Obesity and COVID-19: An Epidemic Aggravating a Pandemic

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ABSTRACT

COVID-19 has been declared by WHO as a pandemic since March 2020. The pandemic has caused major deaths in the world and has become the candidate for the third largest pandemic in history after the Black Death pandemic and the Spanish Flu pandemic. Many conditions have made the deaths in the COVID-19 pandemic become large, including collision with the obesity epidemic. The aim of this literature review is to discuss the relationship between obesity as a risk factor for high mortality COVID-19 and its management.

Keywords: COVID-19, endemic, obesity, pandemic

Obesity is Epidemic and COVID-19 is Pandemic

Endemic disease is a disease that appears and becomes characteristic in certain areas. This disease will always exist in the area, but with a low frequency or number of cases. An epidemic occurs when a disease has spread rapidly to a certain region or country and begins to affect the population of that region or country. A pandemic is a disease outbreak that occurs widely throughout the world. In other words, this disease has become a common problem for all citizens of the world.

Coronavirus disease 2019 (COVID-19) has been declared by WHO as a pandemic on March 9, 2020.⁽¹⁾ At the time of writing this article, the number of world population infected with the SARS-CoV-2 has reached 208,019,700 and in Indonesia it has reached 3,854,354. Deaths caused by COVID-19 have reached 4,375,028 worldwide, and 117,588 in Indonesia.⁽²⁾ One of the risk factors related to mortality in COVID-19 is obesity.⁽³⁾

In 2016, the World Health Organization (WHO) revealed that 39% (1.9 billion people) of the world's population were overweight, of which more than 650 million were obese. There were 340 million adolescents (5-19 years

old) who were overweight and obese in the same year.⁽⁴⁾ There were 38 million children under 5 years old who were overweight and obese in 2019. The global incidence of obesity has nearly tripled since 1975, according to the WHO. Much of the world's population resides in countries where more people are killed by obesity and overweight than underweight.⁽⁵⁾

In Indonesia, basic public health survey or known as Riset Kesehatan Dasar (Riskesdas) 2007 showed that 10.5% of the population were obese, Riskesdas 2013 showed 14.8% of the population were obese and Riskesdas 2018 showed 21.8% of the population were obese and 20% of elementary school children were overweight and obese.⁽⁶⁻⁸⁾ Obesity is a form of malnutrition besides stunting and wasting.⁽⁹⁾

Obesity has become rapidly increased in the United States since 1990s with worsen lifestyle.⁽¹⁰⁾ The American Centre for Disease

Control and Prevention (CDC), in a report dated February 3, 2021, mentioned about confirmed medical conditions related to the severity of COVID-19 (**Table 1**). They divided these medical conditions into: (1) might be at an increased risk and (2) at increased risk for severe illness from the virus that causes COVID-19. Overweight was included in “might be at an increased risk”, while obesity was included in “increased risk”.⁽¹¹⁾

The aim of this article is to review all aspects of obesity, including its definition, diagnosis, epidemic status and its relationship to the COVID-19 pandemic. Concerning the COVID-19 pandemic, we discuss how the pathophysiology of obesity can aggravate COVID-19 and how to manage it. Controlling obesity is expected to reduce COVID-19 morbidity and mortality.

Table 1. Medical Conditions as Risk of Severe COVID-19.⁽¹¹⁾

Might be at an increased risk	At increased risk
– Asthma (moderate-to-severe)	– Cancer
– Cerebrovascular disease	– Chronic kidney disease
– Cystic fibrosis	– Chronic obstructive pulmonary disease
– Hypertension or high blood pressure	– Down syndrome
– Immunocompromised state from blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of other immunosuppression medicines	– Heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
– Neurologic conditions, such as dementia	– Immunocompromised state from solid organ transplant
– Liver disease	– Obesity (body mass index [BMI] of 30 kg/m ² or higher but < 40 kg/m ²)
– Overweight (BMI > 25 kg/m ² , but < 30 kg/m ²)	– Severe obesity (BMI ≥ 40 kg/m ²)
– Pulmonary fibrosis	– Pregnancy
– Thalassemia	– Sickle cell disease
– Type 1 diabetes mellitus	– Smoking
	– Type 2 diabetes mellitus

