Impact of COVID-19 on Destiny of Bariatric Patients

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Obese patients reported worse outcomes of COVID-19 related to prothrombotic and low-grade inflammation status. During the SARS-CoV-2 outbreak, all non-elective surgeries were postponed, including bariatric surgery (BS).

bariatric surgery | metabolic surgery | obesity | COVID-19 | SARS-CoV-2

1. Introduction

Since December 2019, SARS-CoV-2 has been spreading worldwide until it became a pandemic [1].

In Italy, the first reported case was in February 2020, and in May, the amount was 211,938, with 29,079 deaths and probably about 5,000,000 infected people [2]. Obese patients reported worse outcomes, complications, and intensive care therapies due to the typical illness related to the prothrombotic status and low-grade inflammation of obesity, namely: insulin resistance, dyslipidemia, hypertension, atherosclerosis, and type 2 diabetes mellitus (T2DM) [3].

In 2016, according to the body mass index (BMI), 45% of adults worldwide were overweight or obese. The lockdown measures taken to limit the spreading of the virus have indeed increased this number because of the changes in eating habits and decreased physical activity [4]. The time spent at home is associated with an unhealthy diet and a sedentary lifestyle.

It is essential to describe the true meaning of obesity. Obesity is a very complex disease due to individual, environmental and genetic factors, which lead to an excessive accumulation of fat mass and is related to systemic inflammation [5]. Even though BMI is the most common parameter used to define obesity, as it is useful to describe a population, it lacks significance for a single patient because it does not consider body composition. It is known that the percentage of fat mass behind BMI is the real trigger of metabolic syndrome, insulin resistance, dyslipidemia, hypertension, and several other illnesses and chronic diseases [6]. Furthermore, a crucial role is played by the distribution of fat mass. Particularly, visceral adipose tissue (VAT) is associated with cardiovascular and metabolic risks [3], and it is clear that the positive relationship between bariatric surgery and weight loss improves cardiometabolic risks [7]. Moreover, the endocrine mechanisms of the chronic inflammatory response in adipose tissue favor infections. In obese patients, there is an increased synthesis of pro-inflammatory cytokines, hence the reduced immune response and the difficulty in treating the infection [8]. A further unfavorable factor that

proved to be of particular relevance in this pandemic is the high expression in adipose tissue of the receptor for angiotensin-converting enzyme 2 (ACE2), through which the coronavirus enters the cells [8].

During the outbreak of SARS-CoV-2, despite the following increase in the obesity rate, all non-elective surgeries were postponed, and there was the cessation of obesity management services, particularly bariatric surgery [9]. Although insufficient data are available during this pandemic, by providing substantial and sustained weight loss in most patients, bariatric surgery has been shown to reverse the negative pathological impacts of obesity. It is associated with improved survival and quality of life in patients with severe obesity [3].

For all those reasons, it is essential to implement all bariatric and metabolic surgery procedures independently from the possibility of new waves of SARS-CoV-2 [10].

2. Obesity Pandemic

It is well established that obesity is a predisposing factor for SARS-CoV-2 infection and an adverse prognostic factor. Worldwide, individuals with a body mass index (BMI) greater than 25 kg/m^2 (thus pre-obese) are about 39%, while those with a BMI greater than 30 kg/m^2 (therefore obese) are 13%. The most affected countries are the United States and Europe [1].

The SARS-CoV-2 pandemic started in China in December 2019 and spread globally in early 2020. As of the paper's writing, 464,809,377 confirmed cases since the start of the pandemic, and 6,062,536 deaths worldwide were reported. The average age of death was 75 years, with mortality rates varying from nation to nation (e.g., in Italy, 26% of patients who ended up in intensive care died; in China's Hubei province, where the pandemic began, only 2.3%) [11].

Recent studies investigating the relationship between respiratory viruses and obesity have recognized obesity as a risk factor for a higher likelihood of hospitalization, intensive care unit admission, and mortality. Patients with severe obesity, with BMI above 40 kg/m^2, who contracted SARS-CoV-2 infection were also found to have a higher rate of hospitalization than normal-weight subjects [4].

The pandemic of obesity has grown exponentially in recent years. In this context, obesity deserves to be considered a "social disease" and not just a disease of the individual, reflecting the profound influences of the many environmental and socioeconomic factors that condition eating habits and lifestyles [12].

During the first lockdown in Italy (9 March 2020 to 4 May 2020), changes in eating habits and lifestyles were evident. Therefore, issues related to unbalanced diets, along with the near cessation of physical activity, were exacerbated, and both of these factors worsened the obesity pandemic [13].

