



COVID-19: Major Metabolic and Immunological Relationships in Obesity

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DOI: <https://doi.org/10.34256/mdnt2135>

Received: 14-05-2021; Accepted: 06-06-2021; Published: 10-06-2021

Abstract: Introduction: In the scenario of chronic non-communicable diseases, obesity stands out as a multifactorial disease that can cause several public health problems. Currently, about 30% of the world's population is overweight or obese. Estimates suggest that the prevalence of severe obesity in 2030 will be 11%, approximately twice the current prevalence. By 2025, Brazil will be in fifth place in the world ranking, with an estimated 18.0 million people. The appearance of the new coronavirus (SARS-CoV-2), which causes the disease COVID-19, has worsened the comorbidities of obesity. **Objective:** to explore, through a concise systematic review, the main metabolic and immunological relationships in obesity, especially in the presence of COVID-19. **Methods:** The present study followed a concise systematic review model (PRISMA). The search strategy was carried out in the databases PubMed, Embase, Ovid and Cochrane Library, Web Of Science, and Scopus. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results:** A total of 76 studies were found that were submitted to the eligibility analysis, and, after that, 15 studies of high to medium quality and with risks of bias were selected that do not compromise the scientific basis of the studies, we found that obesity is an important predictor of worsening SARS-CoV-2 pathology. There are a complex interaction between multiple metabolic, immunological and inflammatory factors that result in meta-inflammation. It has been shown that obesity causes dysfunction in the immune system, increasing susceptibility to infections and death from sepsis, and increased oxidative stress in the body. SARS-CoV-2 amplifies the inflammatory response, enabling greater propensity to alveolar thrombotic microangiopathy and pulmonary thromboembolism. Meta-inflammation and insulin resistance with hyperinsulinemia is the main baseline changes in obesity. **Conclusion:** In the COVID-19 scenario, obesity is an important predictor of the worsening of SARS-CoV-2 pathology, mainly due to the worsening of metainflammation.

Keywords: SARS-CoV-2, COVID-19, Obesity, Meta-inflammation, Metabolism, Immunity.

1. Introduction

In the scenario of chronic non-communicable diseases, obesity stands out as a multifactorial disease that can cause several public health problems [1]. Currently, about 30% of the world's population is overweight or obese. By 2020, it is estimated that more than 60% of the world's population will be overweight or obese. Estimates suggest that the prevalence of severe obesity in 2030 will be 11%, approximately twice the current prevalence [1]. In this context, there are 2.0 billion overweight and obese people in the world [1]. In the United States, the prevalence of obesity is greater than 30.0% for both sexes, and obesity is the cause of death for 2.8 million people per year, affecting 26% of adults. In Europe, it is estimated that 10 to 20% of men and 15 to 25% of women are obese [1].

By 2025, Brazil will find itself in fifth place in the world ranking, with an estimated 18.0 million people, tending to reach more than 70.0 million [2]. Furthermore, in Brazil, this chronic disease has increased by 67.8 % in the last thirteen years, rising from 11.8% in 2006 to 19.8% in 2018. The highest growth rate was among adults aged 25 to 34 years (84.2%) and 35 to 44 years (81, 1%). Today, in the country, 20.7% of women are obese and 18.7% of men [2].

Along with the obesity pandemic, the appearance of the new coronavirus (SARS-CoV-2), which causes COVID-19 disease, has worsened the obesity comorbidities [3]. It is necessary to understand the mechanisms by which obese patients at greater risk of evolving to severe forms of the disease, even death. In this sense, immunity plays a decisive role in

SARS-CoV-2 infection. The lack of regulation and the excessive immune response to the viral stimulus exacerbate pro-inflammatory cytokines (cytokine storm), reaching the state of hyper inflammation, with consequent damage to various tissues of the obese [3].

Therefore, the occurrence of immune dysfunction, greater predisposition to infection, and mortality from sepsis is a reality. Obesity was correlated with high leukocyte and lymphocyte count (except for NK, T suppressor, and cytotoxic T cells), with suppression of lymphocyte proliferation of T and B lymphocytes and with higher rates of oxidative activity and phagocytosis by monocytes and granulocytes, demonstrating the consequences of this pathology on the immune system.⁴ In addition to these changes, it is known that obesity initially favors the development of inflammation in adipose tissue, by increasing the production of pro-inflammatory adipokines, such as IL-6 and the TNF- α .

Thus, the proportion between pro-inflammatory and anti-inflammatory cytokines becomes unbalanced [5]. Consequently, damage to the vascular system occurs, promoting endothelial dysfunction, characterized by a decrease in the production of nitric oxide and an increase in the synthesis of reactive oxygen species, which establishes an inflammatory and oxidative stress state. Regarding innate immunity, in obese patients, there is a modification of the immune environment in adipose tissue [6].

