

The impact of obesity and diabetes mellitus on the clinical outcomes of patients with covid-19: an integrative review

O impacto da obesidade e do diabetes mellitus no desfecho clínico de pacientes portadores de covid-19: uma revisão integrativa

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Andrade AFF, korthals AM, Santos EMF, Gomes JAM, Costa LM, Souza MGGR, Barbosa MGS, Gomes TF. The impact of obesity and diabetes mellitus on the clinical outcomes of patients with Covid-19: an integrative review / O impacto da obesidade e do diabetes mellitus no desfecho clínico de pacientes portadores de Covid-19: uma revisão integrativa. Rev Med (São Paulo). 2021 May-June;100(3):269-78.

ABSTRACT: *Introduction:* COVID-19 (Coronavirus Disease-2019) is a disease caused by the coronavirus SARS-CoV-2 (severe acute respiratory syndrome Coronavirus-2), which poses a challenge to global public health. There is scientific evidence to indicate that patients with COVID-19 and diabetes and / or obesity tend to have a worse prognosis. The aim of the study is to critically review the influence of DM and/or obesity on the the clinical outcome of patients with Covid-19. *Methods:* This article is an integrative review, articles were selected, published from 2019 to 2020, in Pubmed, Virtual Health Library (VHL) and Scielo using the descriptors: “diabetes”, “obesity”, “Covid-19”, “pathophysiology”, “Prognosis”. The inclusion criteria were: studies published in English, Spanish and Portuguese, with randomized clinical trial, cohort study, meta-analyses, systematic reviews and reports. *Results:* It was observed that DM and obesity are important risk factors for severe COVID-19, associated with a worse prognosis and, consequently, the need for intensive treatment. This fact is justified from the perspective of pathophysiological alterations related to both comorbidities (chronic inflammation characteristic of obese and diabetic patients, respiratory impairment, increased expression of viral capsule binding receptors), which together favor a worse clinical outcome. Additionally, it was observed that strict glycemic control in diabetic patients is an important protective factor for severe COVID-19, considering the fact that patients infected with the new coronavirus whose clinical outcome, death, presented higher blood glucose values in fast.

Keywords: Diabetes; Obesity; Covid-19; Pathophysiology; Prognosis.

RESUMO: *Introdução:* A COVID-19 (Coronavírus Doença-2019) é uma doença provocada pelo coronavírus SARS-CoV-2 (síndrome respiratória aguda grave Coronavírus-2), a qual representa um desafio à saúde pública global. Existem evidências científicas que indicam que pacientes com COVID-19 e diabetes mellitus (DM) e/ou obesidade tendem a ter um pior prognóstico. O objetivo deste estudo é revisar integrativamente a literatura disponível sobre o impacto do diabetes mellitus e obesidade no desfecho clínico de pacientes portadores de Covid-19. *Métodos:* Este artigo é uma revisão integrativa. Foram selecionados artigos, publicados de 2019 a 2020, no Pubmed, Biblioteca Virtual em Saúde (BVS) e Scielo usando os descritores: “diabetes”, “obesidade”, “Covid-19”, “fisiopatologia”, “prognóstico”. Os critérios de inclusão foram: estudos publicados em inglês, espanhol e português, caracterizados como ensaio clínico randomizado, estudo de coorte, metanálises e/ou revisões sistemáticas. *Resultados:* Foi observado que o DM descontrolado e a obesidade são importantes fatores de risco para COVID-19 grave, associados a um pior prognóstico e, conseqüente necessidade de tratamento intensivo. Tal fato, se justifica sob a ótica de alterações fisiopatológicas correlatas à ambas comorbidades (descontrole glicêmico e inflamação crônica característica de pacientes obesos e diabéticos, comprometimento respiratório, aumento na expressão de receptores de ligação à capsula viral), as quais em conjunto favorecem um pior desfecho clínico. Adicionalmente, foi observado que o estrito controle glicêmico em pacientes diabéticos é importante fator de proteção para a COVID-19 grave, considerando o fato de que pacientes contaminados pelo novo coronavírus os quais tiveram como desfecho clínico, o óbito, apresentaram maiores valores de glicemia em jejum.

Palavras chaves: Diabetes; Obesidade; Covid-19; Fisiopatologia; Prognóstico.

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INTRODUCTION

By the end of 2019, COVID-19 (Coronavirus Disease-2019), a disease caused by the coronavirus SARS-CoV-2 (severe acute respiratory syndrome Coronavirus-2), had spread rapidly throughout China and other countries. world, due to its high capacity for infection. According to the Pan American Health Organization (PAHO), today, this communicable disease affects more than 100 countries, with 101,053,721 cases of COVID-19 being confirmed worldwide and 2,182,867 deaths in the Region of the Americas, 26,998 .023 people who were infected by the new coronavirus had recovered by January 29, 2021, thus representing a challenge to global public health^{1,2}. The disease is predominantly transmitted through respiratory droplets³. Moreover, its severity varies from asymptomatic, mild self-limited, similar to a flu, fulminant pneumonia, respiratory failure and even death^{2,4}.