The procrastination of bariatric surgery over the past two years has generated a delay in obesity treatment, creating severe consequences given the high likelihood of generating new associated comorbidities or even

leading to death. It is important to consider that high-stress levels, secondary to the COVID-19 pandemic, can exacerbate emotional symptoms, increasing impulsivity and triggering episodes of binge eating. Moreover, lockdown measures often led to increased food intake and decreased physical activity, increasing the risks of morbidity and mortality from pre-existing obesogenic conditions. Still, as is known, obesity itself increases the risk of many diseases, including type II diabetes, hypertension, dyslipidemia, nonalcoholic hepatic steatosis, cardiovascular and cerebrovascular diseases, cancers, osteoarthritis, and, to date, COVID-19. Patients with morbid obesity are more vulnerable to COVID-19 virus infection than the rest of the population. Patients with severe obesity have more associated comorbidities, and this group is at a much higher risk of death due to complications generated by SARS-CoV-2 infection [14].

Obesity is known to negatively affect respiratory function by leading to reductions in ventilatory capacity and respiratory drive. Indeed, the accumulation of fat deposits in the chest and abdominal cavity observed in central obesity and excess visceral fat negatively affect chest wall and lung compliance. Patients with obesity are, therefore, more prone to infections and respiratory diseases, also due to their inflammatory state. Obesity is often associated with hypoventilation syndrome and obstructive sleep apnea syndrome [1]. A higher prevalence of obesity-induced hypoventilation syndrome is observed in patients with a BMI greater than 50 kg/m^2. Furthermore, it is known that a 10% weight gain is associated with a 32% increase in the apnea–hypopnea index and a six-fold increase in the risk of moderate to severe obstructive sleep apnea [15]. It has been observed that overweight patients are associated with an 86% higher risk and obesity with a 142% higher risk of developing severe COVID-19 pneumonia than normal-weight patients [16].

The condition of obesity is characterized by chronic low-grade inflammation with over-expression of inflammatory molecules and markers, such as C-reactive protein (CRP), interleukin 1 (IL-1), and interleukin-6 (IL-6). Tumor Necrosis Factor Alpha (TNF-alpha), and other adipose tissue cytokines, also named “adipokines,” can alter vascular and metabolic homeostasis, regulating target organs through the circulatory system. This mechanism underlies diseases that are often associated with obesity, such as type 2 diabetes, Alzheimer’s disease, and cardiovascular disease [17]. Now it is known that these comorbidities interfere negatively with COVID-19. Chronic low-grade inflammation, which characterizes obesity, exacerbates eventual SARS-CoV-2 infection.

It was demonstrated that IL-6 is responsible for the good maintenance of energy balance and the amount of body fat. Therefore, polymorphisms affecting this interleukin, such as −174 G/C, are capable of making changes in metabolism and energy homeostasis. This polymorphism appears to be associated with increased obesity. It is disadvantageous in terms of longevity [18]. Subjects carrying the polymorphism in the IL-6 promoter at position −174 G/C appear to have fewer results from bariatric surgery than noncarriers. They may have more damaging effects on bone [18]. The benefits of weight loss on obesity complications, insulin resistance, and systemic inflammation are well documented, especially after bariatric surgery [19].

Patients with a history of bariatric surgery also appear to be at potentially higher risk of COVID-19 vaccine breakthrough. These complications may be due in part to a predisposition to multiple comorbidities, typical of obesity, and a micronutrient deficiency due to malabsorption may play a crucial role [20]. Although it has been

observed that higher BMI is associated with lower Ab titres in response to COVID-19 vaccine, the serological response is increased by an adjusted OR of 5.34 in patients with a history of bariatric surgery, compared to patients without a history of bariatric surgery [21].

In this context, it is appropriate to evaluate different strategies for treating obesity, including bariatric surgery (to be considered for patients with obesity with BMI > 35 in the presence of related comorbidities and patients with obesity with BMI > 40). Significantly reducing adipose tissue results in a marked reduction in the inflammatory state [22][23].

3. Double Pandemic: Obesity and COVID-19

There is a link between pandemics and subsequent increases in obesity rates. The culture of isolation, food-seeking behavior changes, and sedentary household activities could further worsen the obesity pandemic. The interruption of obesity management services, including bariatric surgery, during the SARS-CoV-2 pandemic further exacerbated the situation. Therefore, it is useful to know how individuals with obesity cope with this viral pandemic so we can redouble our efforts to combat obesity and its comorbidities. Obesity and age are emerging as two independent risk factors for the susceptibility and severity of COVID-19. Indeed, in older adults, immune senescence is observed, leading to greater susceptibility and more severe complications than in younger individuals. Aging leads to a deterioration in the function of the acquired and innate immune system, also linked to a decrease in the function and number of T-cells, and altered immunoglobulin levels and cytokine production [24].

