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OBESITY IN SARS-COV-2 INFECTION: LITERATURE REVIEW

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KEYWORDS :

INTRODUCTION

In March 2020, the World Health Organization (1) declared COVID-19 as a pandemic and a threat to global public health (2). The virus mainly affects the lungs and can cause acute respiratory distress syndrome (ARDS). In addition, coronavirus 2 severe acute respiratory syndrome (SARS-COV2) also has devastating effects on other important organs, including the circulatory system, brain, gastrointestinal tract, kidneys and liver (3).

Concomitantly, the world faces another pandemic: obesity. For adults, the WHO defines overweight as a BMI greater than or equal to 25 and obesity as a BMI greater than or equal to 30. Current data estimate that more than 1.9 billion adults, aged 18 and over, are overweight. Of these, more than 650 million are obese. And that number tends to continue growing over this decade (4). The exact causes for the development of this condition are still unknown, but it is estimated that it results from a complex interaction between genetic factors and those related to the environment and lifestyle (5).

Several studies indicate that obesity is an important risk factor for an unfavorable prognosis and increased mortality in severe cases of SARS-COV2 infection. In addition, obese patients have a higher risk of morbidity due to the common relationship with dyslipidemia, diabetes mellitus 2, hypertension, cardiovascular diseases, stroke and respiratory problems (6).

This review study aims to assess the influence of specific aspects of obesity on the clinical picture of patients with COVID-19. The aspects investigated will be: the difference in immunity of the obese in response to infection; related comorbidities; if there is specific management for this population and if there is a difference in prognosis.

METHODOLOGY

This is a bibliographic search conducted in November 2020. The literature review was carried out in the Virtual Health Library (VHL), SCIELO and Pubmed database. The research used keywords: "COVID-19", "SARS-CoV-2", "obesity" and "overweight". The filters were: year of publication, type of article and text availability. Inclusion Criteria: papers published from 2020, case reports, simple literature review, controlled and randomized tests, clinical trials, systematic review with or without meta-analysis, texts available in full, and adequacy to the study theme. Exclusion criteria: articles that are not complete electronically and are not available in Portuguese, English or Spanish.

IMMUNITY OF THE OBESE AND SARS-COV-2

Obesity favors the development of several immune-mediated diseases, such as psoriasis. This is due to interference in the various pathways of the immune system, which include the modified function of lymphocytes and monocytes, reduced production of cytokines, dysfunction of natural killer cells (NK), decreased function of dendritic cells and macrophages, and

reduced response to stimulation of antigen / mitogen (7). It was observed that half of the obese individuals infected with COVID-19 are diagnosed with hypercytokinaemia, and in severe cases they have lymphopenia, particularly in the T cells, leukocytosis and increased proportion of neutrophils-lymphocytes (NLR), and higher inflammatory cytokines, including TNF- αIL-6, IL-2R and IL-10 (8).

The high morbidity and mortality rates of COVID-19 in obese individuals affected with cardiac pathologies may be related to epicardial adipose tissue (TAE). TAE can act as a reservoir for SARS-CoV-2, increasing viral spread to cardiac tissue. In addition, dysfunction of the ECA2 angiotensin-converting enzyme axis is related to TEA inflammation, as there is a decrease in the level of Ang protein (1-7), associated with decreased polarization of pro-inflammatory macrophages in this tissue and tends to present higher levels of IL-6 and TNF-α. (9,10)

In exacerbated inflammation caused by chronic fat accumulation, pro-inflammatory cytokines are overexpressed concomitantly with adipocyte hypertrophy and hyperplasia (Figure 1). The intense secretion of IL-6, TNF-α and MCP-1 supports the imbalance of inflammation and leads to several changes in the systemic responsiveness to nosocomial infections, where the incidence of generalized inflammation by the release of cytokine storm increases, (11). In addition, COVID-19 can be associated with acute respiratory distress syndrome, caused by systemic hyperinflammation and cytokine release, in contrast to the increased production of inflammatory monocytes CD14 + and CD16 + (which lead to large production of IL-6) (12).

