REVIEW ARTICLE

Challenge of New Norms: Obesity amid COVID-19 Pandemic

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ABSTRACT

COVID-19 pandemic aggravated the global public health system, which is already overwhelmed by the increasing statistics of comorbidities and burden due to obesity. The number of individuals with obesity and obesity-associated diseases are rising in many regions that could attribute to the growing obesogenic environment and the lockdown implemented to curb COVID-19. This review focuses on the aspects of the obesity epidemic, chronic inflammatory effects of obesity, positive outcomes of obesity interventions and the worsening effects observed in obese COVID-19 patients. The chronic inflammatory effects of obesity are apparent by the increase of pro-inflammatory signals by immune cells in the adipose tissue and reactive species populations. The reduction of antioxidants exacerbates the effects of oxidative stress on genomic and tissue levels. The public must be made aware of the importance of practising a healthier lifestyle, even more now as we are fighting the COVID-19 pandemic.
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INTRODUCTION

The World Health Organisation (WHO) reported that in 2019, 38.2 million children under five were expected to be overweight or obese (1). It is expected that 1 billion adults, which accounts for nearly 20% of the world population, will have obesity by the year 2025 (2). Obesity is a chronic condition marked by an increase in body fat tissue mass and abnormalities in the metabolism of lipid and glucose, genomic stability, occurrence of chronic inflammation, and oxidative stress, all of which raise the risk of a variety of diseases (3). Body mass index (BMI) is used as a screening tool for obesity, and BMI of over 30 is further classified into three subcategories of obesity, which are Class 1, Class 2 and Class 3 (4).

Obesity-related disorders such as diabetes and cardiovascular diseases (CVD) are rising throughout Southeast Asia and Western Pacific region (5). India has the biggest number of diabetics globally, whereas China is in second place (6). Obesity, in addition to being a threat to global public health, also places a financial burden on individuals, families and nations due to increased healthcare costs, reduced productivity, lost workdays, mortality and permanent disability, with an estimated loss of US $2.0 trillion, which accounts 2.8% of the global gross domestic product (GDP), in 2014 (7). This review relates the current COVID-19 pandemic to the long-fought war against obesity. The environmental factors, which promote obesity are discussed and related to the worsening effects observed in COVID-19 patients who are obese. In order to justify this, the inflammation due to obesity is discussed at the biological level. This review also addresses at positive effects of obesity interventions, including a better lifestyle (diet and physical activities), which justifies the need to promote health education.

FACTORS CONTRIBUTING TO OBESITY EPIDEMIC

The obesogenic environment, which refers to the opportunities, conditions of life or influences that the surroundings, have on promoting obesity in individuals, is a crucial player in the ever-increasing obesity pandemic (8). Several studies emphasised the complex nature of an obesogenic environment and its elusive nature, which adds to the difficulty of defining and conceptualising the concept (9).

Lockdown, which was implemented to curb the spreading of COVID-19 cases, adversely affected the obesity epidemic and metabolic health due to the deterioration of socioeconomics, psychological security and metabolic processes (10). Isolation during the pandemic has several negative physiological and psychological

repercussions and drastic lifestyle changes, resulting in insufficient physical activity and movement, as most gyms are closed and outdoor activities are limited (11). A cohort study that followed individuals with obesity reported a significant increase in weight in Northern Italy after one-month lockdown enforcement and attributed it to the negative psychological effects of the COVID-19 pandemic (12).

Besides the obesogenic environment that promotes obesity in the population, it has also been demonstrated that the dietary environment in utero could influence calorie intake, as infants to mothers who were malnourished during pregnancy are born with reduced levels of leptin, which results in a voracious appetite. Infants who are overfed in utero, on the other hand, are born larger and reduced their satiety sensitivity due to their hypothalamus being resistant to high doses of leptin, which results in obesity (13). Leptin is a hormone produced by the adipose tissue in direct relation to the amount of body fat. It is responsible for energy homeostasis that suppresses appetite and increases the individual's energy expenditure. In order to reach the hypothalamus and execute its anorexigenic activities, it must penetrate the blood-brain barrier (14).

OBESITY AND CHRONIC INFLAMMATION

Inflammation is a well-ordered series of events that preserves tissue and organ homeostasis by releasing mediators and expressing receptors at the right times, which are required to complete the tissue-restoration programme (15). Inflammation is a tissue-protective response that occurs when the tissues are wounded or destroyed, and it destroys or dilutes the damaging substances at the site of the affected tissues (16). Inflammation could be grouped into two types; acute inflammation, which is an immediate response that lasts for a short period and is characterised by oedema and leukocytes migration, and chronic inflammation, which continuous and prolonged response and is characterised by the presence of blood vessels and connective tissues (17).

