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Obesity Research & Clinical Practice 15 (2021) 402–405

Contents lists available at ScienceDirect

Obesity Research & Clinical Practice

journal homepage: www.elsevier.com/locate/orcp

Original Article

Impact of obesity and diabetes mellitus in critically ill patients with SARS-CoV-2

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ARTICLE INFO

Keywords:
Obesity
Diabetes mellitus
Critical care
SARS-CoV-2
COVID19
Severe acute respiratory syndrome

ABSTRACT

Purpose: Evaluate the associations of obesity and diabetes with the risk of mortality in critically ill patients infected with SARS-CoV-2.
Materials and methods: This cohort study included 115 adult patients admitted to the ICU with SARS-CoV-2 pneumonia. Anthropometric variables and biochemical (C-reactive protein, ferritin, leukocyte, neutrophils, and fibrinogen) were measured. Multivariate logistic regression analyses were used to investigate the associations.
Results: Mean age was 50.6 ± 11.2 years, 68.7% were male. Median BMI was 30.9 kg/m^2. All patients had invasive mechanical ventilation. Patients with diabetes had increased risk of mortality with OR of 2.86 (CI 95% 1.1–7.4, p = 0.026); among those patients who, in addition to diabetes had obesity, the risk was de 3.17 (CI 95% 1.9–10.2, p = 0.038). Patients with obesity had 1.25 times greater risk of developing a severe SARS-CoV-2 infection (95% CI 1.09–1.46, p = 0.025). Negative correlation was observed between BMI and the PaO2/FiO2 ratio (r = −0.023, p < 0.05). Obese patients required more days of mechanical ventilation and longer hospital stay compared to non-obese patients.
Conclusions: Diabetes and obesity are risk factors for increasing severity of SARS-CoV-2 infection, and they are both associated with an increase in mortality.

Introduction

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has spread quickly from Wuhan, China, to a growing number of countries, posing unprecedented challenges and threats to patients and healthcare systems [1]. As of April 4, 2021, there were 130 459 184 confirmed cases and 2 842 325 deaths from SARS-CoV-2 worldwide [2]. Various studies have suggested that elderly people are at higher risk for severe illness, and some chronic medical conditions, such as high blood pressure, diabetes mellitus, and obesity, can affect the progression of the disease [3–6].

Previous studies have shown a strong association between obesity and complications from serious infections with other coronaviruses, such as the Severe Acute Respiratory Syndrome-associated Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV). This association is relevant since SARS-CoV-2 is genetically similar to the SARS-CoV (80%) and to the MERS-CoV (50%) (7). Studies show that patients with SARS-CoV-2 infection and obesity have a higher risk of hospital admission regardless of their viral status [4,6]. In addition, obesity per se increases the severity of respiratory diseases due to limitation of diaphragmatic expansion and reduced ventilation in patients in the supine position [5]. It is currently unclear whether there is a direct correlation between the degree of obesity and the severity and mortality in patients with SARS-CoV-2 [4,6,7].

On the other hand, diabetes mellitus (DM) is one of the most frequent chronic diseases with devastating multisystem complications. DM patients are at a higher risk of respiratory infections due to a compromised immune system, especially innate immunity [8–10]. It is unknown whether DM influences the severity and mortality of patients with SARS-CoV-2 infection.

As most patients with obesity have obesity-associated conditions, such as DM, the already weakened immune response is further compromised. This, together with the cytokine storm caused by the SARS-CoV-2 infection, contributes to the increased severity of the illness

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https://doi.org/10.1016/j.orcp.2021.05.001
Received 18 April 2021; Accepted 7 May 2021
Available online 12 May 2021

[5]. The goal of the study was to evaluate whether obesity and diabetes mellitus are associated with the risk of mortality in critically ill patients infected with SARS-CoV-2.

Methods

Study design and population

Prospective cohort study of consecutive adult patients, both sexes, showing symptoms of a severe SARS-CoV-2 infection, admitted to the Intensive Care Unit (ICU) in a period of four months. The patients were diagnosed with SARS-CoV-2 pneumonia—according to the criteria of the World Health Organization (WHO)—based on the characteristic symptoms of SARS-CoV-2: dyspnea, tachypnea, decreased O_2 saturation with the need for oxygen (6 L/min), and detection of SARS-CoV-2 by real-time polymerase chain reaction (RT-PCR) assays.

