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SHORT REVIEW

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Obesity And Covid-19: A Descriptive Review

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Abstract: Introduction: According to data provided by the World Health Organization (WHO), 5,941,223 confirmed cases and 366,601 deaths had already been reported by May 31, 2020. Higher rates of infection, hospitalization, submission to the Intensive Care Units, and fatalities were attributed to obese patients. **Objective:** To gather the available data on obesity and SARS-CoV-2 infection. The study specifically covers combined pathophysiology and prognosis and will be updated until September 2020. **Methods**: This is a literature review study with a narrative-descriptive approach. The search was carried out in September 2020, with the totality of articles from that same year, when the pandemic of the new coronavirus was declared by the World Health Organization. **Results:** The search on the data platform resulted in 121 articles, of which 86 were classified as reviews and 35, systematic reviews, totaling 18 reviews and 7 systematic reviews at the end, with a total value of 16 articles with sufficient quality. Obesity is associated with increased severity of COVID-19 in the infected individual with this disease, due to the chronic inflammatory process, with high levels of pro-inflammatory leptin and a lower concentration of anti-inflammatory adiponectin, which causes a response delayed and inferior immune system. **Conclusion:** Individuals with this association have an easier time in the formation of possible clots, due to chronic inflammation and impaired fibrinolysis, which qualifies them as individuals of significant thrombogenic risk. Thus, individuals with obesity are an important risk group when considering its association with the disease of the new coronavirus.

Keywords: COVID-19, SARS-CoV-2, Obesity, Inflammatory processes, Cytokines.

1. Introduction

The year 2020 was undoubtedly marked by something that before was believed to be possible to contemplate only on movie screens or in history books: a pandemic. The protagonist - who would later be designated as COVID-19 (Coronavirus Disease–) was first noticed in Wuhan, capital of Hubei province, China. As an etiological agent, the SARS-CoV-2 virus (Severe Acute) was identified. Respiratory Syndrome Coronavirus 2), from a well-known family - that of the coronaviruses - that has the SARS-CoV and MERS-CoV (Middle East Respiratory Syndrome) viruses as representatives, both were responsible for previous epidemics, in the years 2003 and 2012, respectively.

The first cases of the disease, recorded between December 2019 and January 2020, were quickly followed by thousands of others around the globe. According to data provided by the World Health Organization (WHO), 5,941,223 confirmed cases and 366,601 deaths had already been reported by May 31, 2020 [1]. In August, ten were the countries that had not yet registered cases of the disease [2]. By the end of September, the number of deaths had already surpassed the first million, and the number of cases, 33 million [3].

Given this scenario, it is not difficult to understand why the billions of inhabitants of the entire planet had to be quarantined and to adapt to the "new normal" configured by this reality. For the first time in the contemporary world, there has been an extraordinarily rapid spread of a virus, which causes a disease with a broad spectrum of clinical presentation and severity of symptoms. SARS-CoV-2 infection is typically respiratory, as are those caused by other

known coronaviruses. In the classic form, the initial flu symptoms (fever, dry cough) can quickly progress to interstitial pneumonia and acute respiratory distress syndrome (ARDS) [4]. It is common for patients to evolve with loss of olfactory and gustatory sensitivities, in addition to presenting gastrointestinal symptoms and, eventually, a series of microvascular and inflammatory complications. It is worth mentioning that many of the patients are infected silently and remain asymptomatic. Also, many studies are still needed to address other possible findings, which remain unclear.

Among these findings, the one mentioned below is perhaps the most emblematic. The exacerbated increase in a series of inflammation markers, what became known as a "cytokine storm", and the consequent imbalance between anti- and pro-inflammatory factors lead to an important breakdown of homeostasis, which is closely associated with a worse prognosis of disease. After countless observations and tests carried out in this regard, evidence was found that some situations were related to a more severe form of presentation of this "storm", such as arterial hypertension, diabetes mellitus and cardiovascular diseases [5]. Interestingly - or not - the fact is that the disorders presented have one factor in common: in most cases in which they manifest themselves, they are linked to obesity, a condition that has proven to be one of the greatest risk factors for COVID-19.

Many of the patients hospitalized by COVID-19 have a Body Mass Index (BMI) corresponding to grade I obesity [6]. These patients have a higher chance of complications and need for invasive mechanical ventilation, and most of them have diabetes, which, as already mentioned, is one of the most common comorbidities of obesity. On the other hand, the relationship between high body mass indexes and the development of various types of cancer has long been researched and investigated [7]. Thus, it is clear that excess body weight, especially visceral fat, is linked to the appearance and/or worsening of these and other conditions [8] throughout the evolution of its pathophysiology - a term that is properly applied since obesity is considered and behaves like a disease. Therefore, it is possible to conclude that it can be considered a potential threat in its own right, being as or more relevant than its comorbidities.

