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PRÁTICA CHALLENGE OF THE MANAGEMENT OF COVID-19 IN PATIENTS WITH OBESITY

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ABSTRACT

Obesity is a condition associated with worse outcomes of patients infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is linked to endocrine and immunological dysfunction, making the patient more vulnerable to the disease caused by the virus. Considering that the pathophysiological mechanisms involved in coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 are still unclear, the search for various drugs for the treatment or prevention of the disease is still in progress. Therefore, it is essential to review the mechanisms of action of drugs on severe COVID-19 and their pharmacological interaction with obesity.

Key words: Endocrinology. Coronavirus Infections. Obesity. Obesity Management. Medication Therapy Management.

RESUMO

Desafio do manejo da covid-19 em pacientes com obesidade

A obesidade é uma condição associada a piores desfechos de pacientes infectados com o coronavirus da síndrome respiratória aguda grave 2 (SARS-CoV-2). Está ligada a disfunções endócrinas e imunológicas, tornando o paciente mais vulnerável à doença causada pelo vírus. Considerando que os mecanismos fisiopatológicos envolvidos na doença por coronavírus - 2019 (COVID-19) causada pelo SARS-CoV-2 ainda não são claros, a busca por diversos fármacos para o tratamento ou prevenção da doença ainda está em andamento. Portanto, é fundamental revisar os mecanismos de ação dos fármacos sobre a COVID-19 grave e sua interação farmacológica com a obesidade.

Palavras-chave: Endocrinologia. Infecções por Coronavirus. Manejo da Obesidade. Conduta do Tratamento Medicamentoso.

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INTRODUCTION

Obesity is a low-grade chronic inflammatory disease, which begins with the accumulation of fat resulting from the imbalance between high calorie consumption and low energy expenditure. The accumulation of stored fat triggers an increase in visceral adipose tissue, resulting in local and systemic inflammation (Tchernof and Després, 2019; World Health Organization, 2020).

In addition to being an important factor for the development of other chronic diseases such as systemic arterial hypertension, type 2 diabetes mellitus, and hypercholesterolemia, obesity makes an individual more susceptible to infectious diseases.

Thus, obesity is considered one of the main risk factors for worse outcomes of a patient infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Dietz and Santos-Burgoa, 2020; Johnson, Justin Milner and Makowski, 2012; Kaur, 2014; Williams and contributors, 2015).

The inflammatory process results mainly in immunodeficiency and in greater storage of the virus in the adipose tissue, allowing greater concentration, replication, and mutation of the pathological agent in the body (Luzi and Radaelli, 2020).

SARS-CoV-2 causes a disease, officially called by the World Health Organization (WHO) as coronavirus disease 2019 (COVID-19).

The disease is extremely contagious and capable of causing respiratory problems and pneumonia in infected patients. It may aggravate to include systemic inflammatory response syndrome, shock, organ failure, and death.

The first cases of the disease were registered in the city of Wuhan, province of Hubei, China, at the end of 2019, and in a few days, the condition spread across the world, reaching different countries and continents (Luzi and Radaelli, 2020; Lai and contributors, 2020; Yuki, Fujiogi and Koutsogiannaki, 2020). On March 11, 2020, the disease was declared a pandemic by the WHO (Caesar, 2020; Chade, 2020).

COVID-19 is transmitted from human to human by direct or indirect contact with respiratory secretions, droplets and aerosols or saliva of an infected individual, or through entry of the virus into the oronasal mucosa or ocular conjunctiva.

The gateway for SARS-CoV-2 is the upper airway of the infected person, through which it reaches the lungs, whose cells have the angiotensin-converting enzyme 2 (ACE-2) in their membrane, which serves as a receptor for the binding of the spike protein of the virus.

After the interaction of the virus with ACE-2, it is internalized into the lung tissue through endocytosis. This process results in the fusion of the virus membrane to the host cell membrane, allowing the virus to enter the lung cells and access the nucleus to promote viral replication of the viral genome.

Therefore, when infected, the individual may manifest cough, runny nose, fever, sore throat, and dyspnea, and his condition may vary from being asymptomatic to severe respiratory failure (Lai and contributors, 2020; Jin and contributors, 2020; Atri and contributors, 2020; Guo and contributors, 2020). SARS-CoV-2 infection has shown a very heterogeneous clinical picture, possibly dependent on an individual's viral load and vulnerability.

There are countless antiviral or anti-inflammatory medications considered for the treatment of COVID-19 and used off-label in several countries, even though scientific evidence provided by large-scale randomized clinical trials is still limited.

