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REVIEW

Obesity-Related Inflammation and Endothelial Dysfunction in COVID-19: Impact on Disease Severity

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Abstract: The coronavirus disease 2019 (COVID-19) pandemic has put into evidence another pandemic – obesity. Currently, several studies have documented the association between obesity and COVID-19 severity. The mechanisms underlying the increased risk of complications and mortality in obese patients with COVID-19 are of diverse nature. Inflammation plays a central role in obesity. Metabolic alterations seen in obese patients are related to an inflammatory response, and several studies report elevated levels of circulating inflammatory cytokines in obese patients. Also, deregulated expression of adipokines, such as leptin and resistin, increase the expression of vascular adhesion molecule 1 and intercellular adhesion molecule 1 that contribute to increased vascular leukocyte adhesiveness and additional oxidative stress. Additionally, it is now recognized that the chronic impairment of systemic vascular endothelial function in patients with cardiovascular and metabolic disorders, including obesity, when intensified by the detrimental effects of SARS-CoV-2 over the endothelium, may explain their worse outcomes in COVID-19. In fact, vascular endothelial dysfunction may contribute to a unfavorable response of the endothelium to the infection by SARS-CoV-2, whereas alterations in cardiac structure and function and the prothrombotic environment in obesity may also provide a link to the increased cardiovascular events in these patients.

Keywords: obesity, inflammation, COVID-19, endothelial dysfunction, microcirculation

Obesity, COVID-19 and Inflammation

The coronavirus disease 2019 (COVID-19) pandemic has put into evidence another pandemic – obesity, an increasing threat to societies around the world.[1] The first studies of COVID-19 did not provide body mass index (BMI) data,[2] and the association between disease severity and obesity was not perceived initially. Subsequent data from several countries, however, cast light on this association,[3,4] and several studies have documented the association between obesity and COVID-19 severity.[4–7] Currently, obesity may be considered a true independent risk factor for COVID-19 mortality.[8]

The mechanisms underlying the increased risk of complications and mortality in obese patients with COVID-19 are many, and of diverse nature (Figure 1). Obesity is associated with several disorders, related to defective homeostasis of the dysfunctional adipose tissue, in which local and systemic chronic inflammation, oxidative stress, altered release of cytokines, and impaired immune response play important roles[9–11]; all of these have been demonstrated to be associated with

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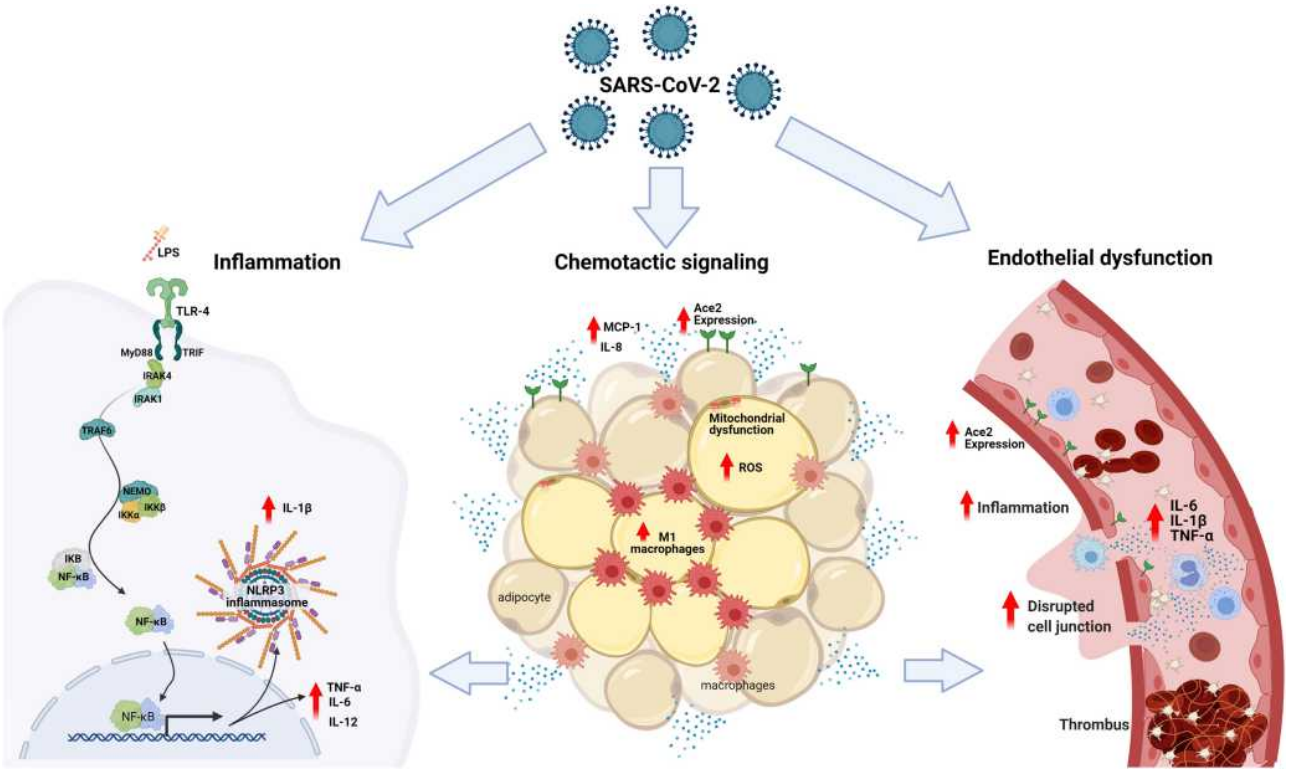