The finding of obesity as a risk factor in COVID-19 by the CDC (Centers for Disease Control and Prevention), an agency of the United States Department of Health and Human Services, was not at all surprising. This factor had already been shown to be relevant in the course of other infectious diseases, including respiratory diseases. So, it was with influenza A, caused by the H1N1 virus and the cause of an epidemic in 2009 [9]. In this context, higher rates of infection, hospitalization, submission to the Intensive Care Units (ICU), and fatalities were attributed to obese patients.

The explanation for this correlation is due to several factors, which will be further explored in the course of this review. First of all are the mechanical obstacles represented by the deposition of body fat, impairing the performance of the respiratory muscles and lungs. On the other hand, there is a series of molecular mechanisms involved in the chronic inflammatory state induced by obesity, which triggers endothelial dysfunction and coagulative disorders. The endocrine-metabolic and immune systems are no less affected by the condition. This evidence exemplifies only some of the ways in which obesity is an entity that must be seriously considered in the midst of the COVID-19 pandemic.

When analyzing the profile of the world population in terms of indicators such as BMI, we are faced with a worrying context, mainly from the point of view of public health and its demand. According to a report released by the WHO in December 2019, about 2.3 billion children and adults worldwide are overweight or obese [10]. The distribution of this number is significant not only in high-income countries but also in those of low and middle income, where it contrasts with high levels of malnutrition [11]. In Brazil, the situation is no different. This chronic disease increased 67.8% in twelve years, from 11.8% in 2006 to 19.8% in 2018. In 2018, 20.7% of women and 18.7% of men were obese [12].

Given the current epidemiological scenario in Brazil and in the world, obesity presents itself as a very interesting and necessary study object, as are the identification, prevention, and intervention strategies to be carried out in the population. Providing support to these patients, from primary to quaternary prevention, is the biggest challenge facing the Unified Health System (SUS) and other systems around the globe. And, in the current pandemic context of COVID-19, it is to be expected that this challenge will be even greater, as well as the relevance of studies that value for historically and technically correlating these two pandemics - COVID-19 and obesity -, coming in line with the purpose of this review.

This review aimed to gather the available data on obesity and SARS-CoV-2 infection. The study specifically covers combined pathophysiology and prognosis and will be updated until September 2020.

2. Methods

This is a literature review study with a narrative-descriptive approach. The database for research was PubMed®, in which the descriptors of obesity and COVID-19 were used to search for articles. Among the descriptors COVID-19, SARS-CoV-2, Obesity, Inflammatory processes, and Cytokines, the booleans "and", "or" or "not" were used. The time frame was 5 years. The search was carried out in September 2020, with the totality of articles from that same year, when the pandemic of the new coronavirus was declared by the World Health Organization.

Only systematic reviews and reviews that covered the selected subject descriptors and were written in English were selected. After the research, the articles were screened by the classification of CAPES journals, so that only articles whose journals were classified as A or B qualifications according to CAPES were used to prepare this review. C-rated or unrated articles were excluded. Finally, the articles were read to verify their agreement with the theme developed for the preparation of the literature review.

3. Results

The search on the data platform resulted in 121 articles, of which 86 were classified as reviews and 35, systematic reviews (Figure 1). From reading the articles to assess the link between obesity and SARS-Cov-2 infection, articles in which there was a causal link between the descriptors used were excluded, totaling 18 reviews and 7 systematic reviews at the end (Table 1), with a total value of 16 articles with sufficient quality and used in full (Table 2).

4. Discussion

Obesity, defined by a body mass index (BMI) above 30 kg/m², is characterized by the expansion and inflammation of visceral adipose tissue, which secretes pro-inflammatory cytokines, adipokines, and molecules with broad pathophysiological effects [11]. Paradoxically, obesity is not synonymous with an excess nutritional status. On the contrary, most obese people are in deficient states of vitamins and nutrients - which contributes to an even worse picture of COVID-19 [12]. The exacerbated consumption of saturated fats, sugars, and refined carbohydrates favors the prevalence of overweight and also type 2 diabetes, frequent comorbidity, and, likewise, identified as a risk factor for COVID-19 [13, 14].