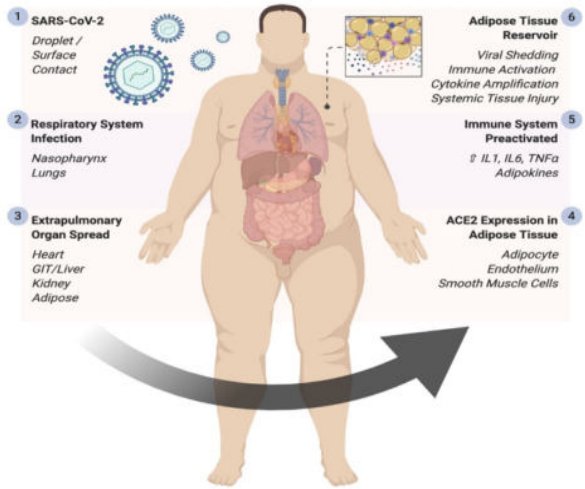

Figure 1. Centrality of adipose tissue as a reservoir for the spread of SARS - CoV - 2 and the subsequent systemic immune activation. The intense release of IL-6 and TNF-α leads to an increase in the incidence of generalized inflammation, inducing an impaired immune response.

Source: Ryan, P.M; Caplice, N.M. (2020) (13).

Hormonal dysregulation and nutrient deficiency can impair the response to infection. Uncontrolled serum glucose generates oxidizing agents and binding products, impairing the function of immune cells and demonstrating a significant increase in COVID - 19 mortality (Figure 2) (14). Equitably, insulin and leptin signaling is critical in the effective inflammatory response of T cells through the positive regulation of glycolysis in the cell, helping in the production of effector cytokines, such as IFN-γ and TNF-α and, consequently, dictating the response pathogens, such as SARS-CoV-2. (15)

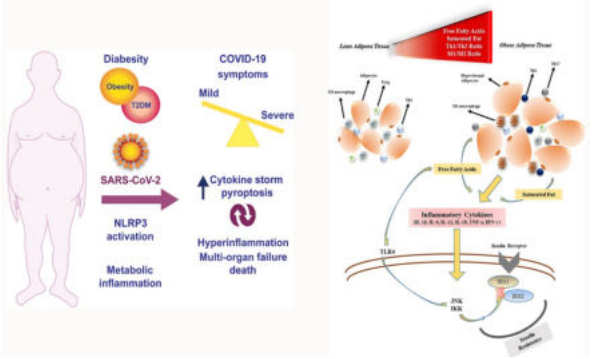

Figure 2. Relationship between diabetes - the association between obesity and diabetes - and the response to SARS-CoV-2 infection. Diabetes increases the susceptibility to exacerbation of COVID-19 through an excessive metabolic inflammatory response that is regulated, at least in part, by the NLRP3 inflammasome complex.

Source: Bertocchi, I. et al. M. (2020) (16).

SARS-CoV-2 is responsible for infecting cells that express the primary virus receptor, the angiotensin-converting enzyme (ECA2), present in the intestinal and respiratory epithelium, as well as in the endothelium. Responsible for initially generating hypoxia due to alveolar injury and subsequently generating endothelial dysfunction due to direct injury mediated by antibodies, cytokine storm and alteration of the balance between angiotensin II and its functional antagonists, with possible thrombosis in the pulmonary and systemic territory, in addition to angiopathic hemolysis and macrophage hyperactivity. The positive feedback between hypoxia, inflammation and angiotensin II potentiates the development of an anxiety syndrome and multiple organ failure, with increasing mortality. The center of the pathogenesis of COVID-19 is the reduction of ECA2 activity in relation to ECA1, with greater production and effect of AngII to the detriment of the effects of angiotensin antagonists Ang1-9 and Ang1-7. As a result, patients who progress to the most severe forms of the disease are those who, before infection, already have increased expression of ECA2 (obese). Another mechanism is that in obese people there is an overexpression of Angiotensin and an overactivation of the Renin Angiotensin Aldosterone System (RAAS) in the adipose tissue, resulting in an increase in the production of angiotensin II (17). This is because, obese people have a greater number of receptors the angiotensin-converting enzyme 2 (ECA-2), where SARS-CoV-2 binds through the spike protein to penetrate host cells and start their viral replication cycle (18).

Therefore, it can lead to worse results for obese patients. In addition, it is known that obesity compromises the responses of the adaptive and innate immune system. Adipose tissue is involved in complex interactions with the immune system. The release of inflammatory adipokines from visceral fat deposits can affect the immune response and contribute to the imbalance between the secretion of anti and pro-inflammatory adipokines from chest visceral fat deposits (19). The unbalanced balance between leptin and adiponectin, increased the secretion of pro-inflammatory cytokines such as TNF-α, IL-6, interferon, impaired cellular immunity and associated sedentary lifestyle induce an impaired immune response among obese individuals. In addition, the obesogenic microenvironment favors prolonged viral dissemination and the emergence of more virulent strains (20). As a result, an obese patient is not only more susceptible to being infected with SARS -CoV - 2, but also cannot fight the infection that leads to increased morbidity in COVID infections - 19 (21).

