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Could obesity be a risk factor for adverse clinical outcomes of COVID-19? Review article

A obesidade poderia ser um fator de risco para desfechos clínicos desfavoráveis da COVID-19? Artigo de revisão

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RESUMO: *Objetivo:* O propósito dessa revisão narrativa foi verificar uma possível associação entre obesidade e os desfechos relacionados à COVID-19. *Métodos:* Uma pesquisa foi feita no PubMed em maio de 2020, e após a aplicação dos critérios de elegibilidade, 10 artigos foram incluídos, os quais foram analisados, e seus resultados comparados. *Resultados:* Foi observado que, devido as mudanças no organismo causadas pela obesidade, essa comorbidade é um importante fator de risco para severidade da infecção pelo Sars-CoV-2 e sua estadia hospitalar. Além disso, a obesidade tem sido considerada um fator de risco para desfechos clínicos desfavoráveis. Também foi possível notar que a maioria dos indivíduos obesos eram do sexo masculino, portanto foi traçada uma relação direta entre homens com obesidade e severidade da COVID-19, e esse grupo necessitou de mais intubação e, aqueles maiores de 20 anos, apresentaram uma taxa de mortalidade maior. Ademais, a associação entre obesidade e outras comorbidades parece piorar ainda mais a infecção. *Conclusão:* No entanto, não foi possível encontrar um mecanismo fisiopatológico que possa explicar completamente essa associação. Portanto, mais estudos são necessários para entender essa correlação.

Palavras-chave: Obesidade; COVID-19; SARS-CoV-2; Fatores de risco.

ABSTRACT: *Aims:* This narrative review's purpose was to verify a possible association between obesity and COVID-19-related outcomes. *Methods:* A PubMed research was done in May 2020, and after the eligibility criteria, 10 articles were included, which were analyzed, and its results compared. *Results:* It was observed that, because of the changes caused by obesity in the organism, this comorbidity is an important risk factor for Sars-CoV-2's infection severity and hospital stay. Moreover, obesity has been considered a risk factor for adverse clinical outcomes. Also, it was possible to notice that most individuals with obesity were male, therefore a direct relation was traced between men with obesity and COVID-19's severity, and this population required more intubation and those older than 20 years old presented higher mortality rate. Besides that, the association between obesity and other comorbidities seems to worsen even more the infectious state. *Conclusions:* However, it was not possible to find a pathophysiological mechanism that can fully explain those associations. Therefore, more studies are vital to understand this subject.

Keywords: Obesity; COVID-19; SARS-CoV-2; Risk factors.

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INTRODUCTION

On December 31st, 2019, the first case of an unknown etiology pneumonia appeared at Wuhan province, China, that later was identified as the novel Coronavirus[1]. Sars-Cov-2 (Severe Acute Respiratory Syndrome Coronavirus 2) was sequenced in January, 2020 in China, which made it possible to understand the Coronavirus in a better way[1]. It is a RNA virus transmitted through people by direct and indirect contact, through droplets and aerosols[2]. The most common symptoms are cough, coryza, fever, sore throat and trouble breathing. Clinical presentation varies from asymptomatic infections to severe respiratory symptoms, requiring hospital care[3]. Therefore, on March 10th, 2020, The World Health Organization (WHO), concerned with the alarming levels of the disease transmission and severity, declared a global pandemic[1]. Some factors and preexisting conditions seem to determine the worsening and the complications of the novel Coronavirus disease (COVID-19) cases, for instance, obesity[4].

Obesity is defined as a multifactorial chronic disease characterized by the abnormal or excessive fat that presents risk for health[5]. It promotes a low-grade inflammation through the release of cytokines and acute phase proteins by adipocytes[6]. The excessive weight is classified by the body mass index (BMI), in which ≥ 25 Kg/m² suggests overweight, while above 30 kg/m² is classified as obesity, that has three stages: class 1 (BMI ≥ 30 kg/m² and BMI < 35 kg/m²), class 2 (BMI > 35 kg/m² and BMI < 40 kg/m²) and class 3 (BMI > 40 kg/m²)[7]. This disease is a risk factor for the development of other chronic conditions, especially hypertension, dyslipidemia, diabetes and cardiovascular disorders[8]. According to WHO, in 2016, 1.9 billion adults (over 18 years old) were overweighed, among those, more then 650 million had obesity[9]. In Brazil, 2018 data characterize 55.7% of the population overweighed[10]. Thus, the association between COVID-19 and obesity is discussed.