Thus, it is essential to understand the pathophysiological mechanisms related to obesity and its associated comorbidities, to analyze its possible interaction with COVID-19, the infectious respiratory disease caused by SARS-CoV-2.

Moreover, it is necessary to evaluate the drug treatments currently available for the clinical management of this disease, to detect probable interactions and adverse effects when used in patients with obesity (Atri and contributors, 2020; Guo and contributors, 2020; Kumar and contributors, 2020).

OBESITY

Obesity is a morbidity represented by ICD-10, the 10th revision of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD).

Information about obesity is available in the section on endocrine, nutritional, and metabolic diseases under the code E660.

This dysfunction is due to an imbalance between high calorie consumption and low energy expenditure, causing significant energy storage in the form of fat,

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especially in the abdominal region (World Health Organization, 2020; World Obesity, 2020).

The prevalence of obesity is increasing significantly, to the point of being classified as an epidemic by the WHO (Tchernof and Després, 2019; World Health Organization, 2020; World Obesity, 2020; World Health Obesity, 2020).

In 2016, WHO estimated for 1.6 billion individuals with overweight over 18 years of age, 650 million of whom had obesity. From 1975 to 2016, the number of cases of childhood obesity increased from 4% to 18% worldwide, and in 2016, 340 million children and adolescents between 5 and 19 years of age had overweight or obesity. Furthermore, these numbers resulted in a greater number of deaths related to obesity than to malnutrition. In 2017, more than 4 million deaths were recorded as a result of obesity (World Health Organization, 2020).

Based on the data presented, a significant increase in obesity has been observed in recent years. Thus, a quick and effective diagnosis as well as monitoring of the condition is essential. The main diagnostic method for obesity is the evaluation of body mass index (BMI), calculated by dividing the weight of an individual in kilograms by the square of the individual's height in meters (kg /m^2). BMI is used by the WHO to diagnose and classify individuals with obesity, in addition to being related to the development of other diseases (World Health Organization, 2020).

However, if used in isolation, BMI is not completely accurate and, therefore, other methods are integrated with it for a reliable diagnosis. Among the methods associated with BMI, the verification of fat distribution by an assessment of waist circumference is the most widely used, but measurement of circumferences, skinfolds, and bioimpedance, and imaging tests are also used to estimate body fat and composition (Anjos, 2013).

PATHOPHYSIOLOGY OF OBESITY

Obesity stems from the disproportion between high calorie consumption and low energy expenditure, which results in a positive energy balance. The energy resulting from the imbalance is stored in the form of triacylglycerol in cells of the adipose tissue, called adipocytes (World Health Organization, 2020; Ohashi and contributors, 2014).

Excess fat from food, modulated mainly by endocrine metabolism, is deposited in adipocytes, causing them to enlarge their cytoplasm in order to allow more space for the fat. This phenomenon is called adipocyte hypertrophy. When hypertrophy is insufficient, tissue hyperplasia occurs, a process in which cells replicate or differentiate, and fat tissue expands (Badimon and Cubedo, 2017).

The increase in adipose tissue, resulting from hypertrophy and hyperplasia, compromises blood supply to existing vessels and hinders the formation of new vessels, consequently causing a local hypoxia (Badimon and Cubedo, 2017; Michailidou, 2019; Trayhurn, 2013).

The lack of oxygenation in the tissue results in necrosis and the resulting breakdown of adipocytes, which allows the release of substances that induce the activation and recruitment of innate immune cells, mainly macrophages, to the tissue (Badimon and Cubedo, 2017; Galic, Oakhill and Steinberg, 2010; Maury and Brichard, 2010; Bollinger and contributors, 2014; Westendorf and contributors, 2017; Muscogiuri and contributors, 2020).

Macrophages are activated by the nuclear factor kappa-β, travel to the necrosis site (Galic, Oakhill and Steinberg, 2010; Bollinger and contributors, 2014; Westendorf and contributors, 2017; Castoldi and contributors, 2016), differentiate and organize themselves into a crown shape around the cells of the adipose tissue, and produce a local inflammatory process through the secretion of pro-inflammatory mediators, such as tumor necrosis factor-alpha (TNF-α), interleukin 1 beta (IL-1β), interleukin 6 (IL-6), C-reactive protein, and adipokines.

The substances produced by the tissue and immune cells at the site reach the bloodstream at the systemic level, causing low-grade systemic inflammation (Johnson, Justin Milner and Makowski, 2012; Badimon and Cubedo 2017; Bollinger and contributors, 2014; Muscogiuri and contributors, 2020; Castoldi and contributors, 2015).