Obesity frequently causes a low-grade chronic inflammatory condition characterised by an increase in systemic inflammatory markers as a result of increased fat storage in tissues (18). The role of inflammatory cells and cytokines in the adipocyte microenvironment is depicted in Figure 1. The first link was discovered when tumour necrosis factor-alpha (TNF-α) levels were shown to be elevated in the blood and adipose tissues of individuals with obesity, and reduction of body weight in these individuals showed reduced TNF-α expression (19). This pro-inflammatory signal would then attract neutrophils and macrophages, which would then produce reactive oxygen species that are involved in apoptosis, mitochondrial oxidative metabolism or enzymatic reaction of superoxide dismutase (SOD),

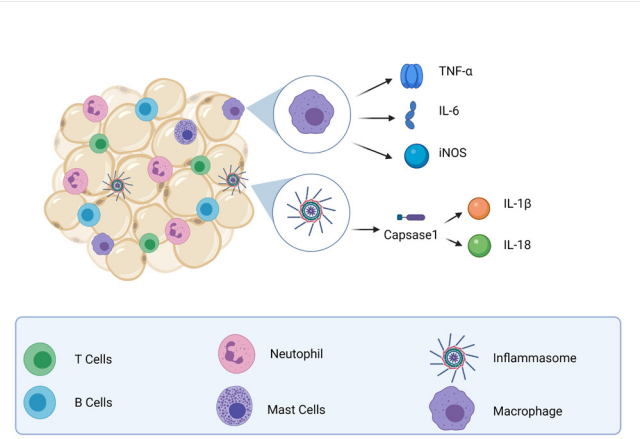

Figure 1: Inflammatory cells and cytokines in adipocyte microenvironment. Overview of the inflammatory cells and the cytokines involved in adipocyte microenvironment. Created with BioRender.com.

nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, nitric oxide synthase (NOS) and myeloperoxidase (MPO) (3,20).

In a study by Weisberg et al. (2003), inflammatory responses associated with chronic inflammation were observed in mice with obesity, with an increase of mast cells, B cells, T cells, macrophages and neutrophils, which surrounding dying adipocytes, which had also been linked to adipocyte hypertrophy, local hypoxia and adipose tissue stress (21,22). The key role is played by adipose tissue M1 macrophages, which change their phenotype during obesity and produce pro-inflammatory cytokines such as TNF-α, interleukin-6 (IL-6) and inducible nitric oxide synthase (iNOS) (23). Adipokines originates from the pool of expanded and activated adipocytes and have actions similar to cytokines and are able to reduce insulin resistance, enhance responsiveness, and inflammatory responses of organs such as the brain, heart, and intestines, cause tissue injuries such as myocardial ischemia, ischemic stroke, sepsis, and non-alcoholic steatohepatitis (24). Besides the role of cytokines and immune cells in obesity-related inflammation, malondialdehyde (MDA), a type of free radical produced in cells by the lipid peroxidation of polyunsaturated fatty acids, is also linked to a variety of disorders and its pathophysiological and is frequently used as a marker for oxidative stress (25). MDA formed from lipid peroxidation can either be enzymatically metabolised or interact with cellular and tissue proteins or even DNA to form adducts that result in biochemical damage (26). Interestingly, anti-inflammatory adipokines such as transforming growth factor-beta (TGF-β), adiponectin, interleukin (IL)-4, IL-10, IL-13, IL-1 receptor antagonist (IL-1Ra) and apelin have been shown to preferentially be secreted by lean adipose tissue, whereas adipose tissue of individuals with obesity primarily secretes pro-inflammatory cytokines, as discussed above (27).

Nutrition status has also been linked to abnormalities in immune responses. A reduced immune response is apparent in malnourished individuals, which increases the risk of infections, while overeating results in an increase in an immune response that generates excessive inflammation and stress to mitochondria, resulting in oxidative stress and, in the long run, would cause meta-inflammation (28). Inflammasomes are activated when fatty acids are excessive and converted to energy, which also causes inflammations (28). The increase in the activity of the inflammasome marker, caspase 1 and its downstream mediators IL-1β and IL-18 in subcutaneous adipose tissue may contribute to increased inflammation, insulin resistance, and subcutaneous adipose tissue fibrosis in patients with metabolic syndrome (29).