Many studies have observed an increased risk of severe disease in COVID-19 patients with underlying health conditions^{1,5,6}. According to data compiled by the COVID-19 Associated Hospitalization Surveillance Network (COVID-NET), they verified hypertension (49.7%), obesity (48.3%), chronic lung disease (34.6%), diabetes mellitus (DM) (28.3%) and cardiovascular disease (27.8%) as the most frequent comorbidities to be verified among patients with COVID-19 hospitalized in the United States^{5,6}.

Diabetes mellitus (DM) is one of the main causes of morbidity in the world, and for the next few decades the trend is an increase in the number of diabetics. There is scientific evidence indicating that patients with COVID-19 and uncontrolled diabetes tend to have a worse prognosis^{1,2}. Poorly controlled DM is characterized by a significant lack of glycemic control, favoring in most cases a state of chronic hyperglycemia, which is linked to defects in lymphocyte proliferation, as well as to the functional impairment of monocytes/macrophages and neutrophils⁷.

Obesity is defined by the World Health Organization (WHO) as an abnormal or excessive accumulation of body fat that can reach levels capable of affecting health. In this sense, it is considered one of the most serious diseases of today and is growing at a fast pace. It is estimated that in

2025 2.3 billion adults in the world will be overweight, of this total 700 million with a BMI above 30, that is, with obesity⁸. Obesity is related to an increased risk for numerous diseases such as hypertension, DM and cardiovascular disease. Furthermore, it has been observed that obesity is also related to severe COVID-19, mortality and greater need for medical interventions^{9,10}.

Given the scenario presented, uncontrolled DM and obesity are evidenced as a strong factor of poor prognosis in the clinical outcome of patients with COVID-19. In this sense, this study aims to carry out a critical review of the available literature, in order to better understand the influence of DM and/or obesity on the worsening of COVID-19, elucidating the main scientific evidence on this subject.

METHODOLOGY

This is an exploratory study, based on the literature review method with synthesis of evidence. Based on the guiding question “Are obesity and diabetes mellitus (DM) determining factors in the pathogenesis of COVID-19?”, an integrative literature review was prepared through electronic searches in the Pubmed databases, Virtual Library in Health (BVS) and SciELO in September, October and November of 2020.

Applying the following descriptors associated with the Boolean operator AND and OR: “diabetes OR obesity AND Covid-19, diabetes AND pathophysiology AND Covid-19, obesity AND pathophysiology AND Covid-19, diabetes OR obesity AND prognosis AND Covid-19”.

The inclusion criteria were: articles that addressed the themes of DM and/or obesity and Covid-19, which were published from 2019 to 2020, and were characterized as qualitative or quantitative primary research, in highlights, observational studies and goal -analyses.

The selected articles were in the languages: English, Spanish or Portuguese.

In addition, the exclusion criteria were literature review articles, monographs and theses, and all works published prior to 2018 were also excluded, as well as those that did not show the influence relationship between DM and/or obesity in the pathogenesis of Covid-19.

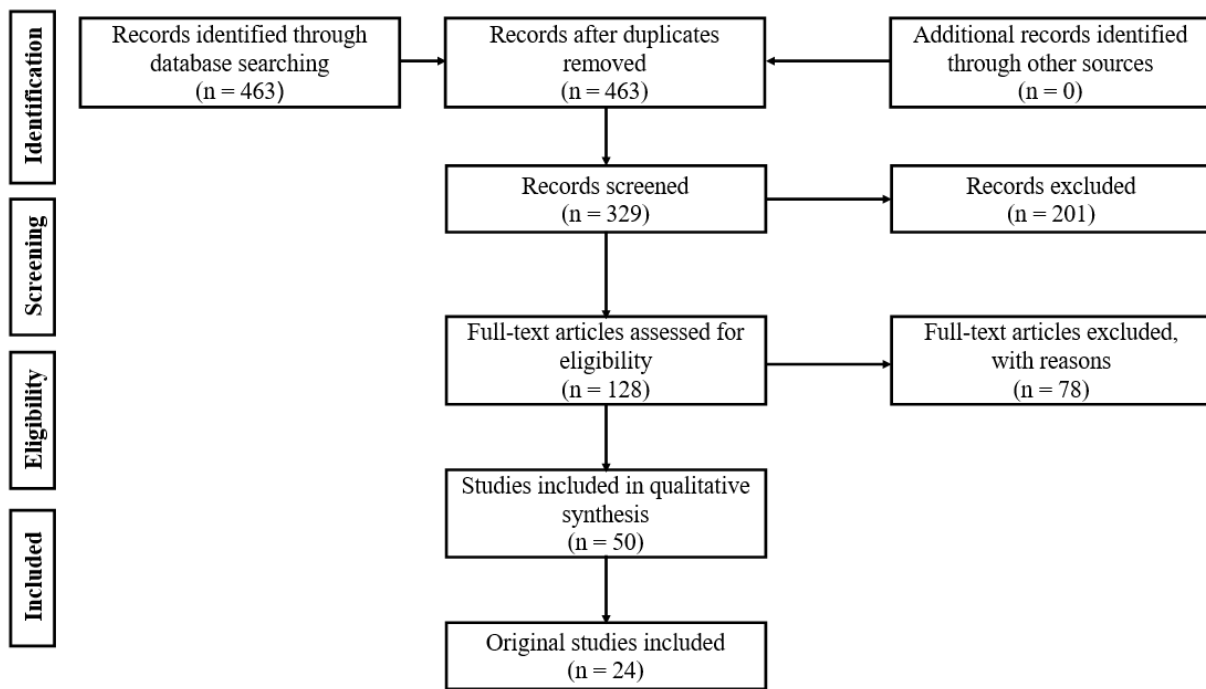


Figure 1 - Flowchart representing the identification, screening, eligibility and inclusion of articles for this review

RESULTS

inclusion and exclusion criteria established in this work were presented in the table below.