Therefore, obesity is a condition associated with fat accumulation, especially in the abdominal region, which triggers a low-grade systemic inflammatory process (Badimon and Cubedo, 2017; Galic, Oakhill and Steiberg, 2010).

This inflammation is associated with the development of several other comorbidities, which can be chronic, such as

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type 2 diabetes mellitus, systemic arterial hypertension, and hypercholesterolemia. Moreover, obesity is an important risk factor for the infection and development of diseases related to fungal, bacterial, and viral sources, including extremely potent ones, such as influenza virus H1N1 and SARS-CoV-2 (Dietz and Santos-Burgoao, 2020; Johnson, Justin Milner and Makowski, 2012; Kaur, 2014; Williams and contributors, 2015; Badimon and Cubedo, 2017).

OBESITY AND COVID-19

Obesity is a condition associated with worse outcomes in patients infected with SARS-CoV-2. Retrospective cohort studies in Europe and North America have proven the clinical interaction between COVID-19 and obesity. An USA study has shown that COVID-19 deaths were more frequently associated with obesity (OR 3.1; 95% CI: 1.5–6.6), with morbid obesity showing the highest level of association (OR 7.6; 95% CI 2.1–27.9) even in patients with no other comorbidities (Kalligeros and contributors, 2020).

A retrospective analysis of BMI in USA SARS-CoV-2 patients, revealed that subjects aged <60 years with a BMI between 30 and 34 were 2.0 (95% 1.6-2.6, p<0.0001) and 1.8 (95% CI 1.2–2.7, p=0.006) times more likely to be admitted to acute and critical care, respectively, compared to individuals with a BMI < 30, while patients with a BMI > 35 and aged <60 years were 2.2 (95% CI 1.7–2.9, p < 0.0001) and 3.6 (95% CI 2.5–5.3, p ≤ 0.0001) times more likely to be admitted to acute and critical care compared to same-aged patients with BMI < 30 (Lighter and contributors, 2020). Additional large retrospective case series from New York confirm that obesity is a major risk factor for COVID-19 disease severity and intensive care unit requirements (Hajifathalian and contributors, 2020).

In a large prospective cohort of 502,543 middle-aged adults in the UK, BMI and waist circumference were independently associated with laboratory-confirmed COVID-19 in a dose-dependent fashion (Yates and contributors, 2020).

Furthermore, in a recent study by Kalligeros and contributors, (2020), that evaluated 103 patients with COVID-19 admitted to a hospital in Rhode Island, the United States, the prevalence of obesity was identified in 47.5% of the patient population. Of the patients with obesity, 56.8% were in the ICU and 65.5% needed mechanical ventilation.

Although it was not initially associated as a risk factor for COVID-19 infection, obesity is a condition that facilitates the activity of the virus in the patient's body and can trigger severe clinical conditions. Obesity is linked to endocrine and immunological dysfunction, making the patient more vulnerable to the disease (Luzi and Radaelli, 2020; Badimon and Cubedo, 2017; Simonnet and contributors, 2020).

The immune system of patients with obesity proves to be dysfunctional in the fight against SARS-CoV-2. During the presentation of the antigen by innate immune cells, there is a deficit in the activation and availability of the cells, mainly macrophages.

These cells are constantly activated and concentrated in the adipose tissue, and together with the high load of pro-inflammatory cytokines (Muscogiuri and contributors, 2020; Castoldi and contributors, 2016; Abduljabbar and contributors, 2016; Park, Park and Yu, 2005; Xu and contributors, 2018; Weghuber and contributors, 2014), cause a series of disorders in tissue homeostasis (Luzi and Radaelli, 2020; Simonnet and contributors, 2020).

In obesity, one of the changes in the white adipose tissue (WAT) is the impairment of its endocrine activity, causing increased secretion of adipokines, such as leptin (Luzi and Radaelli, 2020; Simonnet and contributors, 2020).

High leptin secretion is linked to numerical and functional lymphocyte dysfunction (Galic, Oakhill and Steinberg, 2010; Castoldi and contributors, 2016; Zhang and contributors, 2013).

Therefore, it is understood that this hormone is involved in the modulation of metabolism of adaptive immunity cells, especially B lymphocytes, thus compromising the production of antibodies. This explains the disadvantage of the individual with obesity in acquiring immunological memory from vaccination, in addition to being more vulnerable to bacterial, fungal, and viral infections (Luzi and Radaelli, 2020; Zhang and contributors, 2013).