Figure 1 The mechanisms underlying the increased risk of complications and mortality in obese patients with COVID-19 based on the association of low-grade inflammation, adipose tissue dysfunction and endothelial dysfunction: In obese patients with COVID-19 or SARS-CoV-2, as well as, the bacterial endotoxins (LPS) of the intestinal bacterial translocation promote the activation of TLR4 in favor of the MyD88-dependent pro-inflammatory pathway. The activation of NF-κB is linked to the production of TNF-α, IL-1β, IL-6, IL-12 and other cytokines, contributing to the activation of NLRP3 inflammasomes and increased expression of ECA2. In the adipose tissue of patients with COVID-19, there is an increase in the expression of ECA2, promoting greater entry of SARS-CoV-2, making this tissue a viral reservoir. Metabolic inflammation in obese patients is characterized by dysfunctional adipose tissue, with mitochondrial dysfunction and decreased fatty acid oxidation, causing an amount of inflammatory cells showing an increase in the influx of M1 macrophages and chemotactic signaling, via MCP-1 and release of IL-8 by adipocytes, associated with an increase in reactive oxygen species. Associated with this process of immune activation, obese patients with COVID-19 have systemic microvascular dysfunction and a predisposition to thrombus formation that is exacerbated by higher levels of circulating inflammatory cytokines, such as TNF-α, IL-1β and IL-6, worsening the outcomes in COVID-19.

higher risk and worse prognosis of infectious diseases in this patient population.[12–14]

Inflammation plays a central role in obesity.[15] Obesity promotes profound changes in the structure and function of adipose tissue, as adipocytes undergo hypertrophy and hyperplasia, increasing oxygen need, which remains unmet due to the insufficient vascularization relative to the enlarged adipose tissue. This leads to tissue hypoxia and immune cell infiltration that perpetuates local inflammation.[16–18] Insulin resistance is also a link between obesity-related metabolic disorders and inflammation, as the remodeling of the adipose tissue leads to activation of NLRP3-inflammasome, which ultimately impairs of the insulin-signaling pathway and insulin resistance, a key factor in the development of the metabolic syndrome.[19]

Additionally, mitochondrial dysfunction in adipocytes may be a cause of adipose tissue inflammation and insulin resistance. The defective mitochondrial function and decreased fatty acid oxidation in adipocytes increase triglyceride accumulation, adipocyte enlargement and consequent adipose tissue hypoxia; this, in its turn, leads to accumulation of hypoxia-inducible factor-1α (HIF-1α), which promotes adipose tissue inflammation and fibrosis.[20] This continuous inflammatory cycle also contributes to a neuro-immuno-endocrine dysregulation in the context of the metabolic syndrome.[21] The inflammatory state affecting obese individuals is called metabolic inflammation or metainflammation, in which there is also an increased influx of M1 macrophages occurring, as well as decreased M2 macrophages and Treg cells in the visceral adipose tissue[22] through chemotactic signaling, via MCP-1 and IL-8 released by adipocytes.[23]