The articles previously selected according to the

Table 1: Title and general characteristics of the articles targeted by this study

Title of articles	Country / Year	Study design	Sample
Diabetes is a risk factor for the progression and prognosis of COVID-19 ¹ .	China 2020	Retrospective study	The total sample consisted of 174 COVID-19 positive patients, 37 of whom had DM.
Impaired glucose metabolism in patients with diabetes, prediabetes and obesity is associated with severe Covid-19 ⁶ .	U.S 2020	Observational study	A total of 184 patients were analyzed. About 62% of patients with COVID-19 had DM and 24.0% of patients with moderate-severe COVID-19 had prediabetes.
COVID-19 infection in Italian people with diabetes: Lessons learned for our future (an experience to be used) ²³ .	Italy 2020	Review article	Composed of 1,099 patients and according to the types of comorbidities 33.9% had DM, 22% of infected people suffered from diseases cerebrovascular and 24 to 12% of arterial hypertension.
Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes ²⁴ .	China 2020	Retrospective and multicenter study	Clinical characteristics were collected from a total of 7,337 participants with confirmed cases of COVID-19 including 952 subjects with pre-existing DM2 and 6,385 non-diabetic subjects.
Relationship of D-dimer levels of COVID-19 patients with diabetes mellitus ²⁵ .	India 2020	Cross-sectional study	98 patients in severe and moderate states, with 44% of patients with DM, we have that mean D-dimer in patients with diabetes was in values between 1509-2420 in a total of 45 patients with DM.
Clinical characteristics and outcomes of patients with severe covid-19 with diabetes ²⁶ .	China 2020	Observational, retrospective and multicenter study	The study included 193 critically hospitalized patients with COVID-19. 48 patients (24.9%) with DM, these patients were older and had a more severe inflammatory condition.
Patients with diabetes are at higher risk for severe illness from COVID-19 ²⁷ .	China 2020	Cohort Study	The study had a sample of 339 patients, where 130 were obese and 59 patients had diabetes.
Diabetes as a risk factor for greater COVID-19 severity and in-hospital death: A meta-analysis of observational Studies ²⁸ .	China Europe 2020	Meta-analysis	A total of 83 studies, totaling 78,874 confirmed cases of COVID-19, were included in the meta-analysis. All included studies reported data on the presence of established DM among patients hospitalized with COVID-19.

continue

Table 1: Title and general characteristics of the articles targeted by this study*continuation*

Title of articles	Country / Year	Study design	Sample
Is diabetes mellitus associated with mortality and severity of COVID-19? The meta-analysis ²⁹ .	India 2020	Meta-analysis	Thirty-three studies were included, with an odds ratio corrected at 2.16, where it was shown that DM increases the chances of mortality in patients with COVID-19.
Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia and a systematic review, meta-analysis, and meta-regression ³⁰ .	Indonesia 2020	Meta-analysis	30 studies were included in the qualitative synthesis and meta-analysis. Patients with positive COVID-19 and information regarding DM, which was associated with an unfavorable outcome that includes mortality in relation to COVID-19, were analyzed.
Demographic and clinical features of critically ill patients with COVID-19 in Greece: The burden of diabetes and obesity ³¹ .	Greece 2020	Observational multicenter study	90 patients were analyzed, of which 17 patients had type 2 DM, and obesity was present in 31 cases.
Clinical course and risk factors for adult mortality in patients with COVID-19 in Wuhan, China: a retrospective cohort study ³² .	China 2020	Retrospective multicenter cohort study	Of the total of 191 patients, 91 (48%) had comorbidities, DM corresponding to 36 (19%).
Diabetes and COVID-19 Related Mortality in the Critical Care Setting: A Real-Time National Cohort Study in England ³³ .	England 2020	Real-time database.	6,142 patients were included, of which 23.4% had DM.
Fasting blood glucose at admission is an independent predictor for 28-day mortality in patients with COVID-19 without previous diagnosis of diabetes: a multi-centre retrospective study ³⁷ .	China 2020	Multicenter retrospective study	Total of 1,258 patients, where 111 had a previous diagnosis of DM and 605 patients without a previous diagnosis of DM.
COVID-19: Impact of Obesity and Diabetes in Disease Severity ³⁸ .	Kuwait 2020	Cohort study	1158 patients, of which 271 had DM, 314 had pre-diabetes and 157 had a body mass index greater than 25 kg/m ² .
Diabetes patients with COVID-19 need better blood glucose management in Wuhan, China ³⁹ .	China 2020	Letter to the editor	A sample of 29 hospitalized patients diagnosed with type 2 diabetes and confirmed COVID-19.
The association between obesity, type 2 diabetes, and hypertension with severe COVID-19 on admission among Mexicans ⁴¹ .	Mexico 2020	Observational study	A total of 23,593 patients were analyzed, of which 3844 tested positive for COVID. 17.4% were obese and 14.5% had type 2 DM.
Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019 nCoV ⁴³ .	China 2019	Retrospective study	112 (27.6%) patients out of a total of 406 diagnosed with COVID-19 were analyzed. 23 (20.54%) had DM.
Obesity and COVID-19 Severity in a Designated Hospital in Shenzhen, China ⁴⁴ .	China 2020	COVID-19 case series studies.	Sample composed of 383 COVID positive patients, with an average of 38 patients having diabetes and obese simultaneously, with p: 0.82.
High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation ⁴⁵ .	France 2020	Retrospective cohort study. (Observational)	Patients with pre-existing illnesses such as hypertension, chronic respiratory disease or cancer were evaluated. Of the 124 patients admitted to intensive care for SARS-CoV-2, 28 had DM and 34 had severe obesity.
Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study ⁴⁷ .	France 2020	Multicenter observational study.	Sample composed of a total of 1317 participants with predominantly type 2 diabetes and confirmed COVID-19.
Prognostic factors in patients with hospitalized diabetes for COVID-19: Findings from the CORONADO study and other recent reports ⁴⁸ .	France 2020	Observational Study	1317 patients, 65% male, mean age 69.8 years, body mass index 28.4 kg/m ² . 88.5% of patients with type 2 DM.
Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study ⁴⁹ .	U.S 2019	Cohort study	Sample composed of 5566 patients, where a total of 1195 (22.65%) had DM and 1865 (35.35%) were obese with a BMI greater than or equal to 30.
Presenting Characteristic, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area ⁵⁰ .	U.S 2020	Case series	5700 patients with a mean age of 63 years, where 41.7% were obese with a BMI greater than or equal to 30, 19% were morbidly obese and 33.8% were diabetic.