The presence of comorbidities aggravates the course of COVID-19. Obesity is a pro-coagulant and pro-inflammatory state that increases the risk of thrombosis, cytokine level, and oxidative stress response. It can impair the innate and adaptive immune response to infection [3]. The proinflammatory alteration associated with obesity is an important risk factor for acute lung injury. In addition, low-grade inflammation increases leptin (proinflammatory adipokine) and decreases adiponectin levels (anti-inflammatory adipokine) [8]. Adiponectin deficiency has also increased lung inflammation and reduced apoptotic cell clearance. Interestingly, adiponectin levels in MHO individuals are higher than in those with impaired metabolic health (MUO). The latter group is predisposed to an increased risk of pneumonia and a worse outcome of COVID-19 [1].

Adipose tissue expresses various receptors and enzymes necessary for SARS-CoV-2 to be able to infect. ACE2, the functional receptor for SARS-CoV and SARS-CoV-2, is highly expressed in adipose tissue, particularly in visceral adipose tissue (VAT), compared with subcutaneous adipose tissue (SAT). Importantly, its expression is increased in adipocytes of patients with obesity and diabetes. Therefore, it has been hypothesized that the adipose tissue of obese patients may serve as a target organ of SARS-CoV-2 and as its viral reservoir. This reservoir could act as an accelerator that results in high inflammation, fueling an excessive and counterproductive immune response, the so-called cytokine storm, damaging tissues and causing multi-organ failure, which is the most serious complication of COVID-19 [25]. Among cytokines, it is important to mention TNF-α, a pyrogenic cytokine released in the acute phase of inflammation by macrophages and immune cells. It is known that TNF-α expression in lung epithelial cells is higher during influenza and viral infections. In patients with COVID-19 and obesity, high

serum levels of IL-6 and TNF-α are negatively associated with T cells. In contrast, T-cell levels are restored by reducing concentrations of both IL-6 and TNF-α. These results suggested that these cytokines could be important targets of anti-COVID-19 therapies [4].

IL-6 is also a pro-inflammatory cytokine produced by adipose tissue. Therefore, this endocrine cytokine might be important in regulating the host response during acute infection. Several articles have described the essential role of IL-6 in generating an adequate immune response during different types of viral infection in the lung tract. Others link this cytokine to exacerbation of the viral disease, supporting the hypothesis that up-regulation of IL-6 during viral infections may promote virus survival and clinical disease exacerbation [1]. IL-6 has a pleiotropic function and is produced in response to tissue damage and infection. In particular, at the lung level, the proliferation of innate and adaptive immune cells is strongly influenced by this cytokine [17].

Another aspect that should not be underestimated is the hypothesis that there may be a positive correlation between infectivity and weight gain. There is a paucity of evidence on the infectivity of individuals with obesity during the COVID-19 pandemic. The virus is spread by human-to-human transmission through droplets, aerosolized particles, and direct contact with an incubation time ranging from 2 to 14 days [26]. Some studies would seem to show that obese patients are potentially more contagious than lean individuals in case of viral infections. People with obesity who contract the influenza virus remain contagious 42% longer than people without obesity. Indeed, it was observed that obesity increases the duration of viral shedding and delays the ability to produce interferons, allowing further viral RNA replication and increasing the chances of new, more virulent viral strains emerging [16].

Rapid weight loss after bariatric surgery ameliorates the multiple co-morbidities of obesity. Consequently, it is plausible to argue that early intervention in obesity can help minimize the effects of the disease in the event of a new SARS-CoV-2 outbreak. Furthermore, solid evidence in the literature indicates that a larger obese population increases the likelihood of a more virulent viral strain, prolongs the spread of the virus throughout the community, and ultimately may increase overall pandemic mortality rates [27]. In the meantime, patients should be optimized for surgery by ensuring that their weight and metabolism are controlled through diet, lifestyle, and pharmacological measures. Surgery should be accelerated for patients with morbid obesity who do not respond to these conservative measures [13]. However, even small amounts of short-term weight loss can show substantial metabolic benefits. Some of these positive events happen even few days after surgery, i.e., reduction of hyperglycemia. This is especially important during the COVID-19 pandemic; weight loss must be encouraged as a public health intervention. Healthcare providers should discuss weight loss goals and methods with the patients. Obesity management and bariatric surgery teams must be advocates for their patients during these difficult times. The risk will be that patients' needs will be further ignored because of the public perception that obesity is still a choice and not a disease [28].

4. Benefits of Bariatric Surgery in General and Respect to SARS-CoV-2 Infection

The SARS-CoV-2 pandemic has had devastating effects on obesity, first because it has created an environment conducive to the development of obesity and second because it has reduced access to treatment pathways for obesity and related conditions. In particular, the pandemic has reduced access to bariatric surgery entry and follow-up pathways [4].