The excessive intake of carbohydrates is an important trigger for these processes.[24] In addition, peripheral inflammation and various pro-inflammatory signals in the nucleus accumbens, including reactive gliosis, increased expression of cytokines, antigen-presenting markers and transcriptional activity of NFκB[25] contribute to the

activation of the innate immune response, mainly through activation of Toll-type receptors (TLR), specifically TLR-4, considered an intersection of dysfunctional metabolism and activated immunity in obesity.[26] NF-κB is a molecular hub for pro-inflammatory gene induction both in innate and adaptive immune responses since it is highly regulated and regulates the expression of a vast array of genes.[27] Among many different immune effects, NF-κB activation is linked to the production of TNF-α, IL-1β, IL-6, IL-12 and other cytokines, and is also involved in NLRP3 inflammasome regulation and activation of $CD4^+$ T-helper cells.[28] It is noteworthy that there is evidence that the virus can bind and activate TLR4 signaling in favor of the proinflammatory MyD88-dependent and contributing to increased expression of ACE2 and promoting greater viral entry.[29]

Obesity and Vascular Endothelial Dysfunction

Macrovascular Endothelial Dysfunction

The chronic impairment of systemic vascular endothelial function in patients with cardiovascular and metabolic disorders, including hypertension, obesity, diabetes mellitus, coronary artery disease and heart failure, when intensified by the detrimental effects of the severe acute respiratory syndrome coronavirus (SARS-CoV-2) over the endothelium, may explain their worse outcomes in COVID-19.[30–33] Regarding obesity, a community-based clinical trial (n=521; mean follow-up of 8.5 years) showed that increases in weight, body mass index, waist circumference and body-fat percentage over time were associated with worsening of microvascular endothelial function, assessed by flow-mediated dilation in the brachial artery.[34] Most subjects (84%) were overweight or obese at baseline; those who lost weight over time had improved vascular endothelial function.[34]

In fact, vascular endothelial dysfunction and increased arterial stiffness are thought to contribute to a unfavorable response of the endothelium to the infection by SARS-CoV-2, whereas alterations in cardiac structure and function and the prothrombotic environment in obesity could provide a link for the augmented cardiovascular events in these patients.[35] Moreover, fast increasing evidence from basic science, imaging and clinical observations suggest that COVID-19 could be considered as a vascular disease.[36,37]

Microvascular Endothelial Dysfunction

Obesity is accompanied by functional and structural systemic microvascular dysfunction,[38] and endothelial-dependent microvascular vasodilation is severely impaired in obesity.[39–41] Endothelial-dependent capillary recruitment, induced either by reactive hyperemia or by shear stress, is blunted in obese subjects, compared to non-obese counterparts.[42,43] In the clinical setting, endothelial function and reactivity can be assessed using different technologies that evaluate microvascular flow and tissue perfusion coupled to physiological or pharmacological stimuli,[44,45] to activate different vasodilator pathways resulting in increased microvascular conductance. The most commonly used provocations are the administration of endothelial-dependent vasodilators by transdermal iontophoresis,[46–48] thermal hyperemia[49,50] and post-occlusive reactive hyperemia.[51–53] In this context, the cutaneous microcirculation is now considered as an accessible and representative vascular bed for the assessment of systemic microcirculatory reactivity.[45,54–56] A reduced vasodilation response to these different stimuli is indicative of microvascular endothelial dysfunction and is also considered to be predictive for cardiovascular and metabolic diseases and clinical prognosis.[57–60]