Another factor triggered by chronic inflammation in obesity is the increase in the amount of ACE-2 present in adipocytes (Jia and contributors, 2020; Ryan and Caplice, 2020).

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Since obesity promotes fat accumulation in the WAT (World Health Organization, 2020), and ACE-2 is the main binding site for SARS-CoV-2 (Jin and contributors, 2020; Atri and contributors, 2020; Guo and contributors, 2020), adipose tissue can become a large viral reservoir. Therefore, excess of adipose tissue (World Health Organization, 2020) and the increase in the number of receptors for the virus (Jia and contributors, 2020), added to the dysfunctional immune system of the person with obesity (Badimon and Cubedo, 2017; Muscogiuri and contributors, 2020; Castoldi and contributors, 2016; Zhang and contributors, 2013), may facilitate viral replication and mutation (Ryan and Caplice, 2020; Kruglikov and Scherer, 2020).

However, it is assumed that the tissue damage existing in infected patients with obesity may be linked to atypical T cell activation, even in small numbers, which triggers a potentiated but inefficient immune response (Ryan and Caplice, 2020; Kruglikov and Scherer, 2020) demonstrated a correlation between the increase in available adipose tissue and the presence of pulmonary fibrosis in individuals infected with SARS-CoV-2.

Another important factor involved in lung damage is the “cytokine storm” caused by the high load of pro-inflammatory cytokines present in individuals with obesity, and the increase in secretion of the cytokines in the presence of SARS-CoV-2. It is suggested that a number of unidentified factors may contribute to this phenomenon.

However, IL-6, a pro-inflammatory cytokine, is one of the main cytokines identified as causing this storm, by support and activation of other cytokines. This interleukin and its receptors are abundantly present in the WAT of mice with obesity, which can provide an IL-6 reservoir (Luzi and Radaelli, 2020; Zhang and contributors, 2013; Ryan and Caplice, 2020; Kruglikov and Scherer, 2020.

Although immunological and physiological problems are strongly present in the relationship between obesity and aggravation of COVID-19, these are not the only problems that promote this association. Other comorbidities associated with obesity, such as the risk of thrombosis caused by difficulty in fibrinolysis, vitamin D deficiency, non-alcoholic fatty liver disease (NAFLD), sleep apnea, and intestinal microbiota dysfunction may contribute to worse outcomes of patients infected with SARS-CoV-2. All of these situations can develop into complications associated with severe pulmonary and cardiac impairment in the face of the respiratory disease (Muscogiuri and contibutors, 2020; Zheng and contributors, 2020; McSharry and Malhotra, 2020).

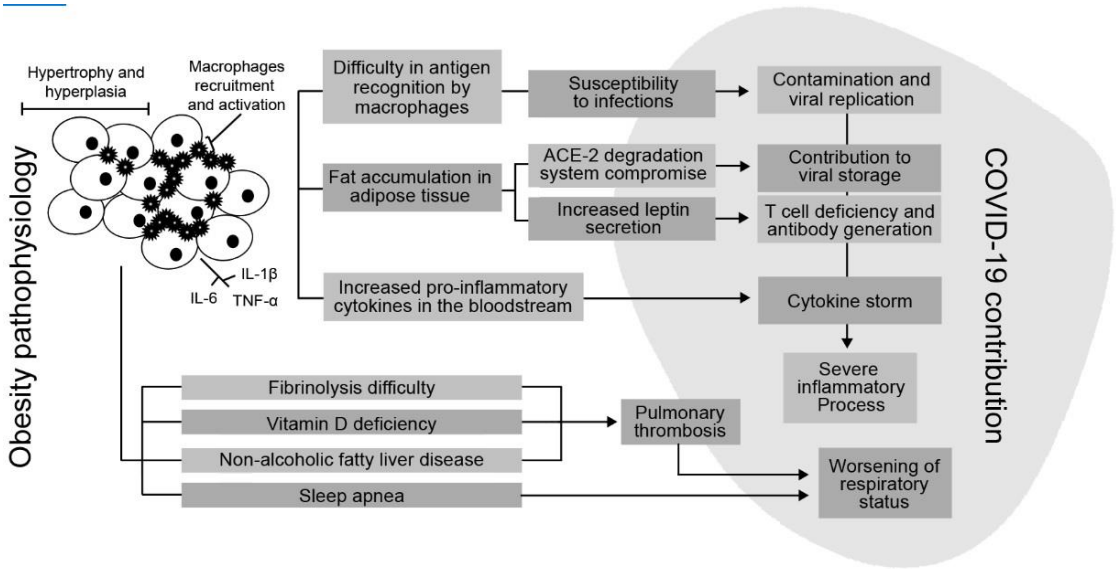

Figure 1 - Relation between the consequences of obesity and the worsening of patients infected with SARS-CoV-2.