DISCUSSION

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus, first identified in Wuhan, China in 2019. Considering the ease of spread of the virus, the disease quickly assumed worldwide proportions, being declared in January 2020, by the World Health Organization (WHO) as a pandemic. The clinical manifestations associated with the disease may vary depending on the patient, who may be asymptomatic, present symptoms characteristic of flu-like illness such as cough, fever, runny nose and myalgia, or even present severe pneumonia¹¹. In order to find scientific evidence that corroborates the understanding of the pathophysiology of the disease, many studies have been developed so far, however not all doubts about the disease have been resolved. Issues related to the development of immunity, the possibility of reinfections and even the in-depth understanding of why some comorbidities are related to a worse clinical outcome still remain unclear. It is known that the severity of COVID-19 is strongly associated with the presence of certain risk factors, including DM and obesity¹². The association between these risk factors and COVID-19 was studied by most of the articles selected for this review, and patients with DM and/or obesity had a higher prevalence of severe COVID-19, supporting a worse prognosis and higher rates of mortality.

COVID-19 and DM

DM is characterized as a chronic disease that affects about 1 in every 11 adults between 20 and 79 years in the world (463 million people), being characterized by numerous complications, such as cardiovascular and renal diseases, diabetic neuropathy and retinopathy, among others¹³. The presence of DM in patients with respiratory tract infections, such as Influenza A (H1N1)¹⁴; Middle Eastern Respiratory Syndrome (MERS)¹⁵ and, more recently, COVID-19 has been shown to be one of the independent risk factors for severe infection, being present in patients who developed fatal complications¹⁶. In these different scenarios, chronic hyperglycemia was considered a robust predictor of disease severity and mortality in infected patients. Based on a national report from China, of 1099 COVID-19 positive patients, found that in the group of patients characterized as severe there was a higher incidence of DM compared to the non-severe group (16.2% vs. 5.7%)¹⁷. Corroborating these findings, data from the pandemic in Italy revealed that DM is the second most common disease associated with COVID-19, second only to arterial hypertension¹⁷. Thus, it is observed that patients with DM have a significant “predisposition” to the development of serious infections. According to studies, the associations between DM and worse clinical outcome in viral infections are not unexpected, as hyperglycemia is detrimental to the control of viremia and

inflammation, aggravating morbidity and mortality in a variety of patients. Additionally, excessively tight glycemic control can increase the risk of severe hypoglycemia, which can also lead to increased mortality^{7,18}. With regard to COVID-19, most of the studies selected in this review showed a direct relationship between uncontrolled DM, worse disease prognosis and consequently higher mortality in patients who contracted the new coronavirus (SARS-CoV2).