In patients with established cardiovascular disease, the reduction of microvascular endothelial-dependent vasodilation (ie, endothelial dysfunction) is associated with increasing BMI, even after adjustment for treated diabetes mellitus, hypertension, hypercholesterolemia, and smoking.[61] In that study, BMI was classified in three different intervals: <25, 25-to 30 and >30 kg/m^2.[61] Moreover, Csipo et al showed that weight loss (reduction of BMI from 31.8 to 27.5 kg/m^2, accompanied by a reduction of serum cholesterol, LDL, triglycerides, and increased HDL) after a low-carbohydrate, low-calorie diet, resulted in improvement of microvascular endothelial function in geriatric obese (class 1) patients,[62] assessed by laser speckle contrast imaging in the skin, after post-occlusive reactive hyperemia. Additionally, endothelial function of resistance arterioles of the gluteal subcutaneous tissue is impaired in non-diabetic subjects with moderate levels of obesity (BMI 34.7 ± 4.0 kg/m^2), in association with systemic inflammation. In women, BMI was significantly associated with high-sensitivity C-reactive protein.[63]

Regarding mechanisms of microvascular dysfunction, using a new methodology of microdialysis in the skeletal

muscle, La Favor et al showed a significant increase in superoxide anions, as well as in NADPH oxidase subunit expression, associated with microvascular endothelial dysfunction in obese subjects relative to lean and overweight/mildly obese subjects.[64] Interestingly, 8 weeks of aerobic exercise training resulted in decreased H_2O_2 levels and improved microvascular endothelial function in the muscle tissue of obese subjects.[64] The study therefore linked NADPH oxidase, as a source of reactive oxygen species, to microvascular endothelial dysfunction in obese individuals, with amelioration induced by aerobic exercise.

Microvascular dysfunction has been considered to be a pathophysiological link between overweight/obesity and cardiometabolic diseases, including arterial hypertension, insulin resistance, and glucose intolerance.[43,65–69] Acknowledged mechanisms include changes in the secretion of adipokines, leading to increased levels of free fatty acids and inflammatory mediators, and decreased levels of adiponectin, all of which may impair endothelial insulin signaling.[70–73] It is also of note that there are changes at the level of the microvascular network in obesity, involving a reduction in the number of arterioles or capillaries within vascular beds of various tissues (such as the skeletal muscle and skin), which is defined as vascular (capillary) rarefaction.[74–77] In fact, obese individuals have both structural and functional alterations in skin microcirculation that are proportional to the increase in the degree of global and central obesity, arterial pressure levels and with the degree of insulin resistance.[42] In non-diabetic, untreated hypertensive patients, reduced capillary density has also been related to obesity and other cardiometabolic risk factors.[78] In addition, in adults and also in prepubertal children, visceral adiposity measured with magnetic resonance imaging is inversely associated with endothelial-dependent skin capillary recruitment, and is accompanied by increased plasma levels of inflammatory markers.[79]

Impaired left ventricular diastolic function and higher risk of heart failure in obese individuals has been suggested to be associated with myocardial microvascular dysfunction.[80] In obese patients undergoing coronary artery bypass graft surgery, coronary microvascular density is significantly lower, compared to non-obese patients, and accompanied by increased body mass index and percent body fat together with increased left ventricular filling pressures.[80] Moreover, in patients with suspected coronary artery disease, increasing body mass index is associated with reduced microvascular endothelial function, even after adjustment for treated diabetes mellitus, hypertension, hypercholesterolemia, and smoking.[61] Interestingly, the study evaluated microvascular endothelial function three different technologies, including peripheral arterial tonometry, laser Doppler flowmetry and digital thermal monitoring.[61]

Reduced skeletal muscle capillary density and microvascular reactivity in obese subjects improved after 4 weeks of either sprint interval training, or moderate-intensity continuous training, together with increased endothelial eNOS content.[81]

It has also been shown that bariatric surgery improves microvascular dysfunction in obese patients who were free of metabolic syndrome after surgery, in association with postoperative increases in HDL-cholesterol levels and decreases in oxidized LDL levels.[82]

Another clinical study investigated microvascular endothelial function – using flow-mediated dilation in arterioles isolated from subcutaneous adipose tissue – in young women presenting with obesity (age: 33 ± 2 years, body mass index: 33.0 ± 0.6 kg/m^2).[83] The results showed that a 6-week low-carbohydrate diet, associated or not with caloric restriction, improve endothelial-dependent microvascular function through increases in nitric oxide bioavailability.[83] On the other hand, this nutritional intervention did not affect macrovascular endothelial function, evaluated using brachial artery flow-mediated dilation.[83]