Hyperleptinemia and insulin resistance in obesity disrupt T cell function, resulting in a suppressed T cell response to infection. This metabolic condition compromises the immune response and leads patients to morbidity and mortality due to SARS-CoV-2 infection, along with the lack of containing viral replication (22). In addition, obesity also results in an increase in the accumulation of ectopic fat in the bone marrow, which is where immune cells develop. Thus, the interaction of adipocytes and immune cells is altered in obesity, compromising the function of immune cells and giving rise to inflammation (23).

COMORBITIES ASSOCIATED WITH OBESITY AND COVID-19

Most studies cite Diabetes Mellitus (DM) / insulin resistance as the main comorbidity associated with obesity. In addition, many articles mentioned the relationship between obesity and cardiovascular diseases, with Systemic Arterial Hypertension (SAH) being the most frequent. It is noteworthy that some studies have discussed cerebrovascular, renal and pulmonary diseases, in addition to the state of hypercoagulability being related to obesity. In addition, advanced age is a factor that adds obesity that makes the individual susceptible to infections, since, both at this end of life, and due to excess weight, the immune system becomes less efficient. In addition, the overlapping of systemic inflammation of obesity and systemic inflammation triggered by SARS-CoV-2 are responsible for the greater severity of COVID-19 in obese patients, which can lead to multiple organ dysfunction (24).

The increase in fat mass and weight gain harmful to health, even in childhood, can lead to an increase in the thickness of the carotid intima and the development of cardiovascular diseases (24), as well as the risk of complications related to COVID -19, since hardening of the arteries, associated with impaired nitrogen performance and chronic oxidative stress, has been pointed out in changes related to the severity of COVID-19, such as inflammation of the endothelium, myocarditis, venous thromboembolism, among others (25).

As an inducer of cardiometabolic dysfunction, obesity is associated with an increased risk for many diseases, such as type 2 diabetes, dyslipidemia, hypertension, coronary heart disease, coagulopathy and vitamin D hypovitaminosis. Chronic inflammation, defined as a low-grade process, but persistent, which disturbs homeostasis and leads to organ dysfunction. During obesity, chronic inflammation is not only associated with metabolic disorders and impaired heart health, but also affects the function of the immune system (26). Several clinical conditions, often associated with obesity, act as independent risk factors for a more severe course of the disease in patients with COVID-19. It has been reported that obesity-related comorbidities are also correlated with increased COVID-19 mortality and morbidity, such as cardiovascular disease (22.7%), hypertension (39.7%), diabetes (19.7%), respiratory diseases (7.9%) and cancers (1.5%) (27).

Acute respiratory distress syndrome (ARDS) is the main complication and cause of death in COVID - 19. In this context, obesity plays a crucial role in ventilation and obese patients have changes in baseline physiology. Obese patients are more likely to have decreased pulmonary ventilation or obstructive sleep apnea, which predisposes them to low levels of blood oxygenation in the beginning and, consequently, to worse respiratory results in case of acute infectious respiratory diseases, making the obese more subject to progress to respiratory failure (24).

In addition, overweight and obesity can decrease diaphragm excursion, forced respiratory volume and forced vital capacity and impair the immune response to viral infections (28).

Chronic inflammation induced by obesity leads to changes in hemodynamic properties and increases the risk of coagulopathies. In addition, activation of the coagulation pathway also triggers inflammation. Some recent reports show thromboembolism as one of the main causes of death for COVID-19 (29).

In the obese, the RAS (Renin Angiotensin Aldosterone System) is chronically activated and predisposes the individual to a multitude of dysfunctions, including cardiac and renal pathologies. These changes are associated not only with hypertension, but also with insulin signaling in peripheral tissues, inflammatory status in the pancreas and cell death profile. In addition, obesity causes hyperglycemia through insulin resistance, while growing evidence demonstrates that SARS-CoV-2 can also cause hyperglycemia by infecting and killing B cells. In addition, some drugs often used to treat patients with complications obesity (such as antihypertensives, statins, thiazolidinediones) can increase the regulation of ECA2, therefore, they can potentially increase viral absorption (30).