The worst prognosis in diabetic patients hospitalized with COVID-19 was observed based on the evaluation of some laboratory parameters. In a study conducted in China, patients with COVID-19 and DM compared to those without DM had significantly higher results in absolute neutrophil count (4.1 vs 2.5), CRP (32.8 vs 16.3), Velocity of Erythrocyte sedimentation (67 vs 23) and D-dimer (1.15 vs 0.54). On the other hand, diabetic patients also had lower absolute lymphocyte count (0.86 vs 0.97), red blood cells (3.9 vs 4.17) and hemoglobin level (117 vs 127). These data demonstrate that patients with COVID-19 and uncontrolled DM are at higher risk for uncontrolled excessive inflammatory responses and worse prognosis¹. In the same way, another author specified the characteristics of patients with DM2 who contracted SARS-CoV-2 compared to non-diabetic patients, with a higher incidence of lymphopenia in the first group (44.5% versus 32.6%), a higher proportion of elevation of neutrophils (17.2% versus 9.9%), elevated serum markers, indicating inflammation (C-reactive protein, CRP [57.0% versus 42.4%] and procalcitonin [33.3% versus 20.3%]), decreased renal function (creatinine [12.0% versus 5.0%]), increased clotting status (D-dimer [50.5% versus 33.3%]), accompanied by higher blood glucose levels⁷. Notably, higher levels of D-dimer in diabetic patients with COVID-19 when compared to non-diabetic patients were also evidenced, indicating that COVID-19 infection in diabetics is more likely to cause a hypercoagulable state with a worse prognosis¹⁹. Other articles obtained results similar to those mentioned above, proving that uncontrolled DM is associated with severe COVID-19^{20,21}.

Similarly, it has been shown that patients with DM when infected with the new coronavirus have a higher risk of mortality, as well as a greater need for intensive treatment, as it has been reported that patients with established diabetes had an approximately twice as high risk of COVID disease -19 severe/critical compared to their non-diabetic counterparts (n = 22 included studies; odds ratio of random effects 2.10, 95% CI 1.71–2.57; I²=41.5%)²². Just like in another study the presence of DM was significantly associated with severe COVID-19 (OR 2.75 [95% CI: 2.09–3.62; p < 0.01]) and mortality due to COVID-19 (OR 1.90 [95% CI: 1.37–2.64; p<0.01])²³. From an evaluated meta-analysis, it was possible to note that DM was associated with an unfavorable outcome that included severe COVID-19, acute respiratory distress syndrome and

higher mortality, however this association was influenced by age and presence of arterial hypertension⁹. Similarly, an observational study conducted in China reported that when compared to patients without diabetes, more patients with diabetes were admitted to the ICU [32 (66.7%) vs 60 (41.4%)], received mechanical ventilation treatment [39 (81.3%) vs 71 (49.0%)], had a shorter length of hospital stay (10 (IQR 6–13) days vs 13 (IQR 9–18) days) and higher mortality (81.3% vs 47.6%)²⁰. In a similar study, DM was present only in patients who died from COVID-19 (30.8%) and had a higher prevalence in the ICU (16.7%), while none of the patients who were discharged had DM ($p = 0.074$)²⁴. Likewise, through a univariate analysis, it was proven that the chance of in-hospital death is greater in patients with diabetes or coronary disease²⁵. The presence of diabetes was significantly associated with mortality as well as with a higher risk of admission to the ICU in other articles, reinforcing the relationship^{9,23,26}. This association may be related to the fact that diabetic patients are more predisposed to severe COVID-19, which generates greater

complications and, consequently, greater need for treatment and mortality.

The association between DM and severe COVID-19 is still being studied and it is not clear whether DM independently contributes to the increased risk for COVID-19. However, some potential mechanisms that may increase the susceptibility to severe COVID-19 in patients with DM are understood, including: lack of glycemic control, higher affinity cell binding between the virus and cell receptors, and more efficient virus entry (associated with a higher expression of ACE2 receptors, decreased viral clearance, decreased T cell function, increased susceptibility to hyperinflammation and cytokine storm syndrome, in addition to the presence of cardiovascular disease, obesity and other comorbidities previously²⁷. These pathophysiological changes are largely related to the lack of glycemic control present in uncontrolled diabetic patients, which is a determining factor in the worst clinical outcome (Figure 2).