In this context, obesity induces a change in the profile of macrophages, with an increase in the M1 phenotype (pro-inflammatory). This effect corresponds to an upregulation in inflammatory genes and a downregulation in anti-inflammatory genes [7]. However, it is not only in adipose tissue that this change occurs in cells of the innate immune system. Thus, the authors demonstrated that circulating obese mononuclear cells are also in a pro-inflammatory state, with an increase in the intranuclear factor κ B (NF- κ B) and, consequently, with an increase in the transcription of pro-inflammatory genes regulated by it [8]. As a corollary, the innate immune response in patients with obesity is altered, resulting in an imbalance in the line of defense against infections, an increase in the inflammatory response, and abnormal activation of T lymphocytes. The primary increase in the inflammatory response in obese patients works as a predictor for the hyperinflammatory state observed in COVID-19.

Therefore, this primary increase can be amplified by the SARS-CoV-2 infection, increasing the production of cytokines such as TNF- α , IL-1, and IL-6 [3].

Therefore, the present study aimed to explore, through a concise systematic review, the main metabolic and immunological relationships in obesity, especially in the presence of COVID-19.

2. Methods

2.1. Study Design

The present study followed a concise systematic review model, following the rules of systematic review - PRISMA (Transparent reporting of systematic reviews and meta-analysis-[HTTP://www.prisma-statement.org/](http://www.prisma-statement.org/)).

2.2. Search Strategy and Information Sources

The search strategy was carried out in the databases PubMed, Embase, Ovid and Cochrane Library, Web Of Science, and Scopus, following the following steps: - search for descriptors: SARS-CoV-2. COVID-19. Obesity. Meta-inflammation. Metabolism. Immunity, and the use of Booleans "and" among descriptors and "or" among historical findings.

2.3. Study Quality and Bias Risk

The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument.

3. Results and Discussion

A total of 76 studies were found that were submitted to the eligibility analysis, and, after that, 15 studies of high to medium quality and with risks of bias were selected that do not compromise the scientific basis of the studies (Figure 1). After a complete analysis of these selected studies, it was found that obesity represents an important predictor of the worsening of SARS-CoV-2 pathology.

There are a complex interaction between multiple metabolic, immunological and inflammatory factors that result in meta-inflammation. In this sense, it was shown that obesity causes dysfunction in the immune system, increasing the susceptibility to infections and death from sepsis, an increase in oxidative stress in the body. Also, SARS-CoV-2 amplifies the inflammatory response, enabling greater

propensity to alveolar thrombotic microangiopathy (primary pulmonary thrombosis) and pulmonary thromboembolism. Also, meta-inflammation and insulin resistance with hyperinsulinemia is the main baseline changes in obesity.

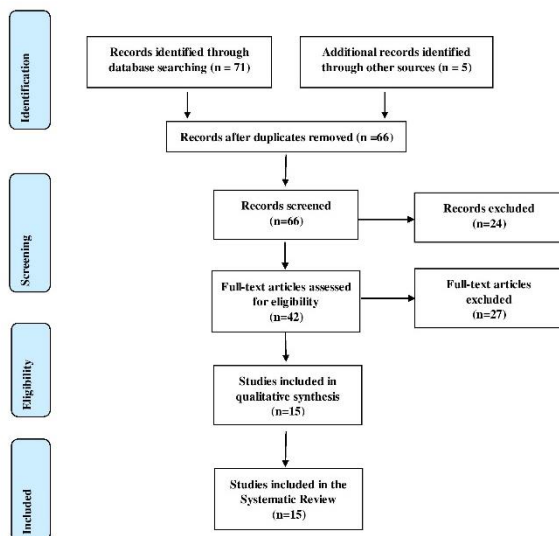


Figure 1. Flow Chart of Study Eligibility.

3.1. Major Inflammatory Aspects – Obesity

The circulating level of cytokines and acute-phase proteins associated with inflammation is high in patients with obesity. Thus, adipocytes secrete various cytokines and acute-phase proteins that increase the production and circulation of factors related to inflammation. The inflammatory process may be due to resistance to the action of insulin and other disorders associated with obesity, such as hyperlipidemia and metabolic syndrome [4].

Thus, the association between obesity and inflammatory disease is highlighted. There are three possibilities, the first of which reflects the production and release from organs other than fat, mainly the liver (and immune cells). The second explanation is that white adipose tissue secretes factors that stimulate the production of inflammatory markers by the liver and other organs. The third possibility is that adipocytes themselves are an immediate source of some or several, of these inflammatory markers [4,5].