Considering the global pandemic scenario, the purpose of this review is to approach obesity as a factor for the increase of morbidity and mortality rate by Coronavirus.

METHODS

The review was elaborated through a PUBMED database research in May 2020, in which were used the following descriptors: [2019 *novel coronavirus disease* OR COVID19 OR COVID-19 *pandemic* OR SARS-CoV-2 *infection* OR COVID-19 *virus disease* OR 2019 *novel coronavirus infection* OR 2019-nCoV *infection* OR *coronavirus disease* 2019 OR *coronavirus disease*-19 OR 2019-nCoV *disease* OR COVID-19 *virus infection*] AND [*Obesity*].

A total of 116 publications were found with these descriptors. After reading all publication's titles, the ones which diverged from the purpose of this research were eliminated. Afterwards, 62 articles remained. Then, all the abstracts were analyzed taking into account inclusion and exclusion criteria. The inclusion criteria were Portuguese, English and Spanish papers, publication in 2019 and 2020 with an abstract that correlates obesity with COVID-19, cohort studies, clinical and experimental trials or case series performed in humans. After the full reading of the 11 papers left, one was excluded for not being relevant enough for this study. Therefore, 10 articles were included.

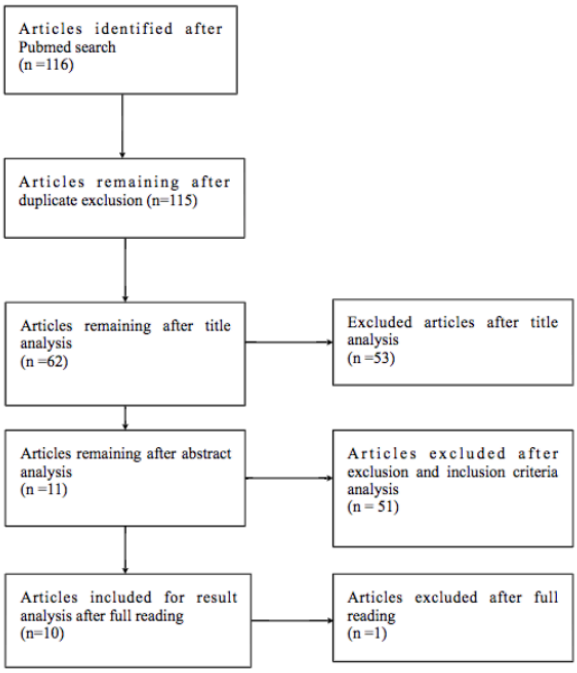

Figure 1- Methodology's Flow Diagram

RESULTS

Most of the 10 articles included were cohort studies. The sample mean of all the papers was 869,1 (the smallest was 67 and the biggest was 5700) both sexes were included with and without obesity, between one month old and 107 years old, according to Table 1.

