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The Problem of Neglicenting a Chronic Disease - Obesity and Covid-19, What is the Relationship?

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Abstract

A growing body of evidence maintains that obesity may be strongly related to greater adverse outcomes from infection with the new SARS-CoV-2 (COVID-19). It is known that obesity is a low-grade chronic inflammatory condition, which leaves its sufferers susceptible to numerous diseases, including cardiovascular diseases, which are particularly related to inflammation and hypercoagulability, mainly. In this literature review work, emerging knowledge about the pathophysiology and pathological mechanisms of COVID-19 was combined with the pathophysiology of obesity, and some hypotheses about the deleterious effects and impact of Obesity in the course of COVID-19 will be evidenced. These hypotheses are testable and can guide future therapeutic and preventive interventions.

Keywords: Obesity; Covid-19; Inflammation; Hypertension

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Introduction

Obesity is already considered by the WHO to be a pandemic that has affected humanity for some time, affecting up to 12% of the world population and causing the death of approximately 2.8 million people per year. Obesity in itselfcan be defined as an excessive accumulation of fat in a harmful way to health, is normally characterized by a Body Mass Index (BMI) equal to or greater than 30 kg/m², considering the physical and physiological conditions of individuals, especially non-athletes. Nevertheless, this disease can be a basic disease for other morbidities, namely diabetes, hypertension, and dyslipidemia, common in the population, allowing a greater susceptibility of these individuals to deficient immune defense processes when exposed to atypical infections of the external environment, especially respiratory characterized by a condition that is difficult to manage in obese people. In this context, the current Coronavirus is known for its ability to develop and enhance atypical pneumonia in the entire world population. Its characteristics allow it to reach more effectively than other mandatory intracellular parasites which also reach the lower respiratory tract, even reaching the promotion of a global event. In this sense, we have the interaction between two pandemics, obesity and SARS-Cov 2, the latter being able to act aggressively on these patients, generating a Severe Acute Respiratory Syndrome, being able to evolve to ARDS, with intensive care needs and even more specified.

Methodology

This bibliographic review was carried out from a compilation of articles and other scientific bases such as doctoral theses, manuals and platforms from the Ministry of Health (MS), with a focus between the years 2013 to May 2020, from the platforms Scholar Google, Scielo and Pubmed, in addition to scientific journals such as Nature, CDC, and Science, initially having 35 articles, of which 23 were selected for bibliographic composition, the others not having been due to the criteria chosen by the group for the selection, which correspond to the year of publication, source, line of thought of the author (s), truthful and presented information.

Epidemiology

There´s many different species of animals that are commonly

affected by the large coronaviruse family, including cats, bats, camels and cattle. The coronaviruses infection that occour on animals are rarely infectuous to people, including MERS-CoV and SARS-Cov. In December 2019 a new version of coronavirus (SARS-CoV-2) infected people, firstly it was identified in Wuhan, a city in China. This coronavirus was spreaded person to person. COVID-19 was the name given to this specific disease caused by this coronavirus, that has a large spectrum of symptoms that goes from asymptomatic to severe conditions. The World Health Organization claimed that 80% of the patients with COVID-19 may be oligosymptomatic (few symptoms) or asymptomatic, only 20% that need hospitalization, because they have difficulty breathing, of which approximately 5% may need ventilatory support. Despite all the prevention measures encouraged and promoted by the State and the population, the situation is evolving rapidly. About one percent of the Brazilian population has already been diagnosed with COVID-19, this number may seem small, but it is considered in a country with more than 200 million inhabitants. The regions most affected are the coastlines and large metropolises in the country, with marked growth in the region of the state of São Paulo.