Also, effects such as energy balance sensors have been attributed to cytokines. Among all adipokines related to inflammatory processes, interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), leptin and adiponectin stand out [5]. In this context, some studies have shown low concentrations of anti-inflammatory adipokine (adiponectin) associated with

the occurrence of several types of cancer and high concentrations to inhibit the growth of tumors [3-5]. Adiponectin and leptin are the most abundant adipokines synthesized by adipose tissue, although there are others such as TNF- α , IL-6, IL-1, CC-chemokine ligand 2 (CCL2), a visceral adipose-tissue-derived serine protease inhibitor (vaspin), and retinol-binding protein 4 (RBP4) [3].

In this sense, the excess of adipose tissue increases the production of several adipokines that have a great impact on several bodily functions. In this case, food intake control and energy balance, immune system, insulin sensitivity, angiogenesis, blood pressure, lipid metabolism, and body homeostasis stand out, situations strongly correlated with cardiovascular disease [7]. They stand out as adipokines with anti-inflammatory the IL1 receptor antagonist (IL-1ra), transforming growth factor- β (TGF- β), those produced by Th2 cells (IL-4, IL-5, and IL-10) and adiponectin [3]. The imbalance between pro and anti-inflammatory cytokines can induce inflammatory or hypersensitive responses. Besides, high plasma adiponectin concentrations are associated with a reduced risk of myocardial infarction in men. Adiponectin is inversely proportional to the concentration of C-reactive protein (CRP). It can downregulate the gene expression of CRP in the adipocyte [3].

Also, it should be noted that the adipose tissue of obese individuals has an upregulation of the expression of the angiotensin-converting enzyme 2 (ECA2), which functions as an input receptor for SARS-CoV-2 in the cell. Thus, adipose tissue serves as a target and a potential viral reservoir. Thus, obesity is a pathology that causes damage to the immune system and amplifies inflammatory responses and this contributes to understanding the interaction between COVID-19 and obesity [3].

3.2. Meta-inflammatory processes of obese individuals at COVID-19

Meta-inflammation describes the junction of inflammation with the metabolic changes that occur in the body of obese patients [4]. Several toxic mediators that contribute to the inflammatory state and tissue damage are present in obesity, such as free fatty acids (FFA), lipid derivatives toxic substances, such as diacylglycerol, toxic nitric oxide metabolites, and inflammatory mediators, such as C-reactive protein, cytokines, chemokines, macrophages, and TNF- α . The imbalance in inflammatory mediators induced by

excess nutrients is the basis of meta-inflammation in obesity, considered a low-grade chronic inflammatory state. Similar to that seen in acute inflammatory diseases, obesity can cause multiple organ dysfunction. Meta-inflammation leads to myocardial dysfunction by direct injury to inflammatory mediators, as well as by the dysfunction of other organs [5], according to Table 1.

Table 1. Summary of the main metabolic, immunological and inflammatory considerations of the relationship between Obesity and COVID-19 [15].

OBESITY AND COVID-19	
✓	Obesity increases the risk of developing severe COVID-19;
✓	Obesity increases the risk of young people presenting with the severe form of COVID-19;
✓	Obesity causes dysfunction in the immune system, increasing the susceptibility to infections and death from sepsis;
✓	Obesity leads to a chronic inflammatory state and oxidative stress in the body;
✓	SARS-CoV-2 amplifies the inflammatory response already originally increased in obese people;
✓	Adipocytes are potential targets and reservoirs for SARS-CoV-2;
✓	Obesity-related venous macrocirculatory characteristics such as immobilization and venous stasis in the lower limbs are related to the increased risk of pulmonary embolism. Therefore, these conditions typical of obese people make them more vulnerable to the respiratory manifestations of COVID-19, with a greater propensity to alveolar thrombotic microangiopathy (primary pulmonary thrombosis) and pulmonary thromboembolism;
✓	Metainflammation and insulin resistance with hyperinsulinemia are the main baseline changes in obesity that trigger a series of harmful events, resulting in damage to the cardiovascular system;
✓	Obese patients have comorbidities and a more reactive endothelium, which favors the evolution to a more severe form of COVID-19;
✓	In autopsies performed on patients with COVID-19, endothelium, microthrombi, neoangiogenesis, and hyaline membrane were more evident.
✓	The main changes observed in coagulation are increased generation of thrombin, D-dimer, fibrinogen (initially), prothrombin time, reduced fibrinolysis and platelet count;

Obese patients stand out among the young population that evolves to the severe form of COVID-

19. The unfavorable evolution is possible because these patients have a more inflamed and hyper-reactive endothelium, which, under the stimulation of SARS-CoV-2, presents an excessive response, responsible for the hyper inflammation with cytokine storm. As a corollary to the exacerbated inflammatory process, the coagulation cascade is unregulated, causing hypercoagulability. Therefore, the endothelial dysfunction caused by SARS-CoV-2 justifies why patients with blood vessel-related comorbidities such as cardiovascular disease, hypertension, diabetes, and obesity are more likely to develop severe cases of COVID-19, even death [3].