Table 1. Main results of included studies in this review

Author	Study design	Sample/ Location	Participant's characteristics	Main Results
Cai et al.[11]	Cohort study.	Clinical, epidemiological and laboratorial data, radiological features, information of treatment and disease evolution of 383 patients (200 female and 183 male) hospitalized with COVID-19 diagnosis/ Shenzhen, China.	≥ 18 years old; 53.1% were normal weight; 4.2% underweight; 32% overweight; 10.7% had obesity.	The obesity group had a higher percentage of men than other BMI groups (78.1% vs. 12.5-59.4%); 39 (19.2%) of all COVID-19 severe cases were in the normal weight group, 36 (29.3%) in the overweight group and 16 (39%) in the obesity group; Patients with obesity, overall, had more cough and fever as initial symptoms compared to patients without obesity; Of all patients, the ones with severe disease had a longer hospital stay compared to non-severe patients (median 33.5 days vs 22 days); The overweight group had 1.84 (OR) fold odds of developing severe COVID-19 compared with the normal weight group, while those who had obesity were at 3.40 (OR) fold odds of developing the disease; Obesity, especially in males, increases significantly the risk of developing severe COVID-19. The association in females was lower due to small number of women with obesity in the study.
Gao et al.[12]	Cohort study.	150 patients with COVID-19 of three hospitals/ China.	Mean age: 48 years old; 62.7% male; 75 patients with obesity (BMI ≥ 25kg/m^2).	At hospital admission, patients with obesity had higher levels of plasma CRP and lower lymphocyte counts (two early indicators of severe COVID-19); Also had a longer hospital stay and a greater proportion had severe COVID-19 compared with patients without obesity; Obesity was associated with approximately three times higher risk of having severe COVID-19; Each unit increase in BMI was associated with a 12% increase in the risk of severe COVID-19; Healthcare professionals should be cognizant of the increased likelihood of severe COVID-19 in patients with obesity.
Chao et al.[13]	Cohort study.	67 patients with COVID-19/ New York City, United States.	Children one month to 21 years old; 67% male.	BMI average was 22.8 kg/m^2; 21 patients were clinically treated; 33 (72%) were admitted to the general pediatric medical unit and 13 (28%) to the PICU; Obesity and asthma were highly prevalent but not significantly associated with PICU admission; The presence of comorbidities, including obesity, has been described to be one of the risk factors for critical illness with COVID-19 in children; The overall high prevalence of obesity could partially explain the higher PICU admission rate.
Hu et al.[14]	Retrospective review.	323 hospitalized patients with COVID-19/ China.	Mean age: 61 years old; Patients were classified into three disease severity groups: 151 non-severe, 146 severe and 26 critical, based on initial clinical presentation; There was no gender difference between the three groups.	Patients over 65 years old were overrepresented within the severe (43.2%) and critical (57.7%) disease groups; Obesity (BMI ≥ 30 kg/m^2), hyperglycemia and diabetes, and cardiovascular disease were distinct risk factors for unfavorable clinical outcomes.
Kalligeros et al.[15]	Retrospective cohort study.	103 patients hospitalized with COVID-19/ United States.	Mean age: 60 years old; 61.17% male.	41 patients (39.8%) were admitted to the ICU and 29 (70.8%) required IMV; The prevalence of obesity was 47.5%; Patients who required IMV were more likely to have had heart disease, obesity and severe obesity; Severe obesity (BMI ≥ 35 kg/m^2) was associated with ICU admission, while history of heart disease and obesity (BMI ≥ 30 kg/m^2) were independently associated with the use of IMV; Increased vigilance and aggressive treatment of patients with obesity and COVID-19 are warranted.
Chen et al.[16]	Retrospective observational study.	145 hospitalized patients/ Taizhou, Zhejiang, China.	Mean age: 47,5 years old; 54.5% male and 45.5% female; 102 patients not severely afflicted and 43 patients severely afflicted (1 of them in the ICU); More afflicted patients: BMI 23.07 - 26.96 kg/m2; less afflicted patients: BMI 21.66 - 25,71.	Patients with comorbidities, such as obesity, are more inclined to have a more severe condition of COVID-19.