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Therefore, obesity brings together in its mechanism a series of factors that, when added together, contribute to the deterioration of the clinical condition of a patient with COVID-19. Thus, several drugs that have been tested for the treatment and management of patients infected with SARS-CoV-2 may not have an effectiveness in patients with obesity equivalent to that in patients without obesity. For this reason, it is extremely important to understand the behavior of the drugs proposed for the treatment of COVID-19 in patients with overweight or obesity, considering their pathophysiological limitations.

TREATMENT OF COVID-19 IN PATIENTS WITH OBESITY

Considering that the pathophysiological mechanisms of COVID-19 are still unclear, the search for different therapies for its treatment and prevention is still in progress. Therefore, many countries started to create specific protocols, considering the off-label use of therapies still under scientific experimentation.

Due to the complexity of the pathophysiology of obesity, and the uncertainty of the treatments for COVID-19, the interaction between medications and comorbidities requires more clinical attention (Luzi and Radaelli, 2020; Muscogiuri and contributors, 2020).

It is necessary to analyze the predisposition of patients with obesity to other associated comorbidities. Obstructive sleep apnea, for example, can contribute to hypoxemia, cytokine storm, and mechanisms involved with the respiratory disease. Early intubation, in these cases, would contribute to symptom relief (McSharry and Malhotra, 2020).

Likewise, thrombosis, whose prophylaxis and therapy may involve the use of heparin, is an associated factor that requires attention in patients with obesity (Muscogiuri and contributors, 2020). NAFLD was also investigated in the context of COVID-19, which includes elevated levels of IL-6 (Zheng and contributors, 2020).

Muscogiuri and contributors, (2020), mentioned other comorbidities related to obesity, such as vitamin D deficiency, with its supplementation resulting in improvement of immune response and reduction of inflammation. Intestinal dysbiosis is also associated with obesity, and probiotic therapy optimized the patient's immunity.

Type 2 diabetes mellitus is also an obesity-related comorbidity, arising in the form of adipose tissue growth and increased peripheral resistance to insulin. As evidenced by Wu and contributors, 2020, it as an important fatality factor in COVID-19, and is still a risk factor for respiratory infections, such as influenza and pneumonia, which usually present in more severe clinical conditions and in worse prognosis of infectious diseases. Thus, lifestyle changes and glycemic control are indispensable for therapeutic success in type 2 diabetes mellitus (Singh and contributors, 2020; Gupta and Misra, 2020).

Cardiovascular disease, a comorbidity often associated with obesity due to physical inactivity and poor diet, also demonstrated great interaction with the respiratory disease. A meta-analysis including six studies, with a total of 1,527 patients, found an incidence of hypertension and cardio-cerebrovascular disease of approximately 17% and 16%, respectively, in patients diagnosed with COVID-19.

These comorbidities are also associated with the severity of the disease, with up to three times higher incidence among ICU patients when compared to patients in less severe cases.

Though cardiovascular diseases have the potential to aggravate COVID-19, the inverse is also true, where the cell entry of SARS-Cov-2 using ACE-2 cell receptors can cause myocardial injury and chronic cardiovascular damage (Zheng and contributors, 2020; Li and contributors, 2020).

Based on the pathophysiology of obesity and its associated comorbidities, several drug classes have been considered for the management of obesity in patients infected with SARS-CoV-2.

Modulators of lipid metabolism, such as metformin, glitazones, and 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR), enable improvement in blood glucose and circulating fats, culminating in immunological optimization and reduction of inflammatory effects (Luzi and Radaelli, 2020; Kruglikov and Scherer, 2020).

However, further studies are needed to prove their contribution in the presence of COVID-19.

In addition to these drugs, it is essential to review the pharmacological mechanisms of drugs used off label in patients with COVID-19. Different scientific evidence and isolated experiences indicated the use of

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some drugs for the clinical management of COVID-19 to avoid complications and deaths resulting from the infection and its complications. Over the period, based on different studies being published, there were changes in the care protocol. In some cases, compassionate drug treatment was provided at the request of the patient or family members.

Considering that this recent epidemic has a new etiological agent whose natural history has not yet been fully clarified, there is no effective treatment protocol, although recent evidence suggests that dexamethasone may reduce mortality in patients on mechanical ventilation (Recovery Collaborative Group, 2020) and the use of prophylactic anticoagulants reduces the risk of thrombosis (Atallah, Mallah and AlMahmeed, 2020).