EFFECT OF OBESITY ON PROTECTIVE ANTIOXIDANT ENZYMES

One strategy for the body to overcome oxidative stress and the effects of reactive species produced is by utilising endogenous and exogenous antioxidants (30). A study by Colak et al. (2019) observed that obesity is strictly linked to changes in redox state, and it also reported a significant association of antioxidant defence parameters with anthropometric, lipid and inflammatory markers in individuals with obesity and highly recommended screening of antioxidant markers (31). Superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), among many others, are major antioxidant enzymes that neutralise reactive species. However, when adipose tissue grows, antioxidant enzyme activity decreases, resulting in a range of issues such as decreased bioavailability of nitric oxide (NO), which is a mediator of vasodilation in blood vessels and an increase in endothelium-derived contractile factors that favours atherosclerotic disease (32).

COVID-19 AND OBESITY

In the recent COVID-19 pandemic, a cohort study found that those who were overweight had a 44 % increased risk of critical illness from COVID-19, and those who were obese had an almost doubled risk (33). Patients with COVID-19 and a BMI of 35 are seven times more likely to require invasive mechanical breathing than those with a BMI of less than 25 kg/m^2 and 3.6 times more likely to be admitted to critical care than those with a BMI of less than 30 kg/m^2 (34). Patients with obesity-related diseases such as diabetes mellitus, cardiovascular (including hypertension), respiratory or kidney disease are in the vulnerable group that is prone to more severe COVID-19 outcomes and these problems are concentrated in certain racial groups (African American and Asians) (35).

The overactivated inflammation and immune response in obese patients, as discussed in the previous section, may induce an excessive inflammatory response and cause immune exhaustion following COVID-19 infection in these patients (36). Nearly 20 to 50% of COVID-19 patients had diabetes, which is much higher than the world incidence rate of diabetes (37,38). Diabetic patients are at a higher risk of developing an infection because their innate immunity is compromised, which affects neutrophil chemotaxis, phagocytosis, and cell-mediated immunity and they also have a higher prevalence of cardiovascular disease, which is linked to COVID-19 fatal outcomes (37). Besides that, obesity-related metabolic syndrome, such as diabetes, hypertension and heart disease, could also play a role in the increased severity following COVID-19 infection, as it could cause damage to organs, which may turn into function failure following additional stress due to COVID-19 infections (36).

Another probable explanation for the severity of COVID-19 in obese patients is that their larger adipose results in higher expression of angiotensin-converting enzyme-2 (ACE-2), which the SARS-CoV-2 virus uses for cell entry purposes (39). Figure 2 depicts the role of ACE-2 in the viral entrance mechanism at the cellular level. COVID-19 also plays a role in metabolic dysfunction caused by obesity-induced adipose tissue inflammation, leading to dyslipidaemia, insulin resistance, type 2 diabetes mellitus, hypertension, and CVD (40). As seen in relation to infection of influenza virus in patients with obesity, obesity alters the immune responses and leads to weakened immunity, increasing the severity of cytokine storm effect following COVID-19 infection (34,41). The adipose tissue also acts as a viral reservoir and due to impaired immune response, the virus shedding is prolonged in obese patients, which causes the patients to be more contagious due to prolonged viral shedding (42).

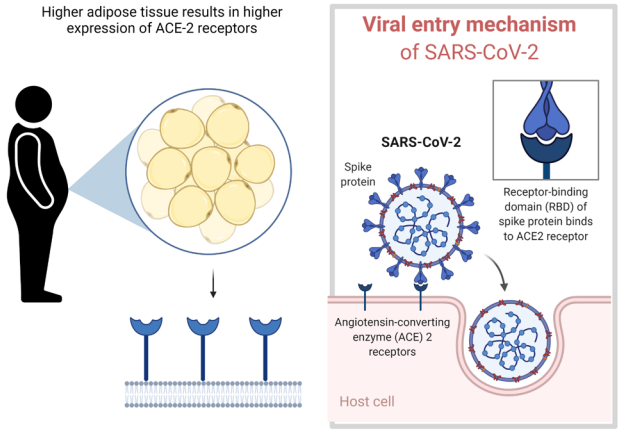

Figure 2: Higher expression of ACE-2 receptors in individuals with higher adipose tissue and SARS-CoV-2 entry mechanism. Adapted from "Proposed Therapeutic Treatments for COVID-19 Targeting Viral Entry Mechanism", by BioRender.com (2021). Retrieved from https://app.biorender.com/biorender-templates.