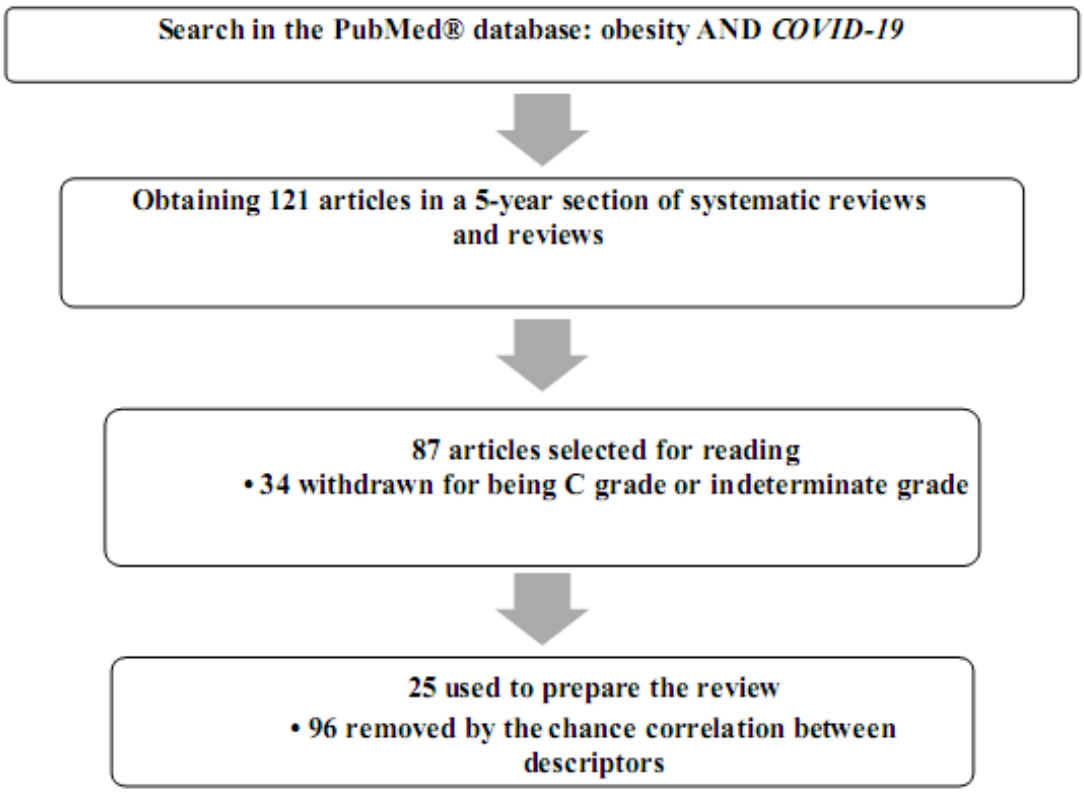

Figure 1 Results obtained from the adopted methodological sequence.

Table 1 Number of articles obtained and classification according to the type of study

	Reviews	Systematic Reviews	Total
Articles Found	86	35	121
Selected Articles	18	7	25

Table 2 Articles found and used according to the classification of CAPES journals

	Articles Found	Articles Used
Qualis A	42	11
Qualis B	45	14
Qualis C	7	unused
Qualification undetermined	27	unused

Both clinical entities are characterized by a chronic inflammatory process, with higher values of leptin (pro-inflammatory molecule) and a lower concentration of anti-inflammatory adiponectin, causing a delayed and lower immune response, with a decrease in macrophages in the course of infection [14, 15].

The excessive inflammation found in obese individuals with COVID-19 is a result of metabolic tissue stress induced by weight gain and unilocular adipose tissue dysfunction. This tissue is an important energy reservoir, formed by adipocytes (continent of lipids), immunity endothelial cells, and other components [16]. In obesity, adipocytes undergo hyperplasia and hypertrophy, which results in a large expression of pro-inflammatory cytokines, causing hypoxia toxicity of the microenvironment, with tissue necrosis and activation of the immune system response.

B, T lymphocytes and NK cells (natural killers), together with macrophages, secrete high rates of IL-6 and TNF-α, which lead to the establishment of chronic inflammation. This affects the metabolism, leading to the appearance of comorbidities. In addition, the drop in IFN-1 and other molecules that help to regulate the desirable performance of the immune system constitutes a deficient immune response and greater susceptibility to an aggressive viral infection [17].

The literature reveals a direct metabolic link between the inflammatory state of obesity and the "cytokine storm" seen in those infected with the SARS-CoV-2 virus.

This hyperinflammatory state leads to a rapid respiratory decline in these patients [18], proving the direct implication of excess weight in the prognosis of the disease. The performance of physical activity, with moderate frequency and intensity, controls adiposity, the inflammatory profile, the immune response, and the endocrine activity of the individual, which results in a decrease in the inflammatory process of adipose tissue [19].