Regarding putative pathophysiological mechanisms, a study by Dimassi et al[84] in young individuals with obesity (BMI >30 kg/m^2, n = 69), compared with controls with normal weight, suggested that the expression of circulating microparticles containing endothelial nitric oxide synthase (eNOS) is significantly reduced in obesity individuals with endothelial-dependent microvascular dysfunction characterized using cutaneous laser Doppler flowmetry.[84]

Multiple Pathways for COVID-19 Severity in Obese Patients

Low-grade inflammation is the common feature that encompasses all the high-risk patients for developing severe COVID-19. Obesity is associated with a fivefold increased risk of developing SARS in SARS-CoV-2 infected individuals, and the well-documented increased susceptibility of obese patients to develop severe forms of COVID-19 may be linked to the elevated systemic metabolic inflammation in these patients.[19] Metabolic alterations seen in obese and in diabetic patients are related to

an inflammatory response,[85,86] and several studies report elevated levels of circulating inflammatory cytokines such as TNF-α, IL-1β and IL-6 in obese patients.[87] Furthermore, visceral fat shows significant univariate association with the need for intensive care in COVID-19 patients,[15] and deregulated expression of adipokines, such as leptin and resistin, increases the expression of vascular adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) that contribute to increased vascular leukocyte adhesiveness and additional oxidative stress.[88] To further complicate the scenario, adipose-derived mesenchymal stem cell (ASCs), a specialized cell population in adipose tissue, are functionally compromised in obesity and changes its regulatory protective activity to a pro-inflammatory profile increasing its ability to secrete TNF-α, IL-8, IL-6 and MCP-1.[89,90] Therefore, ASCs from obese patients may not be able to modulate the immune response and tissue repair in SARS-CoV-2 infection contributing to more severe tissue injury.[10]

SARS-CoV-2 uses its viral spike (S) protein to invade target cells, such as epithelial cells, through binding to angiotensin-converting enzyme 2 (ACE2) after proteolytic activation by transmembrane protease serine 2 (TMPSS2).[91] Others enzymes like furin, trypsin and elastase may also activate the S protein and facilitate cellular entry by the virus.[92–94] Interestingly, adipose tissue highly expresses ACE2 and the expression is even higher in visceral adipose tissue.[95] Of relevance, ACE2 expression is upregulated in obesity.[96] Also, another suggested receptor for SARS-CoV-2, dipeptidyl peptidase 4 (DPP4), is expressed in adipose tissue and is upregulated in obesity.[97,98] Finally, CD147, the alternative receptor for SARS-CoV-2, is positively correlated with an increase in body mass index.[99] Taken together, the evidence of high expression of different SARS-CoV-2 receptors in adipose tissue may be the basis for increased severity of COVID-19 in obese patients involving at least two different possibilities: First, infection of adipocytes with SARS-CoV-2 may exacerbate the innate immune response through pathogen recognition receptors in an already inflammation-primed tissue, increasing the magnitude of the response. Second, adipocytes may function as a reservoir for the SARS-CoV-2 and therefore may fuel the inflammatory response in adipose tissue and elsewhere in the organism by releasing viral NA and antigens that, by reaching the circulation generate ripple inflammatory effects across the organism. Importantly, these two possibilities are not mutually exclusive and may well combine their pathophysiological potential towards a deregulate systemic inflammatory response with widespread tissue injury and consequent organ dysfunction. It is important to add that as the pandemic evolves, new mechanistic interactions may unravel. For instance, new virus variants with mutations at the receptor-binding domain of the S protein may change the infectivity of the virus by changing its interactions with cellular receptors. In Brazil, a variant designated as P1, with multiple mutations in the S protein, was recently identified and is seemingly more infective than previous lineages of the virus.[100] How this variant may interact with adipocytes increasing infectivity to these cells or potentiating the formation of an adipocyte reservoir of the virus causing a more severe disease in obese individuals is yet unknown. What is known is that a second wave caused by this new P1 variant is promoting devastating effects in Brazil with apparently higher mortality and a faster progression of the disease.