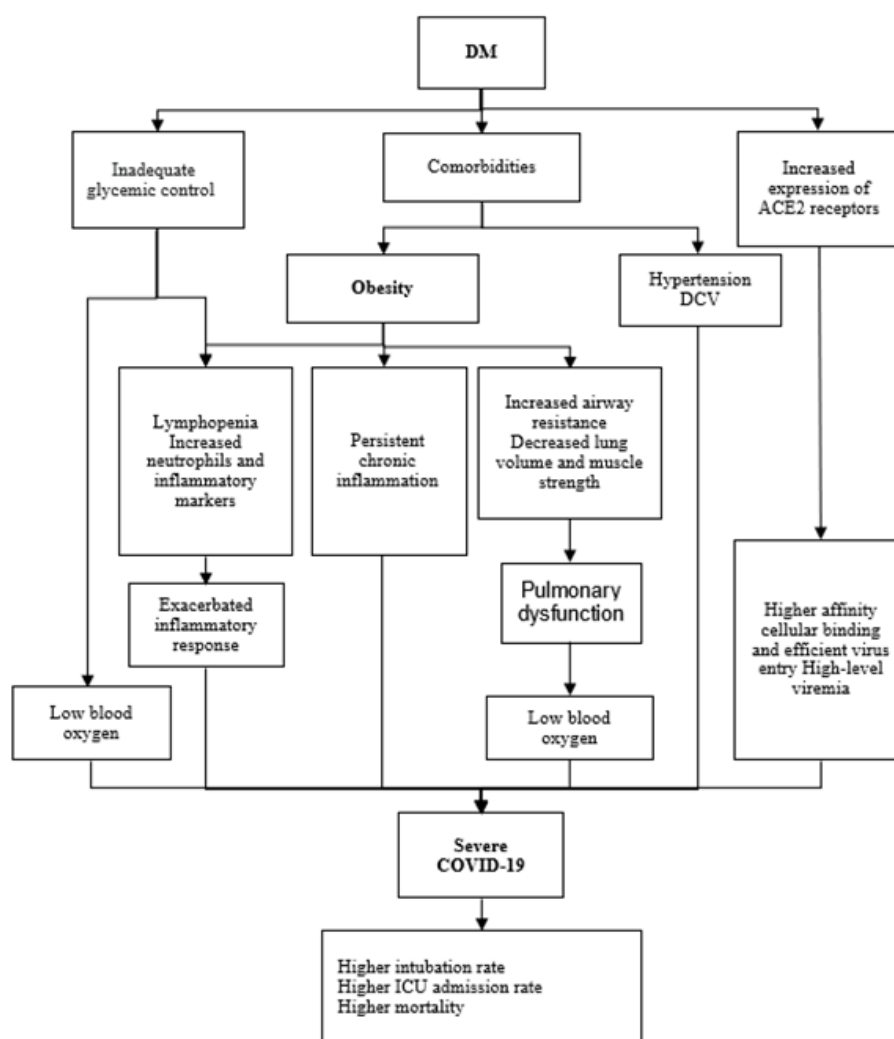


Figure 2 - Organizational chart summarizing the main pathophysiological mechanisms of DM and obesity responsible for the development of severe COVID-19

Association between glyceemic control and serious COVID-19

DM is a metabolic disorder characterized by persistent hyperglycemia, which is associated with chronic micro and macrovascular complications, increased morbidity, reduced quality of life, increased mortality rate and lower limb amputations²⁸. Lack of glyceemic control was associated with worse disease status and higher mortality in patients with COVID-19, especially in those with pre-existing DM. It is known that plasma glucose levels are important indicators for the control of DM, as well as being independent predictors of mortality and morbidity in patients with SARS-CoV-2²⁹. From this, it was observed that of the patients contaminated by the new coronavirus, those non-survivors had higher values of fasting glucose (≥ 7.0 mmol/L on admission). The 28-day mortality was higher in patients with fasting blood glucose between 6.1 and 6.9 mmol/L (crude HR 2.06 [CI 95% 1.20, 3.54]) and greater than or equal to 7.0 mmol/L (crude HR 3.54 [95% CI 2.33, 5.38]) when compared to those with values less than 6.1 mmol/L. Furthermore, compared to patients with admission fasting blood glucose less than 6.1 mmol/L, patients with admission values greater than or equal to 7.0 mmol/L (OR 3.99 [CI 95% 2.71, 5.88]) and between 6.1 and 6.9 mmol/L (OR 2.61 [CI 95% 1.64, 4.41]) had higher levels of in-hospital complications³⁰. A similar study compared patients with DM2 with well-controlled and poorly controlled glyceemia and who tested positive for COVID-19, and the mean blood glucose level was much lower in the well-controlled group than in the poorly-controlled group (6, 4 mmol/L vs 10.9 mmol/L). From these data, it was possible to verify that patients in the well-controlled group had significantly lower incidences of lymphopenia (30.5% vs 49.6%), lower rates of white blood cell counts (6.3% vs 12.2%) and neutrophils (10.7% vs 19.4%), lower serum CRP values (47.5% vs 59.5%) and procalcitonin (24.2% vs 35.0%). The same pattern was observed for aspartate transaminase (11.3% vs 20.4%) and D-dimer (37.6% vs 55.4%). In addition, fewer patients in the well-controlled group had oxygen saturation below 95% compared to the poorly-controlled group (12.6% versus 22.7%). Patients with COVID-19 and DM2 with well-controlled blood glucose also required fewer integrated treatments. Thus, poor glyceemic control in patients with COVID-19 and DM2 was associated with a worse prognosis, greater need for medical interventions, multiple organ injuries and higher mortality⁷. Furthermore, it was found that the intubation rate among patients with poorly controlled DM (HbA1C $\geq 7.5\%$) was significantly higher than that of patients with HbA1C $< 7.5\%$ (31.5% vs 17.8%; $P = 0.045$). The mean fasting blood glucose on admission for intubated patients was also significantly higher when compared with that of patients without the need for intubation (238.0 vs 163.7mg / dL; $P = 0.013$;