Despite supportive treatment for clinical manifestations in each patient, there is no consistency in the standardization of these protocols (Yuki, Fujiogi and Koutsogiannaki, 2020).

For this, a careful analysis of the pathophysiology of obesity, and consideration of its mechanisms of action in relation to pharmacodynamics, pharmacokinetics, and potential adverse effects of drugs, is essential. Given these facts, since the beginning of the pandemic, several drugs such as chloroquine and hydroxychloroquine (Sun and contributors, 2020; Zou and contributors, 2020; Skipper and contributors, 2020; Horby and contributors, 2020, lopinavir / ritonavir (Cao and contributors, 2020), nitazoxanide (Pepperrell and contributors, 2020) and ivermectin (Santos, 2020) were studied. However, these drugs had their uses discouraged, as they did not demonstrate clinical change in the patient's outcome or did not have sufficient evidence, and therefore, they were not effective for the treatment of COVID-19.

Although some drugs have been excluded from the protocols for the treatment of symptoms and worsening related to COVID-19, other drugs have a scientific basis for their safe use. Considering the risks related to the patient with obesity, the drugs currently administered to patients, whether hospitalized or not, must have an analysis related to their application in these patients.

REMDESIVIR, COVID-19 AND OBESITY

Remdesivir is a broad-spectrum antiviral drug that has shown some satisfactory results in a few studies related to COVID-19 (Beigel and contributors, 2020).

It is a nucleoside analog prodrug, and its mechanism of action is based on inhibiting viral replication and competing with endogenous nucleotides for incorporation into the replicating viral RNA (Al-Tawfiq, Al-Homoud and Memish, 2020; Jorgensen, Kebriaei and Dresser, 2020).

Thus, this drug was approved on October 22, 2020, by the Food and Drug Administration (FDA) for the treatment of COVID-19 in patients older than 12 years hospitalized (Food and Drug Administration, 2020).

However, the existing results do not demonstrate clinical benefits to patients, and those that bring good results are still limited and insufficient to support the application of this medication (Spinner and contributors, 2020).

In a study with mice, remdesivir minimized the effects of a high-fat diet. Its effects include attenuation of metabolic syndrome, relief from lipid accumulation, improvement of liver function, and inhibition of inflammatory response. Thus, the study demonstrated the presence of an additional property of remdesivir, of high scientific importance in the treatment of obesity, especially in association with dyslipidemia and NAFLD (Li and Su, 2020).

The reported side effects of remdesivir include gastrointestinal and allergic changes, elevation of liver enzymes, and hypotension, and it can present in about 60% of patients (Jorgensen, Kebriaei and Dresser, 2020; Wang and contributors, 2020).

The drug requires significant clinical attention, considering these side effects as risk factors contributing to or deregulating the comorbidities involved with obesity, such as intestinal dysbiosis, NAFLD, and cardiovascular changes.

AZITHROMYCIN, COVID-19 AND OBESITY

Azithromycin is a macrolide antibiotic approved in the treatment of bacterial infections of the respiratory tract, skin, and soft tissues. This drug has been studied for the management of COVID-19 but has not shown satisfactory results when used in isolation. Therefore, the use of azithromycin is indicated to treat COVID-19 only when associated with bacterial lung infection, as well as other antibiotics (Gbinigie and Frie, 2020).

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Studies have also been found that discuss possible side effects of the drug in vivo. In mice, chronic exposure to azithromycin demonstrated increased cardiovascular risk and sudden death from pro-arrhythmia caused by the drug (Yang and contributors, 2017).

The interaction requires further investigation on account of the frequently observed association between obesity and cardiovascular changes.

Moreover, based on the hypothesis of predisposition to childhood obesity caused by antibiotics, a study on azithromycin found an increase in adipogenesis in mice, changes in the intestinal microbiota, the production of short-chain fatty acids, and metabolism of bile acid (Li and contributors, 2017).

Even though the use of azithromycin remains effective for bacterial pneumonias and secondary infections, its effectiveness and safety in the treatment of COVID-19 is still inconclusive (Gbinigie and Frie, 2020). Therefore, further investigation is required to recommend azithromycin in the management of the respiratory disease caused by SARS-CoV-2 in patients with obesity.

GLUCOCORTICOIDS, COVID-19 AND OBESITY

Glucocorticoids, a class of corticosteroids, are widely available and low-cost drugs, whose mechanism of action includes decreasing vasodilation and capillary permeability and inhibiting the production of proinflammatory substances in diseases such as rheumatoid arthritis and asthma.