Table 1. Main results of included studies in this review

Author	Study design	Sample/ Location	Participant's characteristics	Main Results
Zheng et al.[17]	Cohort study.	214 patients /Wenzhou, China.	Mean age: 47 years old; 74.2% female; 66 patients had MAFLD; More severely afflicted (COVID-19 and MAFLD): BMI average = 28.3 ± 3.2 Kg/m^2) (89.5%); non-severe COVID-19: BMI average = 22.7 ± 2.1 Kg/m^2) (59.6%).	Patients with obesity and MAFLD had higher severity of the COVID-19 (35.5%) when compared to patients with MAFLD and without obesity (9.5%).
Richardson et al.[18]	Cohort study.	5700 patients with COVID-19/ New York, United States.	Between zero and 107 years old; 39.7% female.	The most common underlying conditions were hypertension (56.6%), obesity (41.7%), and diabetes (33.8%); 14.2% of hospitalized patients were treated in the ICU, 12.2% required IMV and 21% died; The mortality rate was higher among males; The infected rate was bigger among white people than in black or Asian people.
Garg et al.[19]	Cohort study.	1482 patients hospitalized with COVID-19/ United States.	> 50 years old; 54.4% male.	178 (12%) patients had some underlying condition and 89.3% had more than one; Prevalence of obesity was 48% (fluctuating according to age = 41% - 59%); Admissions due to COVID-19 in the United States are higher among older adults, and almost 90% of admitted people have one or more comorbidities; Underlying conditions were associated to a higher admission rate.
Simonnet et al.[20]	Retrospective cohort study.	124 patients with COVID-19/ Lille, France.	Mean age: 60 years old; 73% male; 47.6% had obesity; Admitted in the ICU.	60 patients were discharged, 18 died and 46 remained in the ICU; Obesity and severe obesity were more common in patients with COVID-19 than in patients of the control group; 85 participants required IMV, 62 at admission. Those had a BMI median of 31.1 kg/m^2 compared to 27.0 kg/m^2 of those that didn't needed IMV; High frequency of obesity in patients admitted in the ICU because of COVID-19; Disease severity increased according to BMI.

Description: COVID-19: Coronavirus Disease; OR: Odds ratio; BMI: body mass Index; CRP: C-reactive protein; ICU: intensive care unit; PICU: pediatric intensive care unit; IMV: invasive mechanical ventilation; MAFLD: Metabolic Associated Fatty Liver Disease.

DISCUSSION

Epidemiology

Sex

In all the papers, except for the data reported by Zheng et al., most of the patients infected by Sars-Cov-2 were male[11-20]. Furthermore, male individuals were the majority in the groups with obesity, presented higher severity of COVID-19, required more invasive ventilation and had higher mortality rates[11]. However, the data may be biased, considering that the samples consisted predominately of men. Therefore, it is suggested that male gender is a risk factor for Sars-Cov-2 infection and its evolution to worst outcomes.

Age

The majority of the studies with COVID-19 patients had adult subjects, with an age average of 47 years or older[12,14-18,20]. Otherwise, it should be mentioned that one of the papers had a sample with a range of one month to 21 years old, and the mean age of hospitalized patients was 13 years old[13]. People over 65 years old had more severe COVID-19 cases, therefore, had higher hospitalization rates[14,19]. Although we have not found studies that correlated obesity with COVID-19, exclusively in the elderly population, these results led us to believe that seniors with advanced age tend to develop the most severe form of the disease, requiring hospitalization.

Disease Severity and Mortality

Cai[11] and Chen[16], in China, defined severe COVID-19 in patients that had respiratory rate more than 30 times per minute, oxygen saturation in the resting state 93% or lower, oxygen arterial pressure/fraction of inspired oxygen 300 mmHg or lower, sepsis, respiratory failure or shock[11,16]. It was also reported that plasma C-reactive protein was an early indicator of severe COVID-19, as much as minor lymphocyte count at hospital admission in patients with obesity[12].

An increased risk of disease severity was observed for each BMI unit increase[11]. The same thing was reported in another study, but with Metabolic Associated Fatty Liver Disease (MAFLD) patients afflicted by COVID-19[17]. Moreover, it has been noted that most novel Coronavirus hospitalized patients also had comorbidities, obesity the second most common and associated with COVID-19 severity[16,19].

It was reported higher hospital stay in people with obesity compared to those without obesity as well[12]. In that sense, obesity and its severity have also been associated to Intensive Care Unit (ICU) admission and intubation necessity in COVID-19 patients[15,20].

In the light of these findings, obesity was considered a risk factor for unfavorable clinical outcomes.