Definition and Pathophysiology of Obesity

Obesity is the accumulation of excessive fat due to an imbalance between energy intake

and energy expenditure for a long period of time. Energy intake that exceeds energy expenditure, will cause obesity. Energy intake

comes from foods and drinks calorie. Energy expenditure includes: (1) energy used for organs works such as digesting, absorbing food and food metabolism, named as the thermic effect of food (TEF), (2) energy used at rest, or resting metabolic rate (RMR) and (3) energy used for physical activity.⁽¹²⁾

Criteria of Obesity

Obesity can be determined based on the following examinations. First, measuring body mass index, which is obtained from body weight (kg) divided by the square of height (m²). Second, measuring waist circumference in standing position. The tape circles the abdomen in the middle between the arch of the lower ribs and the iliac crests. A body mass index of more than 27 kg/m² and/or a waist circumference of more than 80 cm for women and more than 90 cm for men meet the criteria of obesity.^(13,14)

Aetiology of Obesity

The causes of obesity include: sedentary lifestyle, overeating, genetic factors, hormonal

imbalances, use of illegal drugs or potions, psychological factors and environmental factors. Diets related to obesity are: eating large amount of sugar and salt, eating less vegetables and fruit, irregular eating schedules, skipping breakfast and increasing lunch or dinner portion, snacking frequently, and processing food using a lot of oil, thick coconut milk and lots of sugar.⁽¹⁴⁾

Sedentary activities are activities that are performed outside of bedtime, with a characteristic of very little calorie output, less than 1.5 metabolic equivalent (MET). Examples of sedentary activities are: lying down or sitting for long time, such as watching television, playing video games, sitting for a long time in front of the computer, and lack of exercise.⁽¹⁵⁾

Genetic factor and hormonal imbalances also contribute to obesity. Many genes involved in obesity are shown in **Table 2** and hormones involved in obesity are shown in **Table 3**.

Table 2. Genes Involved in Obesity.^(16,17)

Gene Symbol	Gene Name	Gene Product and Role in Metabolism
<i>ADIPOQ</i>	<i>Adipocyte-, C1q-, and collagen domain-containing</i>	Produced by adipocytes, adiponectin increases energy expenditure
<i>FTO</i>	<i>Fat mass- and obesity-associated gene</i>	Increase food intake
<i>LEP</i>	<i>Leptin</i>	Produced by adipocyte
<i>LEPR</i>	<i>Leptin receptor</i>	When it binds to leptin, it inhibits appetite
<i>INSIG2</i>	<i>Insulin-induced gene 2</i>	Regulation of cholesterol and fatty acid synthesis
<i>MC4R</i>	<i>Melanocortin 4 receptor</i>	When it binds to alpha-melanocyte stimulating hormone, it stimulates appetite
<i>PCSK1</i>	<i>Proprotein convertase subtilisin/kexin type 1</i>	Regulates insulin biosynthesis
<i>PPARG</i>	<i>Peroxisome proliferator-activated receptor gamma</i>	Stimulates fatty acid uptake and adipose tissue formation

Many other factors contribute to obesity. It is more likely that pregnant women who smoke or who are overweight or obese will have children who are overweight or obese.⁽¹⁹⁾ The health choices of people can be affected by environmental systems, schools, workplaces, income, media, and access to health care, and the availability of healthy food. In order to be more easily active in physical activity and healthy eating, it is necessary to build a healthy atmosphere.⁽²⁰⁾ Study suggests that when affected by mental

health issues such as depression, anxiety, or other feelings, certain individuals appear to over-eat.⁽²¹⁾ Ghrelin and leptin, which contribute to obesity, can interfere with lack of sleep.⁽²²⁾ Sleep-deprived individuals may be less driven to exercise, resulting in less burned calories. Obesity-associated medicines are: some antidiabetics, antipsychotics, antidepressants, anticonvulsants, hormonal agents, anti-inflammatory agents, corticosteroids, and antihistamines.⁽²³⁾