CI = 9.02–135.9) suggesting that uncontrolled blood glucose is a significant risk factor for severe COVID-19⁶. In convergence, it was also observed that the median glyceemia of patients admitted to the ICU was 147 (108–208) mg/dL, being significantly higher than that presented by non-ICU patients (median [IQR]: 98.6 [86.2–118] mg / dL; p -value < 0.001)³¹. From this, it was observed that of the patients contaminated by the new coronavirus, those non-survivors had higher values of fasting glucose (≥ 7.0 mmol/L on admission). The 28-day mortality was higher in patients with fasting blood glucose between 6.1 and 6.9 mmol/L (crude HR 2.06 [CI 95% 1.20, 3.54]) and greater than or equal to 7.0 mmol/L (crude HR 3.54 [95% CI 2.33, 5.38]) when compared to those with values less than 6.1 mmol/L. Furthermore, compared to patients with admission fasting blood glucose less than 6.1 mmol/L, patients with admission values greater than or equal to 7.0 mmol/L (OR 3.99 [CI 95% 2.71, 5.88]) and between 6.1 and 6.9 mmol/L (OR 2.61 [CI 95% 1.64, 4.41]) had higher levels of in-hospital complications³⁰. A similar study compared patients with DM2 with well-controlled and poorly controlled glyceemia and who tested positive for COVID-19, and the mean blood glucose level was much lower in the well-controlled group than in the poorly-controlled group (6, 4 mmol/L vs 10.9 mmol/L). From these data, it was possible to verify that patients in the well-controlled group had significantly lower incidences of lymphopenia (30.5% vs 49.6%), lower rates of white blood cell counts (6.3% vs 12.2%) and neutrophils (10.7% vs 19.4%), lower serum CRP values (47.5% vs 59.5%) and procalcitonin (24.2% vs 35.0%). The same pattern was observed for aspartate transaminase (11.3% vs 20.4%) and D-dimer (37.6% vs 55.4%). In addition, fewer patients in the well-controlled group had oxygen saturation below 95% compared to the poorly-controlled group (12.6% versus 22.7%). Patients with COVID-19 and DM2 with well-controlled blood glucose also required fewer integrated treatments. Thus, poor glyceemic control in patients with COVID-19 and DM2 was associated with a worse prognosis, greater need for medical interventions, multiple organ injuries and higher mortality⁷. Furthermore, it was found that the intubation rate among patients with poorly controlled DM (HbA1C $\geq 7.5\%$) was significantly higher than that of patients with HbA1C $< 7.5\%$ (31.5% vs 17.8%; $P = 0.045$). The mean fasting blood glucose on admission for intubated patients was also significantly higher when compared with that of patients without the need for intubation (238.0 vs 163.7mg / dL; $P = 0.013$; CI = 9.02–135.9) suggesting that uncontrolled blood glucose is a significant risk factor for severe COVID-19⁶. In convergence, it was also observed that the median glyceemia of patients admitted to the ICU was 147 (108–208) mg/dL, being significantly higher than that presented by non-ICU patients (median [IQR]: 98.6 [86.2–118] mg / dL; p -value < 0.001)³¹.

In a survey in which a total of 881 capillary blood

glucose tests, 56.6% (499/881) of the tests had abnormal glucose levels, including 29.4% (58/197) of the preprandial glucose tests and 64.5% (441/684) of the postprandial tests. 69.0% (20/29) of the patients were considered to have non-ideal glucose levels. And 10.3% (3/29) of patients suffered at least one episode of hypoglycemia (<3.9 mmol/L). From this, it was concluded that the results obtained suggested flaws in blood glucose management strategies in diabetic patients diagnosed with COVID-19. As diabetes and hyperglycemia are related to a higher risk of secondary infection and mortality, it has been suggested that the management of blood glucose in these patients is more valued and optimized³². Based on all the data presented, the impact of glycemic control during hospitalization and consequences related to COVID-19 deserve further specific investigation, since glycemic control can perhaps be used as a protective factor in relation to the severity of COVID-19.

COVID-19 and obesity

According to the World Health Organization, obesity is one of the most serious diseases of today and it is growing at a fast pace, it is estimated that in 2025 2.3 billion adults in the world are overweight, of this total 700 million with BMI above 30, that is, with obesity⁸. Obesity is related to an increased risk for numerous diseases such as hypertension, diabetes and cardiovascular disease. Furthermore, from the articles studied for this review, it was possible to observe that obesity is also related to severe COVID-19, mortality and greater need for medical interventions. It was found that when compared to normal weight patients, those with overweight had a probability of developing severe COVID of 1.84 (OR 1.84, 95% CI 0.99-3.43, P = 0.05) while those with obesity had a chance of 3, 40 times greater to develop severe disease (OR 3.40, 95% CI 1.40 to 8.26, P = 0.007)⁹. Accordingly, another study identified that obese patients were 1.43 times more likely to develop severe COVID-19 on admission compared to non-obese patients, as BMI > 40 was one of the factors most associated with critical illness. Furthermore, obesity was also more frequent (46.2%) among those who died from COVID-19 than among survivors (26.7%) (p = 0.077)¹⁰. A plausible explanation for the higher probability of obese individuals to present severe COVID-19 may be related to the fact that obesity has mechanisms that amplify the inflammatory response, such as lack of control in the production of cytokines and abnormal T-cell response, an effect that also occurs in syndromes metabolic, which are frequently present among the obese³³. In convergence, it was seen that obese patients infected by the new coronavirus when compared to non-obese patients have lower lymphocyte counts [$0.74 (0.34, 0.94) \times 10^9 / L$ than $0.99 (0.71, 1.29) \times 10^9 / L$, P = 0.03] and higher than C-reactive protein [106.98 (81.57, 135.76) Mg / L ratio 34.34 (9.55, 76, 54) mg / L, P <0.001] and procalcitonin [0.20 (0.15, 0.48) µg / L ratio 0.11 (0.06, 0.20)

µg / L, P <0.001], which are important factors associated with inflammation and immune response³⁴.