Severe COVID-19 is characterized by a massive production of pro-inflammatory mediators, in special cytokines. Frequently, the term "cytokine storm" is called up to describe the massive production of cytokines that occurs in viral infections (including SARS-CoV and MERS-CoV) , in sepsis and more recently, in severe COVID-19.[101] Increased levels of IL-6, TNF-α, IP10 are commonly found in patients with severe COVID-19.[102] It is reasonable to propose that obese patients who already have an underlying chronic inflammation when infected with SARS-CoV-2 are prone to develop a more intense and deregulated response, and in doing so, developing a severe presentation of the disease. In addition, dysfunctional metabolism, endothelium, and overall immune response would further contribute to an unfavorable evolution of the disease in the obese patients. The questions about the molecular mechanisms behind this disproportional response remain unanswered, but our knowledge about this disease is growing in an unprecedented velocity and we may soon have the answer. However, a few possibilities may be put forward (Figure 1).

As stated above, obesity is characterized by the induction of a low-grade chronic proinflammatory state and NF-κB is described as a key factor in the low-grade inflammation state in atherosclerosis and hypertension.[103,104] Also, the NF-κB pathway is involved in insulin resistance, a condition frequently seen in obese patients, and in β-cell dysfunction.[105] In addition, free fatty acids can also promote inflammation and activate the NF-κB and JNK1 pathways.[106] All those pieces put

together may point to NF-κB being a key player in obese patients with COVID-19. Importantly, cell culture experiments combined with system biology approach showed that overexpression of Nsp1 during infection with SARS-CoV-2 strongly increases signaling through the nuclear factor of activated T cells (NFAT) and increases cytokine production and immune-dependent pathogenesis. Both NF-κB and NFAT pathways share common regulation signals, such as Foxp3 and Foxd1, and a similar mechanism of activation against infection.[107]

We must also consider that binding of SARS-CoV-2 to ACE2 leads to receptor internalization and high cytosolic levels of angiotensin II, which is a recognized activator of NLP3 inflammasome in the lung[108] and other tissues. The NLRP3 inflammasome regulates pyroptosis through gasdermin D, along with the release of cytosolic contents into the extracellular spaces. The release of alarmins, ATP, ROS, cytokines, chemokines, LDH and viral particles elicits an immediate reaction from surrounding immune cells, inducing a pyroptotic triggered reaction further fueling inflammation. Interestingly, different studies have reported elevated levels of LDH, a cytosolic enzyme that is measured for monitoring pyroptosis in patients with the severe form of COVID-19.[109] On the other hand, diet-induced alterations in the gut leading to increased gut permeability to bacterial endotoxins are known to promote activation of NLRP3 inflammasomes via Toll-like receptors (TLRs). This event is followed by the accumulation of IL-1 family cytokines, which modulate insulin production by pancreatic beta cells.[110] Importantly and at the same time, a decrease in endogenous protective mechanisms occurs.[111] NLRP3 inflammasome activation is involved in endothelial lysosome membrane permeabilization, cathepsin B release, and impaired glycocalyx thickness,[112] thus further contributing to the endothelial cell dysfunction, enhanced susceptibility to cardiovascular injury and thrombotic events, a common complication in severe COVID-19 patients.

In fact, thrombotic events are now recognized as a common feature in COVID-19 patients, and COVID-19 has recently been suggested to be a thrombotic viral fever.[113] Obese patients are prone to thrombotic events for many different reasons,[113] and COVID-19 may contribute even further to this complication. The imbalance of the ACE/ACE2 system caused by internalization of ACE2 after binding to virus S protein causes a switch towards pro-thrombotic activity by decreasing Ang-(1-7)-Mas axis (antithrombotic) and increasing angiotensin II (prothrombotic). This mechanism may be of central pathogenic relevance explaining the poor outcome of obese patients with COVID-19.[113]

In summary, there are many different ways by which low-grade inflammation caused by metabolic changes in obesity may contribute to the worse prognosis of obese patients infected by SARS-CoV-2, in a combination of factors and mechanisms leading to a subversion of the defensive responses of the organism against the virus.

Disclosure

The authors report no conflicts of interest in this work.

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