Demographic variables

The demographic data recorded were sex (women and men), age (years), history of smoking, diabetes mellitus, systemic arterial hypertension (SAH), dyslipidemia, hypothyroidism, and chronic lung disease.

Anthropometric measurements

The measurements included weight (kg), determined through the use of metabolic beds and height (m) referred by the patient. The body mass index (BMI) or Quetelet index was then calculated using the formula BMI = weight (kg)/height^2 (m), and subjects were classified according to the WHO reference ranges into patients with class I or mild obesity with a BMI of 30–34.9 kg/m^2, class II or moderate obesity with a BMI of 35–39.9 kg/m^2, and class III or morbid obesity with a BMI $\geq$ 40 kg/m^2. For the data analysis, patients with a BMI $>$ 30 kg/m^2 were considered to be obese.

Biochemical measurements

The biochemical markers analyzed were C-reactive protein, ferritin, total leukocyte count, neutrophils, and fibrinogen. The determination of the biochemical parameters was carried out in venous blood according to the standardized method used in the central laboratory of the hospital.

The Sequential Organ Failure Assessment (SOFA) score and the Acute Physiology and Chronic Health Evaluation (APACHE) II prognostic classification were used to assess the severity of each patient's illness.

Outcomes

The primary outcome was to determine the association between obesity and diabetes mellitus with the risk of mortality in patients admitted to the ICU. The secondary outcomes evaluated were severity of the disease, number of days of mechanical ventilation, number of days of ICU stay, and biochemical markers.

Statistical analysis

The results were expressed as means $\pm$ SD or medians p (25, 75) for continuous variables, and frequencies (percentages) for categorical variables. For demographic and clinical characteristics, chi^2 or Fisher's exact tests were used for categorical variables, and Student's t or U Mann-Whitney tests for ordinal variables. The association between obesity and DM with mortality, as well as between predictive markers, was determined by multivariate logistic regression analysis. Statistical significance was assessed using 95% confidence intervals, a statistical power of 80%, and a significance level of 0.05. Data were analyzed using the statistical program of IBM Statistics SPSS v21 for Windows (Chicago IL, USA). Verbal consent via telephone has been obtained from of the relatives of each patient, this due to the national policies to reduce the approach due to pandemic. The study was approved by the Hospital Research and Ethics Committee and was conducted in accordance with the guidelines of the Declaration of Helsinki.

Results

The study population consisted of 115 patients, of which the average age was 50.6 $\pm$ 11.2 years, with a higher proportion of male patients (68.7%). The median BMI was 30.9 kg/m^2, with the majority of patients classified as having class I obesity (37.4%). All patients had invasive mechanical ventilation. The most prevalent comorbidities within the population were hypertension (31.3%) and DM (25.2%). Table 1 shows other demographic characteristics of the study population.

Regarding the primary outcome, statistically significant differences were found between those patients that had both obesity and DM compared to the rest of the study population (p = 0.012). The analysis showed a relationship between DM and mortality, and patients with DM had a mortality risk 2.86 times greater than patients without DM (OR = 2.86, CI 95% 1.1–7.4, p = 0.026); 64.2% of deaths were attributed to the disease. Among those patients who, in addition to DM, had obesity, the risk was 3.17 times greater (OR = 3.17, CI 95% 1.9–10.2, p = 0.038); 68.5% of deaths were attributed to DM among patients who had a BMI $\geq$ 30.

Regarding secondary outcomes, obese patients had a 1.25 times greater risk of developing a severe SARS-CoV-2 infection (OR = 1.25, 95% CI 1.09–1.46, p = 0.025), compared to non-obese patients. Furthermore, a negative correlation was observed between BMI and the PaO2/FiO2 ratio (r = −0.023, p $<$ 0.05).

Obese patients required more days of mechanical ventilation (12.63 $\pm$ 7.2 vs. 11.57 $\pm$ 6.7 days, p = 0.384), and longer hospital stay (13.17 $\pm$ 7.3 vs. 12.04 $\pm$ 6.5 days, p = 0.359) compared to non-obese patients. Likewise, patients with DM required more days of mechanical ventilation (12.49 $\pm$ 6.3 vs. 12.01 $\pm$ 7.3 days, p = 0.565), and longer hospital stay (12.78 $\pm$ 6.2 vs. 11.6 $\pm$ 7.2 days, p = 0.733) compared to those who do not have DM.