Table 3. Hormones Involved in Metabolism.⁽¹⁵⁾

Hormone name	Role in Metabolism
Thyroid hormones	Hypothyroidism causes decrease metabolism and weight gain
Leptin	Excess leptin, which is produced by excess adipose tissue, makes the brain insensitive to signals of satiety
Insulin	Insulin helps store energy reserves from glucose in the form of fat storage
Estrogen	Estrogen that is too low or too high can cause weight gain
Cortisol	High levels can cause hyperinsulinemia and visceral fat accumulation
Progesterone	Decreased levels cause weight gain
Ghrelin	Increased levels increase appetite
Testosterone	Decreased levels cause weight gain
Melatonin	Decreased levels cause weight gain
Glucocorticoid	Increased levels cause weight gain
Glucagon like peptide 1 (GLP1) and dipeptidyl peptidase-4 (DPP4)	Increased DPP4 and decreased GLP-1 levels are associated with obesity

Body Image Versus Body Mass Index

Many obese people believe they have healthy weight. Researchers asked volunteers in a survey of 2,056 obese individuals in Dallas to select figures of ideal body shape along with one that most closely resembles their body shape. There were 8% of respondents preferring the same or bigger body shape than them, reflecting a misunderstanding regarding

a healthy weight. People who misrepresent the size of their body feel healthier than people who are conscious of their obesity.⁽²⁴⁾

Health Consequences of Obesity

The physical effects of obesity include: sleep apnea, asthma, breast cancer, intestinal disease, fatty liver, gallbladder disease, kidney disease, prostate disease, varicose veins, stroke, diabetes mellitus, hypertension and coronary heart disease, abnormal reproductive

hormones, polycystic ovary syndrome, osteoarthritis of the knee and pelvis.⁽¹⁴⁾ The psychological effects of obesity include: movement becomes slower resulted in decreased work productivity, reduced self-confidence, less attractive appearance and withdrawing from social interactions.⁽²⁵⁾

The Difference between Non-Obese and Obese Adipose Tissue

In non-obese adipose tissue, the profiles shown are anti-inflammatory, antioxidant, optimal insulin sensitivity, and normal angiogenesis. A healthy immune system supported by normal adipose tissue protect us from disease. In contrast, in obese people, what occurs is predominantly pro-inflammatory profile, high oxidative stress, insulin resistance, and poor angiogenesis. The effects on the immune system are: decreased function of T cells and macrophages, decreased response to vaccination, and decreased response to antivirals.⁽²⁶⁾

Molecular Mechanism of Severity in Obese COVID-19 Patients

Adipose Tissue as Reservoir of SARS-CoV-2

Obese adipose tissue is also thought to be a reservoir for SARS-CoV-2. Adipose tissue in non-obese people shows moderate expression of molecules known to act as SARS-CoV-2 receptors, such as angiotensin converting enzyme 2 (ACE2), Dipeptidyl peptidase-4 (DPP4), CD147, and furin. These molecules are highly expressed in obese adipose tissue. It is also suspected that SARS-CoV-2 circulates by attaching to circulating ACE2 and DPP4, making it easy to spread throughout the body. In addition, the DPP4 circulating in large amounts in obese can increase inflammation, fibrosis, and excessive immune response.⁽²⁷⁾ In obese

adipose tissue itself, the viruses replicate, making body difficult to clear them.⁽²⁸⁾

Increased Ratio of Angiotensin II to Angiotensin (1-7)