On the other hand, we have obesity, a pandemic characterized by a state of chronic inflammation with increasing numbers, which affects about 1 in 8 adult individuals according to the World Health Organization. The projection is that, in 2025, about 2, 3 billion individuals are overweight, over 700 million of whom are obese [1]. The number of overweight and obese children can reach 75 million if nothing is done - including 427 thousand children with pre-diabetes, 1 million with high blood pressure, and 1.4 million with an increase in Metabolic Fatty Liver Disease. Data from the Surveillance of Risk and Protection Factors for Chronic Diseases Survey by Telephone Survey (Vigitel) show that more than 50% of the Brazilian population is overweight. The entities warn that obesity is a chronic disease that tends to worsen over the years if the patient is not subjected to adequate and continuous treatment [2]. In addition to all this information, it is known that the association of both pandemics generates the probability of about 340 percent of developing a serious

condition, due to the overlap of the subclinical chronic inflation already promoted previously by obesity and the acute inflammation brought by new conditions that COVID-19 infection promotes, requiring greater care [1].

Physiopathology and Discussions

It is a fact that obesity is a disease of a chronic inflammatory character [3-4], with the accumulation of adipose tissue at supraphysiological levels of extreme maleficence for the body in a global physical-metabolic perspective, which causes a systemic impact to the individual. Besides, it is feasible that large amounts of adipose tissue will generate a greater release of pro-inflammatory adipokines, not necessarily directly proportional to the gain in fat mass,but interconnected by biochemical and metabolic relationship [5-9].

Adipose tissue as an endocrine organ is associated with its intrinsic relationship with the hypothalamus and pituitary gland, regulatory glands of the general neuroendocrine system, body homeostasis, and the human energy system. Being produced by white adipose tissue, for example, leptin protein is one of the main regulators of thermogenesis, eating behavior, and, above all, neuroendocrine function [10-14]. Also, we can highlight the relationship between hormonal production, also part of the aforementioned system, and adipose tissue, due to so many other proteins and mechanisms, such as glucocorticoids, insulin, and gonadotropic hormones [15-17].

"Obesity is associated with a wide range of adverse health outcomes with several underlying pathogenic processes [18]. T2D (Type 2 Diabetes Mellitus) is one of the most common sequelae of obesity [19]. An increase in circulating insulin levels in fasting and postprandial status is one of the first metabolic disorders associated with obesity, and is due to the impaired action of insulin, mainly in the liver and skeletal muscle. This "insulin resistance" clearly predisposes an individual to develop T2D, which occurs when an assessment of β cells fails. The mechanism by which overnutrition leads to insulin resistance seems to involve mainly not the expanded fat tissue itself, but the excess of additional nutrients that are stored ectopically in the main insulin-responsive tissues, muscles, and fat. A considered alternative required that adipose tissue inflammation directly to insulin resistance in obesity. Inflammation undoubtedly occurs in obesity; however, it has less convincing base support from human genetics or human pharmacology [20-23].

There are, in the human species, some types of adipose tissue, each having a characteristic that distinguishes it from the others [24-25]. They are white, brown, and beige adipose fabrics. In a general perspective, adipose tissues are formed by subcutaneous adipose tissue (TAS) and visceral adipose tissue (TAV) which, in addition to their intrinsic characteristics, also have different occurrences in the body that imply different metabolic aspects [26].

TAV is better located and abundant in the abdominal region, being more active than the others in terms of metabolism, performing a greater number of lipolysis and release of fatty acids. Besides, we are talking about a tissue that has greater insulin resistance and secretes a significant amount of pro-inflammatory adipokines, namely, PCR, IL - 6, PAI - 1, Angiotensin I, and Resistin. Notwithstanding the TAS better located in the gluteal, femoral, and abdominal regions, expressing large amounts of leptin and Acylation Stimulating Protein (ASP) [27].

White Adipose Tissue

It is spread over several areas of the body, having as its core the energy reserve in the modulation of triglycerides, body homeotherms, and damping of mechanical shocks. This type of adipose tissue also has other peculiarities, being composed of 50% by adipocytes and the other half being connective, nervous tissue, lymph branches, leukocytes, fibroblasts, mesenchymal cells, and preadipocytes [28].

Brown Adipose Tissue

Much has been unveiled about this type of fabric, which was believed to be available only in children - hence also called Baby Fat 30 but today, through imaging tests such as positron

tomography, it has been discovered that it is also found in adults who live in low temperatures or are there for a certain period [29].