The glucocorticoid dexamethasone, a synthetic adrenal steroid with anti-inflammatory and immunosuppressive effects, is a drug widely considered for use during the current pandemic (Selvaraj and contributors, 2020; Solinas and contributors, 2020).

Unpublished results from a randomized clinical trial, with approximately 2000 patients with COVID-19 treated with dexamethasone, reported a reduction in deaths by one-third in patients on mechanical ventilation, and by one-fifth in patients on oxygen therapy, but with no benefits in patients without the need for ventilatory support (Recovery Collaborative Group, 2020). Dexamethasone demonstrates effectiveness in the management of patients with moderate to severe COVID-19, decreasing the levels of C-reactive protein in patients (Solinas and contributors, 2020).

Therefore, dexamethasone is currently part of the treatment protocol for patients infected with SARS-CoV-2 in a moderate to severe state (Pan-American Health Organization, 2020).

The long-term use of glucocorticoids results in an increase in inflammatory markers and lipogenesis, generating an increase in body mass and hepatic lipid accumulation, in addition to increasing visceral obesity and arterial hypertension. This manifestation is mainly due to the activation of mineralocorticoid receptors (John and contributors, 2016; Noppe and contributors, 2016).

However, treatment of COVID-19 does not usually need to be long-term, and evidence suggests that acute management of COVID-19 with glucocorticoids results in anti-inflammatory and lipolysis-promoting processes with loss of adipose tissue, given the divergent character of glucocorticoid receptors compared to mineralocorticoid receptors (John and contributors, 2016).

Another side effect of this drug treatment is the risk of diabetes. Glucocorticoid-induced hyperglycemia has an early onset and is dose and time-dependent, with peaks in glycemic elevation, especially postprandial, which predisposes the patient to the onset or dysregulation of diabetes, and mortality. Manifestations occur mainly in predisposed patients with some degree of obesity or previous insulin resistance (Paredes and Alves, 2016; Tamez-Pérez, 2015).

Therefore, attention should be paid to the patient's risk of hyperglycemia. Glucocorticoids, especially dexamethasone, are considerably safe for use in patients with obesity, without diabetes or with controlled diabetes. However, probing for more evidence to justify its application in COVID-19, and waiting for the early release of results of the RECOVERY Trial (Recovery Collaborative Group, 2020), is necessary. However, individual assessment of each case is necessary for the application of this medication.

ANTICOAGULANTS, COVID-19 AND OBESITY

Obesity is known to increase the risk of venous thromboembolism (VTE) through various mechanisms. It induces platelet hyperactivity and increases several pro-coagulation factors, such as fibrinogen, von

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Willebrand factors, and coagulation factors VIII, IX, XI, and XII, resulting in increased thrombin generation.

Furthermore, adipose tissues release adipokines and free fatty acids, which cause inflammation, leukocyte recruitment, platelet aggregation, and endothelial dysfunction, leading to thrombosis (Morange and Alessi, 2013; Badimon and contributors, 2013; Rosito and contributors, 2004; Eichinger and contributors, 2008; Darvall and contributors, 2006).

Although not primarily a thrombotic process, the inflammation and hypoxia, along with acute lung injury caused by COVID-19 also lead to a profound inflammatory state due to the storm of cytokines, macrophages, and processes related to endothelial activation, associated with an increase in interleukins IL-1, IL-6, IL-8, and TNF-α. This provides biological evidence for the presence of a thrombotic process in COVID-19. Evidence of coagulopathy has also been reported, in which patients demonstrate frequently elevated serum levels of D-dimer, lactate dehydrogenase, and total bilirubin, with slight prolongation or no change in partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT) (Shi and contributors, 2020).

As COVID-19 is associated with arterial and venous thrombosis, all hospitalized patients without evidence of active bleeding should receive prophylactic anticoagulation (Tang and contributors, 2020).

The anticoagulant of choice is low molecular weight heparin (LMWH), unfractionated heparin (UFH) or subcutaneous fondaparinux (Atallah, Mallah and AlMahmeed, 2020). UFH is a naturally occurring glycosaminoglycan with anti-thrombin and anti-inflammatory activity, that has little interaction with the drugs used to treat COVID-19 (Zhou and contributors, 2020).

Some authors advocate the use of therapeutic anticoagulation at intermediate intensity doses, such as subcutaneous enoxaparin at 0.5 mg/kg body weight of patient, twice daily as prophylaxis for patients without evidence of thrombosis, particularly those who are being treated in the ICU, with elevated D-dimer, fibrinogen, and factor VIII levels (Wang and contributors, 2015).