Obese adipose tissue produces angiotensinogen, which is subsequently converted with the help of renin to angiotensin I and then angiotensin I with the help of ACE is converted to angiotensin II. Angiotensin II is a potent vasoconstrictor. Angiotensin I is converted to angiotensin II, and with the help of ACE2 it is converted to angiotensin (1-9) and angiotensin II is converted with the help of ACE2 to angiotensin (1-7). SARS-CoV-2 binding to ACE2 inhibits conversion to angiotensin (1-7), and increases the ratio of angiotensin II to angiotensin (1-7). This will trigger vasoconstriction, inflammation, fibrosis, and oxidation. Consequently, lung injury occurs, pulmonary vascular permeability increases and induces pulmonary oedema and acute respiratory distress syndrome.⁽²⁹⁾ In addition, there are many comorbidities associated with obesity, including: hypertension, type 2 diabetes mellitus, cardiovascular disease, inflammation of epicardial adipose tissue, atherosclerosis, renal disorders, cancer, and psychological/psychiatric disorders. All can aggravate COVID-19.⁽³⁰⁾

Immunosuppression State and Excess Proinflammatory Cytokines

Adipose tissue produces excess leptin, actually in an attempt to suppress appetite, but this excessive leptin will increase the production of interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF- α) which are proinflammatory.⁽³¹⁾ In individuals with obesity, the intestinal lipopolysaccharide (LPS) composition may be changed from

immunosilent/immunoinhibitory subtypes of Bacteroidetes LPS, to subtypes of proinflammatory LPS due to gut microbiome dysbiosis. In addition, presence of mixed infection with bacteria that is very easy to occur in obese patients, especially with comorbid type 2 diabetes mellitus, also increases the production of lipopolysaccharide and endotoxemia which then activates macrophages to produce IL-6 and TNF- α , thus increasing inflammation.⁽³²⁾ Endotoxemia also increases IL-10 which in turn activates dendritic cells to induce an immunosuppressive state, increases susceptibility to viral infections.⁽³³⁾ Viral infection itself also induces immunosuppression.⁽³⁴⁾ These conditions will form a vicious cycle of worsening COVID-19.

Impaired Tissue Remodeling

In non-obese COVID-19 patients, pulmonary vasoconstriction and remodeling also occur, but injury is prevented, and due to angiogenesis is working well, a vascular shunt may occur to compensate and improve the ventilation perfusion ratio that is impaired due to lung parenchymal damage.⁽³⁰⁾ And in non-obese, there are no other comorbid conditions that aggravate the condition.

Poor Pulmonary Conditions

The pulmonary condition of obese COVID-19 patients can become very severe as a result of: dysfunction of the resident mesenchymal stem cell, defects in the respiratory tract (decreased mucociliary escalator), chronic inflammation, immune system deregulation, mechanical defects due to diaphragmatic movement disorders due to oppression by massive abdominal adipose tissue, and pulmonary artery hypertension. These conditions will aggravate the infection,

inflammation persistence, increase fibrosis, functional failure, and increase the need for intubation and artificial ventilation.⁽²⁷⁾ Related to the physiological function of the lungs, in obese COVID-19 patients, there are a reduction in force expiratory volume, a reduction in force vital capacity, and an increase in thoracic oppression.^(27,35)

Poor Extrapulmonary Conditions

The extrapulmonary conditions that are affected by obesity, which further increase the worsening of COVID-19 in obesity are as follows. In the heart: heart failure preserved ejection function, cardiomyopathy and increased risk of atrial fibrillation. In the kidneys: podocyte dysfunction and hypertrophy, hypertrophy and glomerular capillary hypertension, glomerulomegaly, glomerulosclerosis, proteinuria and end state renal disease. In vascular: endothelitis, endothelial dysfunction associated with apoptosis, vasoconstriction and vasodilation imbalances, prothrombotic and proatherogenic conditions, platelet hyperactivity, increased leukocyte adhesion and oxidation. In coagulation: adipocytokine hyperactivity, hypercoagulation and low fibrinolysis.⁽³⁵⁾