BENEFITS OF OBESITY INTERVENTIONS

Managing obesity demonstrates improved health outcomes and would help reduce the severity following possible COVID-19 infection in patients, which would help reduce the burden to the healthcare system during the pandemic. Weight loss following a low-calorie diet has been demonstrated to reduce DNA damage, improve genomic stability and lower inflammatory cytokines. It is supported by a study that reported the reduction of oxidative damage in saliva following weight loss in morbidly obese patients who had bariatric surgery (3). Another clinical study published in 2021 reported a significant reduction of plasma inflammatory cytokines such as MIP-1b, IL-6, IL-8 and TNF-α in subjects of the study, who were observed through a caloric restriction diet (43). Induction of DNA damage and inhabitation of DNA repair following oxidative stress increases the frequency of mutation and alters gene expression, promoting proliferation, migration and apoptosis resistance in cancer cells (44).

Implementing healthy diets have shown great positive outcomes as opposed to obesity which is often linked to a state of micro deficiencies, as it is often caused by excessive eating of ultra-processed food with low nutritional values (45). Consumption of fruits and vegetables in the diet, which is rich in flavonoids, has shown a significant reduction in biomarkers of inflammation, improved microvascular reactivity, and even been shown to prevent and treat influenza viruses by reducing viral replication (38). A healthy diet providing balance or essential and non-essential nutrients is very important, and vitamin A, C, D and E deficiency, which is very common in individuals with obesity, has been shown to be detrimental and linked to various inflammations, systemic infections and lung disease (45,46). A clinical trial that studied the effects of consumption of curcuminoid, which is the active ingredient in turmeric (Curcuma longa) with the daily dosage of 1 gram for eight weeks, had been shown to significantly increase serum levels of SOD while reducing the serum levels of MDA and C-reactive protein compared to the placebo group and this could be beneficial for individuals with obesity (47).

A cross-sectional study on 206 COVID-19 patients found that increasing levels of physical activity and changing one's diet to include more fruits and vegetables, while reduced intake of poultry and teas may reduce the severity of COVID-19 disease in patients and this suggests that during the pandemic, public health recommendations should emphasise the importance of encouraging physical activity in additions to other measures to protect against COVID-19 severe infection (48). The World Health Organization (WHO) recommends accumulating 150 minutes of physical activity per week, which consists of moderate-intensity aerobic conditioning and the addition of muscle-strengthening exercises for at least two times per week in bouts of at least 10 minutes (49).

Exercise stimulates the release of cytokines and other beneficial factors into the blood, which contributes beneficial effects and this is an emerging concept in the field of exercise biology (50). Exercise is also thought to be an effective non-pharmacological therapy for preventing and treating chronic non-communicable diseases and infections (51). However, more research is needed on the latter claim because an acute response to high-intensity exercise results in transient suppression of the immune system, rendering people to be more susceptible to infections and viral reactivation, whereas continued moderate-intensity training strengthens the immune system's defences against microorganisms and pathogens, making people more resistant to infections and viral reactivation. Low-intensity exercise is thought to be beneficial for beginners and individuals with chronic health issues (51,52). Increased physical activities have psychological benefits. In a cross-sectional study conducted by Brand, Timme, and Nosrat in 2020, it was discovered that during the pandemic, individuals who exercised frequently reported to have the most positive mood effects, and interestingly, persons who habitually avoid exercise are more likely to see early positive effects when they try to exercise almost every day (49).
One way to increase the interest in implementing healthier lifestyles in individuals is by taking advantage of the wide influence of social media influencers, who are constantly observed by the large population, especially in the current state of the pandemic. These influencers could be recruited to promote a healthy lifestyle by sharing balanced, healthy and simple recipes, and daily workout routines that would encourage their followers to implement such habits in their lives.

CONCLUSION

As more evidence emerges confirming the severity of COVID-19's impacts on individuals with obesity and metabolic disorders linked to obesity, there is an urgent need to educate the public about the necessity of leading a healthy lifestyle. Maintaining a healthy weight, eating a healthy diet and exercising regularly can help reduce inflammation and better prepare the body in the event of an infection, hence lowering obesity and COVID-19 related morbidity and mortality, which will possibly reduce the burden on the healthcare system. It is important to understand the complex factors relating to motivation to lead a healthy lifestyle and health providers should be able to guide patients towards achieving better health outcomes. The barriers in obesity care, including gaps in medical education, obesity care programs and the psychological aspects, should be identified to ensure effective implementation of programs and interventions could be explored and implemented.

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