When comparing patients with and without obesity, significant differences were observed regarding age, sex, SOFA score, PaO2/FiO2 ratio, and total leukocyte count (Table 2). No significant differences were found regarding the presence of comorbidities and the APACHE II score. When comparing the patients with and without DM, significant differences were observed in terms of age, sex, total leukocyte count, and fibrinogen (Table 3), in addition to the presence of SAH (p = 0.04).

Table 1
Characteristics of study participants.

Characteristics	Total n = 115
Age (years)	50.6 $\pm$ 11.2
Sex (n, %)	
Women	36 (31.3)
Men	79 (68.7)
Weight (kg)	85 (75, 97)
Height (cm)	115 $\pm$ 8.8
BMI (kg/m^2)	30.9 (28.3, 34.6)
BMI Classification (n, %)	
Normal	9 (7.8)
Overweight	37 (32.2)
Obese class I	43 (37.4)
Obese class II	14 (12.2)
Obese class III	12 (10.4)
Pre-existing conditions (n, %)	
Hypertension	36 (31.3)
Type 2 Diabetes	29 (25.2)
Hypothyroidism	4 (3.5)
Alcoholism	23 (20.0)
Smoking	14 (12.2)

Table 2
Clinical characteristics of patients with and without obesity.

Characteristics	Without Obesity	With Obesity	p
Age (years)	54.06 ± 11.2	48.4 ± 10.7	0.008*
Sex women, n (%)	20.8	38.8	0.044
APACHE II	18.27 ± 7.7	18.06 ± 6.9	0.878
SOFA	9.08 ± 3.8	10.5 ± 4.0	0.046*
PaO2FiO2, mmHg: %	129.8 ± 67.8	105.2 ± 55	0.041*
C-reactive protein, mg/L	14.9 ± 8.7	13.6 ± 7.8	0.417
Ferritin, ng/mL	892.4 ± 434.9	771.5 ± 393.6	0.123
Neutrophils, ×103/ul	10.49 ± 3.9	8.49 ± 3.7	0.07
Total leukocyte count, ×103/ul	12.30 ± 4.2	10.06 ± 3.8	0.004*
Fibrinogen, mg/dL	624.8 ± 156.2	631.7 ± 172.4	0.826
Creatinine, mg/dL	0.99 ± 0.36	1.15 ± 0.69	0.094

* $p<0.05$

Table 3
Clinical characteristics of patients with and without diabetes.

Characteristics	Without Diabetes	With Diabetes	p
Age (years)	49.04 ± 11.1	55.5 ± 10.2	0.005*
Sex women, n (%)	26.2	45.2	0.070
APACHE II	17.65 ± 7.1	19.48 ± 7.5	0.231
SOFA II	9.60 ± 4.0	10.9 ± 3.7	0.010*
PaO2FiO2, mmHg: %	113.2 ± 56.3	121.5 ± 74.8	0.525
C-reactive protein, mg/L	14.5 ± 7.5	13.3 ± 9.8	0.490
Ferritin, ng/mL	826.0 ± 414.7	648.2 ± 145.4	0.862
Neutrophils, ×103/ul	9.72 ± 4.1	8.26 ± 3.3	0.079
Total leukocyte count, ×103/ul	11.4 ± 4.1	9.7 ± 3.8	0.05*
Fibrinogen, mg/dL	648.2 ± 145.4	576.4 ± 203.2	0.038*
Creatinine, mg/dL	1.11 ± 0.58	1.02 ± 0.57	0.481

* $p<0.05$

Discussion

This study provided information on the course of the disease in patients with SARS-CoV-2 infection hospitalized in ICUs in the national context. The mean age and gender propensity of our patients mostly men are similar to those with severe SARS-CoV-2 disease in neighboring countries [11,12].

Obesity is associated with a negative role in respiratory function. Scientific literature suggests that obese patients with SARS-CoV-2 infection tend to have a more severe disease [13], as we observed in our study, where most patients were either overweight (32.2%) or obese (60%). These percentages exceed those reported by other authors, but overall agree with an increased mortality in obese patients [14,15].