Obesity itself increases inflammation in sustentacular cells of olfactory mucosa and tongue taste buds. This condition reduces the smell and taste perception of obese patients. ACE2, which is the SARS-CoV-2 receptor, is found on sustentacular cells and also on the tongue. In COVID-19 patients, inflammation occurs in these cells as well. In obese patients, of course, it becomes even more severe due to even before contracting COVID-19, they already experience inflammation. In fact, pre-existing inflammation, which reduces smell and taste, will mask the anosmia and/or ageusia from

COVID-19 and thus delay diagnosis. Whereas in non-obese people, the presence of anosmia and/or ageusia can be an early indication of COVID-19 infection.⁽³⁶⁾ In obese persons, the gut microbiota changes, make it susceptible to microbes' entry and replication, including SARS-CoV-2 in the intestines.⁽³²⁾ The gastrointestinal tract itself is very abundant in ACE2 receptors which is well known as the entry route for SARS-CoV-2 in the body.⁽³⁷⁾

Micronutrients Deficiency in Obese Patients

Obese patients despite appearing to be over nourished, in fact, many of them have nutritional deficiencies, especially micronutrients. Many of them are deficient in vitamin D, ascorbic acid, zinc and selenium.⁽³⁸⁾ As is well known, these micronutrients are related to the function of the immune system. Many studies have shown that the severity of COVID-19 is also related to deficiency of these substances.⁽³⁹⁾

Table 4. Micronutrients deficiency in Obesity.⁽³⁸⁾

Micronutrient	Prevalence of Deficiency in
	Obesity
Thiamine B1	15–29%
Pyridoxine B6	0–11%
Cobalamin B12	3–8%
Folic acid	3–4%
Ascorbic acid	35–45%
Vitamin A	17%
Vitamin D	80–90% ^c
Vitamin E	0%
Zinc	14–30%
Chromium	—
Selenium	58%

Increased Morbidity and Mortality

COVID-19 with obesity increases hospitalization, intensive care, invasive mandatory ventilation requirements, and

mortality for patients. Excess visceral fat tissue is associated with the severity of COVID-19.^{((40),41)}

Poor Response to Vaccination

The influenza vaccine response is reduced in obesity. Hemagglutination inhibitor titers were similar in obese and normal weight hosts measured immediately after vaccination, but decreased more rapidly in the obese population. The switching of IgM to IgG classes is also impaired. The cellular immune response to vaccination in obesity has been shown to decrease activation and decreased maintenance of memory T cells. COVID-19 vaccine response in obese has not been known yet, but might be the same.⁽⁴²⁾

General Management of Obesity

The management of obesity includes: limiting intake of sugar, salt and fat, consuming more fruits and vegetables and doing physical activity to lose weight to normal. A balanced low-energy diet is a reduction of 500-1,000 kcal of energy from daily needs, by: reducing the consumption of complex and simple carbohydrates, reducing fat consumption, such as processing fried foods, using thick coconut milk, butter, and margarine, and eating a T pattern plate.⁽¹⁴⁾ Recognize the emotions of eating, avoid distracting emotions by eating lots of food when angry, stressed, bored and others are very important.⁽⁴³⁾

Obesity can occur at any age, even in young children. But with age, hormonal changes and a sedentary lifestyle increase the risk of obesity. In addition, the amount of muscle in the body tends to decrease with age. Generally, lower muscle mass leads to decreased metabolism. These changes also reduce calorie requirements and can make weight loss more difficult.⁽⁴⁴⁾

The Endocrine Society suggests that alteration of diet, exercise and behavior be part of every solution to obesity management. Since certain antidiabetic are associated with weight gain, medications that promotes weight loss or have no impact on body weight should be offered to diabetics who are obese or overweight as first and second-line treatments. For type 2 diabetes mellitus and obesity, metformin is the first-line agent. Glucagon-like peptide-1 analogues (GLP-1) or sodium-glucose-linked transporter-2 (SGLT-2) inhibitors are second-line drugs. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and calcium channel blockers can be used as first-line treatment for high blood pressure. They are effective medication for blood pressure that are less than beta-adrenergic antagonists to lead to weight gain.⁽⁴⁵⁾