MANAGEMENT OF THE OBESE PATIENT WITH COVID-19

At first, it was observed that, in general, for the obese patient with the SARS-CoV-2 infection, the care and treatment protocol is not stratified and specific, when compared to the management of individuals with other comorbidities. Obesity is associated with an increased risk of admission to the ICU in patients with COVID-19. Among COVID-19 patients admitted to the ICU, 40% to 100% require IMV (31). Thus, it appears that some measures are essential and the treatment of these people requires special attention. In obese patients admitted to the ICUs, it is necessary to prioritize erect positioning and avoid supine positioning, as well as placing them in an inclined position and also encouraging early mobilization, with the aim of improving the aeration of dependent lung areas and, consequently, reducing the time of using mechanical ventilation in hospital services. The prone position was also responsible for significantly increasing the ratio of alveolar pressure in oxygen to the inspired fraction of oxygen (PaO2 / FiO2) in patients with obesity (32).

In addition, it must be emphasized that the measurement of body weight and the assessment of adipose tissue, if possible, is important for all individuals admitted with COVID-19, since obesity alters the course of infection and is associated with increased mortality. For people with changes in these parameters, it is important to offer nutritional and behavioral support (33). Regarding infant patients with COVID-19 and concomitant obesity, it is seen that they can have inflammatory conditions as severe as in adults. In this context, health professionals must diagnose excess weight; advise on general health care, especially during isolation; screening for comorbidities; measure immunonutrients, and guide the family (24).

Regarding drug treatment, there is little difference from the one usually used for patients with multiple comorbidities. Most patients in the studies analyzed used antimicrobials (azithromycin, hydroxychloroquine, ivermectin, remdesivir), corticosteroids (methylprednisolone, dexamethasone), anticoagulation schemes, mechanical ventilatory support, nutritional support and mental health interventions (24).

In a way, the fight against obesity should be encouraged by the general population. The adipose tissue of obese people, unlike the adipose tissue of lean people, is characterized by several changes that impair the antiviral response (i.e., increase in immune cells, increase in pro-inflammatory cytokines and overexpression of ECA2) (34). Faced with this problem and the current context, physical activity is consecrated in a positive way, since it improves most of these

mechanisms, correcting immunomodulation and the anti-inflammatory mechanism of regulation. (34). Therefore, physical exercise should be part of prevention as a recommendation of the practice in order to reduce overweight and its consequences in cases of association with COVID-19.

PROGNOSIS

Obesity, understood here as a BMI equal to or greater than 30 kg / m^2, is a disease that is commonly present in patients with COVID-19, ranging from the most frequent comorbidity, with 42.55% in the study by Fernando Mejía et al (2020) (35), in Peru, up to the fourth most frequent, with 8.6% in the study by Fabiana Schuelter-Trevisol et al (2020) (18), in Brazil. We also found frequencies of 41.7% (36), 25.9% (37) and 17.6% (38) in other observational studies. Finally, a systematic literature review with a meta-analysis of 10 retrospective studies found a frequency of obesity of 33.9% in all patients and 37.6% in critically ill patients (21). It is then noticed that obesity is frequent in patients infected with sars-cov-2, but will this be a coincidence or is there any correlation?

Three systematic literature reviews with meta-analysis investigated the risk of patients with obesity being hospitalized. The values found for Odds Ratio (OR), with a 95% confidence interval, were 1.4 (1.30-1.60) (39), 1.54 (1.33-1, 78) (40) and 1.76 (1.21-2.56) (41). When comparing different BMI ranges, the study by Yang et al (2020) showed that a higher BMI predicts a greater possibility of hospitalization: 25 ≤ BMI <30 vs. BMI <25 resulted in OR = 1.30 (1.09-1.57); 30 ≤ BMI <40 vs. BMI <25 resulted in OR = 2.09 (1.34–3.26); BMI ≥ 40 vs BMI <25 resulted in OR = 2.76 (1.76–4.32). The significance of these results indicates that obese people are more likely to be hospitalized, and this chance is proportional to the BMI presented.

In a cross-sectional study it was seen that obesity was the most observed condition among ICU patients of both sexes, with an OR of 2.88 (2.03-4.07) (42). In addition, obesity in the ICU is being found more in young people, which corroborates the change in the age range affected by covid-19 (43) (44). A peculiarity in relation to obese children is that they have inadequate immune responses to other infections, such as bacterial pneumonia, which is a common serious complication caused by SARS-CoV-2 (25). Correlation between obesity and ICU admission was found in a cohort study and in three meta-analyzes. The Odds Ratio result found in the cohort was 3.46 (1.29-9.24) (18), while the meta-analyzes resulted in: 1.21 (1.002-1.46) (31), 1.48 (1.24-1.77) (41) and 1.67 (1.26-2.21) (42). When correlating obesity and fatty liver disease associated with metabolism, Peres et al (2020) (45) found in his meta-analysis an OR of 5.77 for ICU admission. Obesity alone is an independent factor of chance of admission to the ICU and can increase when associated with other comorbidities (31) (40) (41).