The first case of human-to-human transmission in Italy was on 21 February 2020. After that, cases increased rapidly, and several restraining measures and hospital bed reallocations were necessary. By the end of February 2020, almost all non-oncologic elective surgeries had been cancelled to make way for the flow of patients with COVID-19. Bariatric surgery, considered elective surgery, was suspended and gradually, but still partially, restarted from 4 May 2020, when epidemiological data showed the effectiveness of the restraining measures undertaken [2]. Following waves brought to a new reduction in bariatric surgery, with negative consequences for the patients on the waiting list [29].

Bariatric and metabolic surgery results in massive weight loss in most patients and reduces the negative effects of obesity on body health and respiratory mechanics. In patients with severe obesity, body weight reduction following bariatric surgery results in improved survival and quality of life. In addition, some studies show that weight loss from bariatric surgery is protective against severe SARS-CoV-2 infection [3]. Delaying bariatric surgery in patients with morbid obesity may cause the worsening of obesity-associated diseases.

A French study of 124 ICU patients reports that obesity and morbid obesity affected 47.6% and 28.2% of patients who became ill with COVID-19. Supporting this evidence are data from previous outbreaks attributable to different viral agents that also show a correlation between obesity and the severity of clinical manifestation of viral disease [30]. The largest prospective observational cohort study conducted in Europe with near real-time data collection and analysis, using a pre-approved questionnaire adopted by the World Health Organization, conducted in 166 hospitals in the United Kingdom between 6 February and 18 April 2020, and involved 16,749 people with COVID-19, reported that obesity was associated with higher mortality. In addition, in a cohort study of critically ill patients with confirmed SARS-CoV-2 infection admitted to the intensive care unit in Brescia (Lombardy, Italy) between 2 March 2020 and 13 March 2020, 31% of patients were obese, and an additional 58% were overweight [2].

Afterward, restraining measures were taken, and elective surgeries, including bariatric surgery, were postponed. During the epidemic peak, patients were operated on for cancer surgery or underwent emergency surgery between March and April 2020 in northern Italy. Still, when differentiated pathways between COVID and non-COVID patients had already been created, they did not have a higher morbidity and mortality rate compared with the same months in the previous year. This would prove that the separation of COVID/non-COVID pathways is safe.

5. Economic Aspects

In addition to the purely medical aspect, in a world where resources are starting to become scarce, an analysis of the costs of obesity and COVID-19 deserves attention.

Obesity determines an economic burden for the individual and health care systems. The costs of obesity can be divided into direct and indirect costs. Direct costs are those associated with the treatment of obesity and its complications, while indirect costs are those associated with lost productivity and lost workdays due to disability and obesity-related physical and psychological problems [31].

In 2014, a report by the McKinsey Global Institute estimated that the economic impact on the world economy due to obesity amounts to US$2 trillion, equivalent to 2.8% of global gross domestic product (GDP) [32]. In this era, when it is becoming increasingly important to pay attention to the distribution of health care investments and beyond, it seems clear that proper care of patients with obesity is necessary to derive an economic benefit as well. At this moment in history, this issue deserves increasing attention because obesity and its associated costs are bound to increase unless appropriate measures are taken to combat it.

COVID-19, in addition to having a huge impact on health, has resulted in huge losses in economic terms. Again, there were direct costs related to medical expenses and indirect costs related to lost productivity (lost workdays due to illness and isolation and lost productivity related to long-term complications of the infection). The lockdown has resulted in an economic contraction and the closure of many manufacturing activities. According to the International Monetary Fund (IMF), there has been a 3.3% contraction in global GDP in 2020 [32].

In this context, a strategy must be found that combines the possibility of offering the best care to the patient with obesity with the option of economic savings. The implementation of bariatric surgery is one of the possible strategies to achieve this goal.

Bariatric surgery remains the gold standard treatment of morbid obesity and has been widely shown to improve associated comorbidities. Although bariatric surgery has high costs, a 2019 meta-analysis, which only considered the direct costs associated with obesity, demonstrated a lifetime cost advantage over conventional weight loss methods [33].

A 2018 systematic review also supports the evidence that bariatric surgery is cost-effective [34]. This benefit is related to improving or resolving the obesity and related conditions. Specifically, weight loss resulting from bariatric surgery reduces addiction to drug therapy. Also, it is understood how reducing the need for pharmacological therapy for diabetes, hypertension, dyslipidemia, and other chronic conditions associated with obesity decreases the economic burden on the healthcare system [35]. A cost-utility analysis conducted in the United Kingdom supports that bariatric surgery determines an annual saving of US$2689 per patient and an increase of 0.8 life-years and 4.0 quality-adjusted life-years [32].

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