This curious phenomenon is due to the great increase in sympathetic nerve activation in adipose tissues, through the Transient Receptor potential channels (TRP) receptors. Noradrenaline is released by this nervous system that will bind to its respective receptors in adipose tissue, that is, β-adrenergic (BAR) that will initiate successive events of signaling and hydrolysis of the energy reserve tissue. This great release of fatty acids activates the uncoupling protein 1 (UCP - 1), which will be oxidized serving as an energy source for the body in the form of heat dissipation. If this mechanism is sustained chronically, it will produce hyperplasia of brown adipose tissue, as well as induce the formation of beige cells, which increases the energy output body in the form of heat dissipation. If this mechanism is chronically sustained, it will produce hyperplasia of brown adipose tissue, as well as induce the formation of beige cells, which increases the body's energy output and drop in body fat.

Beige Adipose Tissue

There is also another strain of brown fat, from white fat, beige fat. This is defined as the `` darkening '' of its precursor. This subtype of fat has a particular sensitivity to the hormone Irisin, which is released during physical activity. This activity propagates the expression of a receptor called peroxisome proliferator 1 - Alpha (PGC - 1α) in muscle fibers [23,24],This plays a protective role in weight gain, loss of lean and bone mass, oxidative stress, as well as improving insulin sensitivity. Subsequently, there is a great expression of the Fibronectin type III domain containing 5 (FNDC5) protein, which is responsible for the greater release of Irisin. This transforms the white adipose tissue into brown by binding to a receptor not yet elucidated in white adipocytes, which induces the release of peroxisome proliferator-activated gamma receptor (PPARG), increasing the expression of UCP1, which causes increased energy expenditure, promoting favorable effects on metabolism and resistance to metabolic diseases [22].

“The production of tumor necrosis factor from pro-inflammatory cytokines α (TNF-α) and IL-6 was in the range of 0 to 400 copies per 10 4 -actin. Comparing the DCs simulated and infected with SARS-CoV, there was a moderate induction of TNF-α and IL-6 at 3 and 9 hours after infection (Figure 1). The positive regulation of IL-6 in the DC of CBs infected by SARS-CoV was significantly greater than in the DC of adults [12].

Much has been studied about the pathophysiology of SARS-Cov-2. What is currently known is that one of the entry points that the virus uses to infect cells the ACE2 receptors, through the protein S (Spike) present in the envelope of the virus, present in large amounts in cardiac tissue, renal epithelium, adipose tissue - the virus will go to the individual's cells, having a greater affinity for the adipose tissue, especially for the adipocytes present in the alveoli, also explaining its present prevalence to respiratory symptoms. Cytokine release syndrome (CRS - Cytokine Release Syndrome in English) is also common in patients with COVID-19, which is a form of systemic inflammatory response syndrome that arises as a complication of some diseases or infections.

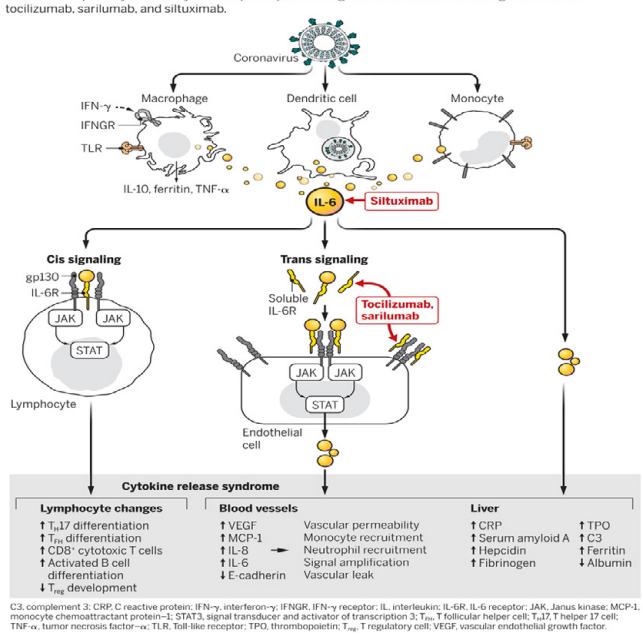

Figure 1 Pathway leading to cytokine release syndrome.