In a retrospective study conducted by Tang and contributors (2014) (Tang and contributors, 2020), treatment with LMWH was associated with a lower 28-day mortality among patients with severe COVID-19 infection, with a sepsis-induced coagulopathy score ≥ 4, and a D-dimer level greater than 3 μg/mL (more than 6 times the upper limit).

For patients with atrial fibrillation, prosthetic heart valves, and preexisting venous thrombosis, who are currently being treated with a vitamin K antagonist (warfarin) or direct oral anticoagulants (DOAC), it is important to note that these drugs may interfere with the antiviral therapy used for COVID-19. In this scenario, an individual patient-based approach would be appropriate, and a decision can be made to change the patient's existing treatment to a parenteral LMWH, which would be more convenient during the critical period of the disease (Instituto Superiore di Sanità, 2020).

In addition, the dosage of anticoagulants, especially enoxieparin, is administered according to the patient's BMI, so that patients with obesity may receive overdoses and are more likely to bleed. Therefore, frequent monitoring of the patient's condition and coagulation factors is important (Vandiver, Ritz and Lalama, 2016). It is also recommended to start treatment with low doses with adaptation according to each case (Thompson-Moore and contributors, 2015).

CLINICAL MANAGEMENT, COVID-19 AND OBESITY

The patient with obesity is a patient with a high chance of worsening COVID-19 and often requires critical treatment and intensive care. Faced with the difficulties of hospital care, patients with obesity present themselves as a group that requires specialized practical training for the care team (Bucher Della Torre and contributors, 2018).

Given these facts, a study by Salazar-Sepúlveda and Villarreal-Pérez (2019) showed that doctors still find it difficult to identify and diagnose a patient with overweight or obesity, which makes it difficult to target treatment for patients in this group, and moreover, no treatment to mitigate the aggravation of comorbidities related or enhanced by obesity is prescribed.

Considering the lack of identification and prescription of treatment adapted to the patient with obesity, the clinical management of the patient is also limited.

A study by Bucher Della Torre, and contributors, (2018), which interviewed 834 healthcare professionals, revealed that more

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than half of respondents say they do not have enough training to deal with patients with obesity.

Furthermore, many patients with obesity need mechanical ventilation during the treatment of COVID-19. In this sense, patients with obesity have a higher risk of complications in actions such as intubation and extubation, with a higher risk of post-extubation stridor and a chance of rapid desaturation and respiratory failure (Selim, Ramar and Surani, 2016; De Jong, Chanques and Jaber, 2017).

Concomitant to this, the change of the patient's position to the prone position is indicated to reverse episodes of hypoxia or assist in oxygenation, including in cases of SARS-CoV-2 infection (Lindahl, 2020).

Although it is a simple and effective technique, professionals can present difficulties in pronation of the patient with obesity, as this technique in the patients in question requires many professionals, specific training, and physical strength.

In addition to all the facts, the excess of adipose tissue can be an aggravating factor in the difficulty of venous access, tests, and the use of equipment.

CONCLUSION

COVID-19, an infectious respiratory disease caused by the new SARS-CoV-2, has been widely studied by scientists around the world. The present pandemic has affected many people and has had unfavorable outcomes.

The studies still seek to understand the pathophysiology of the disease, the reasons for heterogeneous clinical conditions and the greater vulnerability of groups with specific characteristics such as the elderly, and individuals with comorbidities such as obesity.

The drug treatments that have been tested, from the list of products registered for use, even off-label, lack robust scientific evidence to guarantee their effectiveness and safety in the treatment of COVID-19.

With the worsening of the pandemic, it is essential to review the association between obesity and COVID-19, as well as the response of patients with obesity to the therapies that are being tested.

Moreover, even with pharmacological treatments available for the management of obesity and the options that are being studied to combat COVID-19, it is essential to take preventive measures based on lifestyle changes.

The prevention of weight gain and obesity, as well as the first-line treatment, is based on a change in diet, mainly as a reduction in caloric intake and an increase in energy expenditure by the practice of physical activity.

These measures can promote weight reduction and reduce inflammation caused by obesity, and consequently, restore the immune system.

Based on this, in addition to the aforementioned preventive measures related to weight loss, when considering individuals with obesity as an important risk population, the protective measures, such as the use of masks, the socially distant and adequate hygiene, should be reinforced for this population.

Therefore, the possibility of including the population with obesity within the priority groups for vaccination campaigns becomes interesting, to prevent the unfavorable outcomes of the interaction between COVID-19 and obesity.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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