The mechanism by which obesity contributes to the severity of SARS-CoV-2 infection has been associated with a decrease in residual functional capacity and in expiratory residual volume, as well as with hypoxemia and alterations in ventilation-perfusion ratios. This adds to the damage that obesity causes to the immune system, and the associated increased expression of ACE-2 receptors in adipose tissue. Our patients required invasive mechanical ventilation upon admission to the ICU due to severe ARDS problems, as observed in their very low PaO2/FIO2 ratios.

Diabetes mellitus is recognized as one of the most common comorbidities in patients with SARS-CoV-2 [12] and, since many diabetic patients are obese; this leads to a severe infection with an increased need for intensive care [16]. In large case series, DM was present in 8% of patients with a severe SARS-CoV-2 infection in China, 33.8% in the United States, and 21% in the United Kingdom [17]. Furthermore, marked insulin resistance [4,5] has been reported even in those individuals without a history of diabetes [6]. Epidemiological studies have shown that diabetes increases the risk of hospitalization, admission to intensive care, and mortality from SARS-CoV-2 [10–13]. A multicenter study in Wuhan reported that the risk of fatal outcome was 1.49 times higher in patients with diabetes, while a report from the UK suggested that the risk of mortality could be even up to 2–3 times higher [18]. In our study, we observed a risk 2.86 times higher in those patients with DM and 3.17 times higher among those patients who also had a BMI ≥ 30. We additionally observed a greater association of DM with mortality; the people with diabetes developed a more severe SARS-CoV-2 disease and had a higher mortality.

The interaction between SARS-CoV-2 and DM is complex. Studies have informed about innate immune defects in patients with diabetes, including dysfunction of granulocytes, macrophages, cytokine signaling and NK cells [19]. Although critical illness is characterized by increased levels of glucagon, cortisol, and growth hormone release, inducing insulin resistance and hyperglycemia, some specific mechanisms for dysglycemia in ARDS due to SARS-CoV-2 is that the virus has a selective entry into the pancreatic islets through the angiotensin-converting enzyme 2 (ACE-2) receptor [19,20]. This leads to local cytopathic effects, decreasing the number of beta cells [21]. The ACE-2 receptors prevalent in other metabolic organs and tissues also explain the observed insulin resistance. In addition, the diabetic microangiopathy including perialveolar as well as the microthrombi and endothelitis observed in patients with SARS-CoV-2 infection contribute to impaired blood flow and gas exchange in the lung, increasing the severity of the disease [22].

Interestingly, and supporting these points, we observed higher scores on the SOFA multiorgan dysfunction scale and on the APACHE II prognostic classification in those patients suffering from DM and obesity, which leads to the higher mortality described. SARS-CoV-2 disease will persist, and due to the high worldwide prevalence of obesity and DM, it is imperative that research in these areas is prioritized. We are only beginning to understand the interaction between obesity, diabetes, and SARS-CoV-2. Many details, however, remain to be established, such as the role of glycemic control, the time of evolution, and even the therapy used in the outcomes of these patients.

Our study has some limitations. We did not perform a complete analysis of the subgroups with all confounding factors. Thus, future studies are needed. The published data are derived from a single referral hospital center, which may introduce selection biases, given that outside the hospital unit there is limited access to the SARS-CoV-2 tests, leading to diagnostic access bias that can exaggerate severity and distort mortality.

In conclusion, this study show that diabetes mellitus and obesity are risk factors for increasing severity of SARS-CoV-2 infection, and they are both associated with an increase in mortality.

Ethical statement

The authors of this Ethics Committee-approved study declare they have read and have abided by the statement of ethical standards for manuscripts submitted to Obesity Research &Clinical Practice.

Funding sources

None.

Declaration of interest

The authors have no conflicts of interest to declare.

CRediT authorship contribution statement

Elizabeth Pérez-Cruz: Conceptualization, Methodology, Investigation, Data curation, Validation, Writing - original draft, Writing - review & editing, Supervision. **Jorge Alberto Castañón-González:** Methodology, Formal analysis, Data curation, Visualization, Writing - original draft, Writing - review & editing. **Salvador Ortiz-Gutiérrez:** Investigation, Data curation, Writing - review & editing. **Jessica Garduño-López:** Investigation, Data curation, Writing - review & editing. **Yuritzy Luna-Camacho:** Investigation, Data curation, Writing - review &

editing.

Acknowledgements

We thank all the personnel who took part in this study.

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