The current clinical experience reported in the studies has shown that about 40% of patients with COVID-19 hospitalized in intensive care units are obese and have a higher risk of developing respiratory complications, such as ARDS, in addition to greater difficulty in intubation, when necessary respiratory support [11, 20-22]. This is due to changes in the baseline respiratory mechanics resulting from obesity. As a consequence, there is a reduction in total lung capacity, functional residual capacity, and vital capacity, as well as an increase in pleural pressure and upper airway resistance, with the potential to induce or worsen asthma, dyspnea, and wheezing [16, 23]. In addition, obese patients may suffer from rapid oxyhemoglobin desaturation when previously hypoxemic [23] and represent a greater risk of extubation failure, in view of upper airway obstruction, aggravated by changes in rostral fluid and sedatives, with underlying hypoxemia [23]. Ventilation through the bag-valve-mask is also challenging for the attendant when dealing with an obese patient [23].

Returning to molecular events, it is known that the entry of the SARS-CoV-2 virus into cells is mediated by the receptor for the angiotensin-

converting enzyme 2 (ACE-2). In turn, hypertrophy of fat cells promotes increased expression of this receptor [24], which facilitates infection and makes adipose tissue an important viral reservoir. The infection also blocks the pathway of beneficial vasodilatory effects of angiotensin II [19] and intensifies its vasoconstrictor, pro-inflammatory, and pro-oxidant activity. This increases the risk of acute lung injury [3], making the lungs and the heart vulnerable to the virus [25-27].

As for the endocrine effects, there is leptin. It is a peptide hormone produced by adipocytes, whose main function is to regulate satiety, but it is also an important mediator of pulmonary immunity. Some studies have shown that hunger and leptin deficiency are associated with decreased immune reactivity, in the same way, that hyperleptinemia has also been shown to have detrimental effects on the immune response. Elevated serum leptin levels, as in obesity, are linked to a reduction in the main inflammatory biomarkers and to an attenuated response to ARDS and pneumonia, worsening the results of these conditions [28].

Another aspect of the COVID-19 relationship and obesity addressed in the articles involves furin, a protease found in the basal endothelial membrane. It allows the conversion of some latent precursor proteins to their active form, being used even for certain pathogens to become functional. Some of these pathogens constitute bacterial toxins and certain viral envelopes, as in the case of HIV and Ebola viruses, in addition to the spike proteins of SARS-Cov-2. When activated by furin, the SARS-Cov-2 virus causes endothelial dysfunction, diffuse inflammation of the vascular tissue, and micro and macrovascular thrombosis in the arterial and venous circulations. And, interestingly, protease was found to be abundant especially in mononuclear inflammatory cells, playing a signaling role towards adipocytes. This signaling, in the long term, leads to blood vessel remodeling and atherosclerosis, due to lipid deposition. Entities such as diabetes, hypercholesterolemia, and obesity are associated with increased levels of furin, which constitutes another aggravating factor for the complications associated with COVID-19 [29].

Thus, the focus on furin host cells can bring potential therapeutic options against infections whose agents depend on this protease to become functional and develop high pathogenicity [29]. Obesity also represents a risk factor for thrombotic disorders, such as deep vein thrombosis and pulmonary embolism, due to chronic inflammation and impaired fibrinolysis [30]. In these cases, laboratory markers point to an increase in coagulation factors, such as D-dimer and fibrinogen [31]. In patients hospitalized with COVID-19, the World Health Organization recommends the prescription of low molecular weight heparin or unfractionated heparin in prophylactic doses to prevent venous thromboembolism [14, 29].

5. Conclusion

Obesity is associated with increased severity of COVID-19 in the infected individual with this disease, due to the chronic inflammatory process, with high levels of pro-inflammatory leptin and a lower concentration of anti-inflammatory adiponectin, which causes a response delayed and inferior immune system. Also, the obese patient has drop-in cytokines that help in the immune response to viral infection, which leads to a worse prognosis in these patients when affected by COVID-19. Furthermore, individuals with this association have an easier time in the formation of possible clots, due to chronic inflammation and impaired fibrinolysis, which qualifies them as individuals of significant thrombogenic risk. Therefore, within the reviewed articles and after collecting available data, it is concluded that individuals with obesity are an important risk group when considering its association with the disease of the new coronavirus.

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Data sharing statement
No additional data are available

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Ethics approval does not require for this study

Informed consent
Not applicable

Conflict of interest
The authors declare no conflict of interest.

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Yes

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