On the other hand, obesity was also related to a greater need for intensive care, as compared to normal weight patients, class I and morbid obese patients were 3.5 and 5.2 times more likely to suffer, respectively, being admitted to the ICU (OR: 3.51 [95% CI: 1.60–7.69 for class I obesity; and OR: 5.18 [95% CI: 1.50–17.85] for morbid obesity). Since the median BMI of patients admitted to the ICU was significantly higher than that of those who did not need care in the ICU (median [IQR]: 27.5 [25.3-31.4] kg / m² vs 26 [23 -29] kg / m², respectively; p value <0.001)³¹. In addition, it was also analyzed that intubated patients had a higher mean BMI than non-intubated patients (32.3 vs 29.3; P = 0.030; 95% CI = 0.3-5.8). Patients with a BMI > 40 had a significantly higher intubation rate than patients with a BMI < 25 (47.4 vs 15.6%; P = 0.0078)⁶. Likewise, in a univariate analysis it was possible to note that tracheal intubation and/or death within 7 days of admission was more frequent in patients with higher BMI (median 29.1 [25.9-33.6] vs 28.1 [24.8-32.0] kg / m², p = 0.0009)³⁵. Invasive mechanical ventilation (IMV) was also related to obesity, such that obesity (BMI > 30) and severe obesity (BMI) ≥ 35) were more frequent among patients who required IMV than among those who did not (56.4% vs. 28.2% and 35.3% vs. 12.8%, respectively)³⁶. Possibly, the fact that a obesity is related to a greater need for medical interventions, especially intubation and invasive mechanical ventilation, is associated with respiratory dysfunction, which is frequent in obese and characterized by changes in respiratory mechanisms, increased airway resistance, changes in gas exchange and low lung volume and muscle strength. Obesity is also associated with an increased risk of developing comorbidities such as diabetes mellitus, cardiovascular disease and kidney disease, which are related to greater vulnerability to organ failure due to pneumonia³⁷. Moreover, obese people are also related to higher metabolic risk through the association with hypertension, dyslipidemia, prediabetes and insulin resistance, which damage the immune response and, consequently, lead to more complications due to SARS-CoV-2 infection³⁷. Likewise, in a univariate analysis it was possible to note that tracheal intubation and/or death within 7 days of admission was more frequent in patients with higher BMI (median 29.1 [25.9-33.6] vs 28.1 [24.8-32.0] kg / m², p = 0.0009)³⁵. Invasive mechanical ventilation (IMV) was also related to obesity, such that obesity (BMI > 30) and severe obesity (BMI) ≥ 35) were more frequent among patients who required IMV than among those who did not (56.4% vs. 28.2% and 35.3% vs. 12.8%, respectively)³⁶. Possibly, the fact that a obesity is related to a greater need for medical interventions, especially intubation and invasive mechanical ventilation, is associated with respiratory dysfunction, which is frequent in obese and characterized by changes in respiratory mechanisms,

increased airway resistance, changes in gas exchange and low lung volume and muscle strength. Obesity is also associated with an increased risk of developing comorbidities such as diabetes mellitus, cardiovascular disease and kidney disease, which are related to greater vulnerability to organ failure due to pneumonia³⁷. Moreover, obese people are also related to higher metabolic risk through the association with hypertension, dyslipidemia, prediabetes and insulin resistance, which damage the immune response and, consequently, lead to more complications due to SARS-CoV-2 infection³⁷.

CONCLUSION

It was observed that uncontrolled DM and obesity are important risk factors for severe COVID-19, associated

with a worse prognosis and, consequently, the need for intensive treatment. This fact is justified from the perspective of pathophysiological changes related to both comorbidities (lack of glycemic control and chronic inflammation characteristic of obese and diabetic patients, respiratory compromise, increased expression of binding receptors to the viral capsule), which together favor a worse clinical outcome. Additionally, it was observed that strict glycemic control in diabetic patients is an important protective factor for severe COVID-19, considering the fact that patients infected by the new coronavirus, whose clinical outcome was death, had higher blood glucose values in fast. Thus, the importance of glycemic control and other variables such as body weight in patients with DM is highlighted as a control and protection factor in the COVID-19 scenario.

Authors' contribution: Ana Flávia Freire de Andrade; Anne Moura Korthals; João Antônio Martins Gomes; Laura Medeiros Costa; Maria Gabriela Gonçalves Rezende de Souza; Mateus Gonçalves de Sena Barbosa: Development of the body of the article, synthesis of the main findings, preparation of tables and organization charts and critical review of the final proposal. Edna Messias de Freitas Santos; Thaynara Faria Gomes: Structuring of the main proposal of the article, definition of inclusion and exclusion criteria, evaluation of the articles included, writing guidance and critical review of the final proposal.

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Submitted: 2021, March 18

Accepted: 2021, June 15