Obesity and Other Comorbidities

The most common comorbidities in COVID-19 diagnosed patients were hypertension, obesity, diabetes and chronic pulmonary disease, respectively[18,19]. Despite the high prevalence of hypertension in this population, there was a strong association between obesity and disease severity after adjusting for other underlying conditions[12]. Moreover, approximately 90% of COVID-19 hospitalized patients identified by COVID-NET (COVID-19-Associated Hospitalization Surveillance Network, a department created for hospitalized population surveillance in the United States) had one or more concomitant diseases, but obesity was the most prevalent comorbidity between the ages of 18 and 64 years old[19].

The influence of underlying conditions such as diabetes, hypertension and cardiovascular diseases was observed in the association between BMI and the novel Coronavirus infection severity[11]. People with BMI 35 Kg/m^2 or higher, especially those with associated cardiac disorders, have also been the ones with a greater chance of evolving to severe COVID-19[15].

Patients with obesity and MAFLD presented greater Sars-CoV-2 infection severity than patients without obesity with the same condition[17]. Asthma was another comorbidity reported, highly prevalent in children and teenagers with obesity tested positive for Sars-CoV-2 infection that, despite being described as risk factors for critical disease in this group age for the novel Coronavirus, weren't associated with higher ICU admission[13].

With that in mind, we verified that obesity is one of the comorbidities that most stands out in the COVID-19 severity and its association with other concurring and/or chronic diseases worsen even more the infectious condition.

Pathophysiology

Currently, there is a pathophysiology that explains the findings of this study. Obesity disrupts the balance between cytokines leading to a pro-inflammatory state[21]. In this status, a viral infection could lead to a cytokine storm associated with an increased severity of the disease[21]. People with obesity also present changes in adaptive and innate immune response, causing alterations in leukocyte development and activity[21].

This pro-inflammatory chronic state leads to an up-regulation of multiple cytokines, which excessive release would be related to severe COVID-19 cases. Therefore, high levels of inflammatory markers, such as C-reactive protein and D-dimer in hospitalized patients with Coronavirus' infection were associated with the critical condition of the disease or death[22].

Furthermore, another pathophysiological mechanism which has been suggested and can relate obesity with worse COVID-19 outcomes includes vitamin D insufficiency, angiotensin converting enzyme-2 (ACE-2) expression in the adipocytes and the adipose tissue's potential of working as a viral reservoir and vascular endothelial dysfunction[22]. The ACE-2 receptor is expressed in many organs, including lung tissue[21]. Nevertheless, the adipose tissue has higher level of this receptor than lungs. Therefore, obese patients have more ACE-2 receptors than lean individuals[21], suggesting that obese patients are more susceptible to Sars-CoV-2's infection.

A German research described the correlation between these elements and the raised inflammatory response in an infection, which can be a risk factor to the development of Severe Acute Respiratory Syndrome (SARS) caused by Coronavirus[4]. Another study showed that obesity itself is a condition that predisposes thrombosis[23]. The patient may have a worse Sars-CoV-2 infection prognosis compared to patients without obesity, given the obesity's high thrombogenic potential and source of disseminated intravascular coagulation[23]. Furthermore, it is suggested that there is a deteriorating lung effect caused by obesity, such as a diminished forced vital capacity[23]. Nevertheless, even though those hypotheses were made, those mechanisms are not fully understood and need greater research[22].

CONCLUSIONS

It seems that the changes in the organism caused by obesity lead to an immunological fragility, which is an important risk factor for the infection, the severity and, consequently, for a longer hospital stay for patients afflicted by COVID-19.

According to the studies analyzed in this review, groups of people with obesity and COVID-19 were mainly male. They were the ones that most required intubation, had higher risk for disease severity and those older than 20 years old had higher mortality rate. Therefore, a direct relation between men with obesity and COVID-19's severity was found.

Furthermore, the association between obesity and other comorbidities seems to worsen even more the

infectious state, and obesity may also be a risk factor for adverse clinical outcomes. However, it was not possible to find pathophysiological mechanisms that can fully explain such associations.

It is worth mentioning that there are several limitations found in the studies, such as little diversified sample when it comes to sex, ethnicity, study center and nationality. Therefore, more extensive research is essential for the reproduction and applicability of these data in the present world context, as much as the investigation of the influence of obesity in the COVID-19's pathophysiology.

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