalized COVID-19 patients was not found to be based on preexisting cardiomyopathies [56], and acute myocarditis was the definitive cause of death in 7 % of COVID-19 patients [57]. The direct pathophysiological link between COVID-19 and CVD, however, has not yet been fully clarified. Cardiac biomarkers such as Hs-cTn-high-sensitive cardiac troponin, Creatine kinase MB isoenzyme, and others, have been indicated as prognostic elements for patients with COVID-19, but doubts remain on their efficacy in actual clinical practice. Several reports based on autopsy samples from COVID-19 patients demonstrate direct SARS-CoV-2 virus effects on the myocardium and vascular endothelial cells in the pathophysiology of CVD [58,59]. Intracellular entry of the SARS-CoV-2 virus increases angiotensin II (Ang II) levels and downregulate ACE/Ang-(1–7) in severe COVID-19 patients [41], which in turn has been shown to increase tissue factors in monocytes. Moreover, circulating Ang-(1–7)/Ang II ratio was three-fold higher in COVID-19 patients suggesting also other Ang-(1–7)-forming activity [60].

Indeed, while Ang (1–7) exerts protective effects on cardiovascular and lung organs, Ang II elicits pro-inflammatory and promotes fibrosis with detrimental effects by binding to the angiotensin type 1 receptor (AT1R). Therefore, AT1R blockers (ARBs) and Ang (1–7) agonists seem to be a good treatment options since they alleviate the harmful effects associated with Ang II upregulation [61].

In addition, damage mediated by angiotensin-converting enzyme 2 (ACE2) [62], hypoxia, microvascular thrombosis, and systemic inflammation contributes to clinical outcomes [41,63]. SARS-CoV-2 viral infection also leads to activation of a proinflammatory state [59], which worsens endothelial dysfunction. Robles and colleagues demonstrated that the SARS-CoV-2 spike protein activates the EC inflammatory phenotype in a manner dependent on integrin α5β1 signaling [64]. This finding suggested that spike protein is responsible for vascular leakage and leukocyte adhesion in endothelial dysfunction by activation of NF-κB target gene expression (such as procoagulant genes).

Increased levels of the proinflammatory cytokines IL-6, IL-8, and TNF-α directly cause upregulation of inflammation and endothelial damage [65]. They also cause injury to the lung infrastructure and further induce harmful lesions in the pulmonary blood vessels [66]. In addition, the viral effect in suppressing host antiviral immunity and inducing cell death in infected epithelia/endothelium and virus-bound platelets causes excessive inflammation and is amplified in the cytokine release syndrome (CRS), leading to cardiovascular injury [67]. Clearly, the scale and intensity of virus-host interaction are heterogeneous and lead to different manifestations of COVID-19. Thus, the hyperinflammatory state dysregulates platelet factors [68] and induces hypoxia that further upregulates inflammation by activating IL-6 and TNF-α in a spiral circuit. The hyperinflammatory cytokine response in various tissues leads to acute inflammation such as septic shock and/or multiple organ failure, which can cause further damage to the endothelial lining.

P2X7 purinergic receptors have been shown to play an important role in a variety of cardiovascular diseases due to the activation of the NLRP3 inflammasome, resulting in the release of IL-1β and IL-18 [69]. Indeed, the precursors of IL-1β and IL-18 (pro-IL-1β and pro-IL-18) are inactive and are regulated by post-transcriptional mechanisms involving the activation of the inflammasome. In the same fashion, P2X7R/NLRP3 axis could participate in the immune dysregulation caused by the SARS-

CoV-2 infection [70,71]. Coronavirus has been demonstrated to activate the NLRP3 inflammasome [72].

A closer look at the molecular detail indicates that TLR4 contributes to the pathogenesis of atherosclerosis in several ways. Indeed, many cell types in atherosclerotic vessel walls are enriched in TLR4 expression. TLR4 is also expressed in macrophages and after its activation triggers a cascade of signaling events that activates inflammatory cytokines production and proteases. Another consequence of this activation is to promote the instability of atherosclerotic plaques and enhance their vulnerability to physical damage and acute thrombosis. An in-silico study demonstrated a link between TLR4 and the spread of SARS-CoV2 infection [73], raising the hypothesis that the TLR pathway may play a role in the exacerbation of inflammation in patients with CVD by induction and activation of the NLRP3-mediated inflammasome [74]. SARS-CoV-2 spike glycoprotein binds to TLR4 and activates signaling to increase cell surface expression and facilitate entry of ACE2. Thus, counteracting the action of SARS-CoV-2 induced endothelial dysfunction by inflammasomes or TLR4 activation is a promising target for managing CVD in COVID-19, as shown in Fig. 2.

Endothelial cell damage and thrombi-inflammation are amplified in cardiovascular patients infected by SARS-CoV2. The consequences are related to increasing the entry of the virus in endothelial cells through higher expression of TLR4 and ACE on the cell surface. By P2X7R, the virus activates the NLRP3 inflammasome resulting in the release of IL-1β and IL-18 that accumulate along with other cytokines in the cytokine storm phenomenon.

7. Conclusions

A number of studies have expounded on the relationship between CMD and COVID-19 since the beginning of the global pandemic. The former increases susceptibility to SARS-CoV-2 infection, with an increased likelihood of developing severe illness requiring intensive care and mechanical ventilation. Additionally, CVD, HTN, T2DM, and elevated BMI have consistently been reported as major risk factors for mortality in COVID-19 patients. The pathogenesis of COVID-19 is related to increased inflammation with dysregulation of the immune response and the triggering of a “cytokine storm.” These factors increase the proinflammatory immune response already present in subjects with CMD, significantly affecting the health of patients with COVID-19 illness. This is the reason why in clinical practice it has been noticed a bidirectional impact between COVID-19 and diabetes as well as obesity [16,75]. Targeting of inflammatory biomarkers could be promising for early identification of patients at risk of adverse outcomes.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

None reports was provided by none. None reports a relationship with none that includes: None has patent pending to none. None.

Data availability

No data was used for the research described in the article.

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