Post-mortem histological studies revealed a picture of lymphocytic endothelium in the lungs, heart, kidneys, and liver, as well as cellular necrosis and the presence of microthrombi, which, in the lungs, worsens respiratory failure. Thus, authors found in autopsies evidence of direct viral infection of SARS-CoV-2 in the endothelial cell and diffuse inflammation. The ACE2 receptor is also widely expressed in multi-organ endothelial cells [8].

In this sense, other authors conducted an autopsy study that compared the lungs of patients who died from COVID-19 versus the lungs of people who died from Influenza A (H1N1). The histological pattern on the periphery of the lung was a diffuse alveolar lesion with perivascular T-cell infiltrate. The lungs of patients with COVID-19 also showed distinct vascular characteristics, consisting of severe endothelial injury associated with the presence of intracellular viruses and ruptured cell membranes. Histological analysis of pulmonary vessels in patients with COVID-19 showed a widespread thrombosis with microangiopathy. Alveolar capillary microthrombi were nine times more prevalent in patients with COVID-19 than in patients with influenza ($p < 0.001$) [9].

Also, COVID-19 respiratory failure is related to inflammatory changes and coagulation processes in the alveolar microcirculation. Thus, alveolar thrombotic microangiopathy is a primary thrombosis triggered by COVID-19 and differs from pulmonary arterial thrombosis, as there is a direct action of the virus on the endothelium, which causes diffuse endothelium. Thus, it is suggested that the action of SARS-CoV-2 provides an endothelial stripping due to inflammation, leading to significant exposure of tissue factor, activating the coagulation cascade and subsequent pulmonary thrombotic microangiopathy [10].

In this sense, this process of local activation of cytokines can complicate the evolution of

pneumonia caused by COVID-19, especially in obese patients, since the state of micro thrombosis causes a post-thrombotic endothelial dysfunction, activates the complement system and the release of cytokines. And, when these systems are activated, a continuous state of hypercoagulability occurs. As scientific evidence, authors have demonstrated the relationship between obesity and a higher risk of intubation and mechanical ventilation, in addition to higher hospital mortality. In this series, 46% of the 1150 patients admitted with severe COVID-19 were obese, and invasive mechanical ventilation was required in 79% of the 257 patients who progressed to a critical form of the disease [11].

This was also reported in a multicenter study involving 5,700 hospitalized patients in the metropolitan New York area. Obesity has been described as the second most frequent comorbidity, being present in about 40% of patients with COVID-19. During the hospitalization of 2634 patients, 14.2% were treated in the ICU and 12.2% received invasive mechanical ventilation. Mortality for those who required mechanical ventilation was 88.1% [12].

Still, other authors observed the relationship between obesity and the development of severe respiratory manifestations when analyzing 103 hospitalized patients with COVID-19. They reported that 47% of these patients were obese. In this study, patients who had a BMI of 30 kg/m² were among those most in need of ICU admission and mechanical ventilation [13].

Also, obesity produces hemodynamic changes that contribute to the development of structural and functional cardiac abnormalities. These changes can cause heart failure (HF), even in the absence of other comorbidities, such as hypertension and coronary artery disease (CAD). Therefore, HF-related to severe obesity is called obesity cardiomyopathy. In this context, the inflammatory mediators produced by adipose tissue are direct mechanisms of cardiac dysfunction, and hypertension, diabetes, and CAD are indirect mechanisms [14].

4. Conclusion

In the COVID-19 scenario, obesity is an important predictor of the worsening of SARS-CoV-2 pathology. There are a complex interaction between multiple metabolic, immunological and inflammatory factors that result in metainflammation. The global population is increasingly overweight, obese, and suffering from obesity-related diseases, including many metabolic diseases, cardiovascular and systemic

diseases. In this sense, COVID-19 expressed the vulnerability of obesity to viral infection. Global awareness is needed to adopt measures to mitigate obesity, such as nutritional health, in an attempt to reduce the obesity pandemic and, thus, prepare humanity to avoid worsening health due to future infections.

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Informed written consent obtained from the participant

Conflict of interest

The authors declare no conflict of interest.

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Acknowledgement

Nil

Funding

Not applicable

Data sharing statement

No additional data are available

Informed consent