When it comes to the chance of using invasive mechanical ventilation (IMV), meta-analyzes were unanimous in pointing out that obesity is correlated with this outcome. Four meta-analyzes found the following OR result: 1.47 (1.31-1.65) (41), 2.0 (1.4–2.9) (40), 2.05 (1,16–3.64) (31) and 2.19 (1.56-3.07) (42). The pathophysiology of obesity justifies these higher OR values compared to those of hospitalization and ICU admission, since obese patients can restrict ventilation, decrease diaphragm excursion, forced respiratory volume and forced vital capacity (44), in addition, intubation may be more difficult due to the adipose tissue in the areas around the segments of the larynx and pharynx (46).

The mortality of people by COVID-19 showed no correlation with obesity in three cohort studies (37) (35) (18), but three meta-analyzes showed the opposite. The OR results found were 1.14 (1.04-1.26) (41) and 1.37 (1.06-1.75) (41), in addition to these, the third meta-analysis worked with relative risk (RR), found a value of 3.52 (1.32-9.42) (47). Mortality had the lowest OR among the prognostic factors so far, with some individual studies showing that there is no correlation. Knowledge of the difficulty of treating obese patients, who are prone to require complex management of the ICU, can influence the greater attention given to them, thus avoiding the evolution of the clinical picture for death (48), which is the most common cause being the need for artificial ventilation to treat hypoxemic respiratory failure due to covid-19 pneumonia (49).

Some studies have assessed the correlation between obesity and COVID-19 through composite outcomes. The individual outcomes used by these studies were: saturation <90%, need for supplemental oxygen; acute respiratory distress syndrome; ICU admission; existence of American Thoracic Society (ATS) / Infectious Diseases Society of America (IDSA) severity criteria; and hospital mortality. Four meta-analyzes reached the following results: OR: 1.78 (1.25-2.54) (50); OR: 1.88 (1.25–2.80) (21); RR: 2.35 (1.43-3.86) (47); and mean difference (DM): 1.6 (0.8–2.4) (40). With these values, it can be observed that all analyzes tend to present a higher chance, relative risk or difference in mean for obese people in different situations of prognosis, both individually and collectively, that is, obesity brings a worse overall prognosis (Chart 1).

Obesity does not only affect people's individual health, but it also seems to affect collective health. The study by Caci et al (2020) (46) comments on recent evidence that a large population of obese individuals increases the chance of a more virulent viral strain, prolongs the elimination of the virus in the entire population, and may eventually increase the rate of general mortality from an influenza pandemic.

Regarding the recovery of patients with covid-19 and post-hospital prognosis, no follow-up study was found using the inclusion criteria adopted by this study.

Chart 1 - Chances, risks and difference in mean outcomes of obese patients with COVID-19 compared to non-obese investigated in meta-analysis studies.

Autor	Hospital	UTI	VMI	Doença grave	Óbito
(CHANG et al, 2020) (39)	↑ (OD: 1,40)	-	↑ (OD: 2,00)	↑ (DM: 1,6)	
(YANG et al, 2020) (40)	↑ (OD: 1,54)	↑ (OD: 1,48)	↑ (OD: 1,47)	-	↑ (OD: 1,14)
(HUANG et al, 2020) (41)	↑ (OD: 1,76)	↑ (OD: 1,67)	↑ (OD: 2,19)	-	↑ (OD: 1,37)
(FÖLDI et al, 2020) (31)	-	↑ (OD: 1,21)	↑ (OD: 2,05)	-	-
(SEIDU et al, 2020) (47)	-	-	-	↑ (RR: 2,35)	↑ (RR: 3,52)
(SOEROTO et al, 2020) (50)	-	-	-	↑ (OD: 1,78)	-
(MALIK et al, 2020) (21)	-	-	-	↑ (OD: 1,88)	-

Caption: ↑: A certain outcome is more likely to occur in obese patients. OD: Odd Ratio. RR: Relative Risk. DM: Difference in means.

CONCLUSION

It was observed that obesity contributes significantly to the evolution of severe cases of COVID-19. The obese patient, in addition to presenting metabolic and immunological changes that are associated with severe outcomes of COVID-19, often has other associated clinical conditions; such as cardiovascular diseases, diabetes, coagulopathies and respiratory problems; that act as independent risk factors for an unfavorable prognosis for SARS-CoV-2 infection. Therefore, it is recommended to combat high adiposity in the

general population, the inclusion of BMI in the prognostic scores and the improvement of guidelines for intensive care of patients with high BMI.

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