The delayed release of cytokines and chemokines occurs in respiratory epithelial cells, dendritic cells (DCs), and macrophages in the initial stage of SARS-CoV infection. Subsequently, the cells secrete low levels of the interferon antiviral factors (IFNs) and high levels of pro-inflammatory cytokines (interleukin (IL) -1β, IL-6 and tumor necrosis factor (TNF)) and chemokines (motif chemokine ligand CC (CCL-2, CCL-3, and CCL-5) Like SARS, MERS-CoV infects human airway epithelial cells, THP-1 cells (a monocyte cell line), blood monocyte-derived macrophages peripheral human and DCs, and induce delayed but high levels of pro-inflammatory cytokines and chemokines. After infection by MERS-CoV, plasmacytoid dendritic cells, but not mononuclear macrophages and DCs are induced to produce a large amount of IFNs [19].

Elevated serum IL-6 correlates with respiratory failure, ARDS, and adverse clinical outcomes, thus resulting in CRS.15 Interleukin-6 in our body has three signaling pathways, called cis, trans, and trans presentation. Through the Cis pathway, IL-6 ends up binding to a membrane receptor that is linked with a glycoprotein 130 complex (GP 130), producing a signal that is translated by JAKs and STAT3. When this signal is translated, the immune and innate system undergoes pleiotropism. As for trans-signaling, there is a link between IL-6 with the soluble form of IL-6R generating a dimer of gp130 that is on the surface of all cells. The signal is expressed in cells that do not express mIl-6R and cause an exaggerated production of cytokines, increasing the production of endothelial growth factors, IL-8, reducing the expression of E-cadherin which allows greater permeability of the endothelial vessels. In the Trans presentation signaling, there is a link between IL-6 to mIL-6R which is expressed in autoimmune

cells, later bound to gp130 in helper T17 cells. A biomarker for severe beta - coronavirus infection is elevated serum CRP, a protein whose expression is driven by IL-6.15 [30].

“Dendritic cells are antigen-presenting cells - the immatures reside in the respiratory tract for immune surveillance and respond dynamically to local tissue inflammation in the AV and the distal lung. They signal the presence of danger for adaptive immune response cells modulate their responses through the secretion of pro-inflammatory and/or antiviral cytokines. In particular, DCs secrete cytokines to polarize T-helper cells towards the Th1 and Th2 subsets. The trafficking of DCs is regulated by chemokines that can be classified as homeostatic (expressed constitutively) or inflammatory (induced/increased) according to their immunological functions. Acute respiratory viruses commonly induce inflammatory chemokines [12].

It is known that obesity, a state of overnutrition, and excessive intake generates a picture of accumulation of adipose tissue in the pulmonary region so that the cells of the pulmonary alveolus begin to show ultrastructural abnormalities and altered production of the surfactant fluid [25]. Furthermore, research conducted showed that AT2 cells from elderly mice showed changes in gene expression exhibiting a significant increase in lipid content, suggesting that "fatty lung" could be a common causal pathway in which both obesity and age worsen the manifestations of COVID-19 as pathology [26-30]. This, therefore, must turn our attention to the endothelium; if we neglect this, we may be neglecting important plausible biological mechanisms underlying the association between obesity and more serious results from COVID-19.

Conclusion

The expressive increase in the death rate in obese patients infected with Sars-CoV-2 is, therefore, due to the exacerbated inflammatory response in the pulmonary territory, especially through ILs, with emphasis on IL - 6, which is already predominant in individuals with a BMI ≥ 30 kg/m² and becomes amplified in this type of viral infection. This statement categorically illustrates the close relationship between obesity and the current pandemic, with an initial understanding of obesity as a chronic condition and the search for its treatment being imperative, considering that a simple reduction of 5-10% of body mass reduces chronic inflammation as well as that promoted by the virus and its chances of entry. Besides, we must not forget the need to investigate the pathogenic (immune - physiological) mechanisms of this virus for its clarification and the search for an effective treatment or form of prevention.

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