When patients require weight gain-related medicines, such as antidepressants, antipsychotic and antiepileptic medicines, they should be fully advised and given an estimation of body weight impact of each choice. The weight and waist circumference of patients who are taking antiretroviral therapy should be tracked. Non-hormonal contraception is recommended for women with a BMI > 27 kg/m² with comorbidities or BMI > 30 kg/m² pursuing contraception; if they cannot avoid it, choose oral rather than injection due to injection contraception can increase weight. In patients with chronic inflammatory disease, it is best to use non-steroidal anti-inflammatory drugs and other anti-rheumatic drugs whenever possible, as corticosteroids typically result in weight gain. Weight gain is limited in antihistamines with less central nervous system activity (less sedation) compared to those with more

sedation. Weight loss pharmacological therapy is recommended using non-sympathomimetic medicines, such as lorcaserin and/or orlistat.⁽⁴⁵⁾

The other alternative in obesity management is bariatric surgery. The aim of bariatric surgery is to reduce the amount of food that stomach can accommodate or decrease the absorption of nutrients in the small intestine. Adults who have one of the following conditions will be considered for bariatric surgery: (1) extreme obesity, which is a body mass index greater than 40 and (2) obese with a body mass index ranging from 35 to 39.9, but with health issues, such as diabetes, heart disease, high blood pressure and sleep apnea.⁽⁴⁶⁾

Maintaining the weight, they have lost is often difficult for patients, particularly if they are surrounded by tasty, calorie-rich foods and depend on energy-saving devices every day. Cognitive and behavioral treatment may help preserve healthier habits for patients. Multidiscipline and support system are needed for successful management.⁽⁴⁷⁾

Management of Obesity with COVID-19

Obesity impairs pulmonary ventilation related to diminished diaphragm movement caused by intra-abdominal fat tissue pressure. Obese patients, particularly men whom fat is distributed mainly in the visceral abdomen, will benefit from ventilation interventions. These include: high flow nasal cannula (HFNC), non-invasive ventilation (NIV), high positive end-expiratory pressure (PEEP) and they respond well to prone positioning and extracorporeal support.⁽⁴⁸⁾ When pronation is not possible due to patient discomfort or obesity, an extended semi-sitting or sitting position is preferable. Physiotherapists are highly recommended to be involved in patient management.

Adipose tissue is known to play role in the production of pro-inflammatory cytokines such as IL-6 and TNF- α .⁽³¹⁾ Tocilizumab, a monoclonal antibody that competitively blocks IL-6 against its receptor (IL-6R), is proven to help with cytokine storms and has been recommended by professional organizations as part of COVID-19 management.⁽⁴⁹⁾ COVID-19 may also benefit from drugs that inhibit TNF- α . Deficiencies of micronutrients related to the immune system, such as vitamin D, also must be corrected.

Obesity in women is linked with higher androgen levels compared to non-obese.⁽⁵⁰⁾ High androgen levels, according to several observations, play role in the severity of COVID-19 because androgen increases the expression of TMPRSS2. It is known that TMPRSS2 cleaves viral glycoprotein S, facilitating viral activation and representing one of the important host factors for SARS-CoV-2 pathogenicity.⁽⁵¹⁾ Obese men have a greater COVID-19 burden than obese women.⁽⁵²⁾ It contradicts the theory that obese men have higher aromatase activity, which can convert testosterone to estradiol; and estrogens further suppress IL-6 expression.^(53,54) However, it can be explained by the fact that men have impaired estrogens receptor signaling, resulting in increased androgenic hormone and adipose tissue estrogens production.⁽⁵⁵⁾ Drugs that inhibit androgens action, such as spironolactone, may benefit for improvement. Androgen deprivation therapy has recently been shown to protect against COVID-19 in prostate cancer patients.⁽⁵⁶⁾

Camostat, a TMPRSS2 inhibitor, has been shown in to improve a variety of metabolic abnormalities in obese mice.⁽⁵⁷⁾ Studies of Camostat in COVID-19 patients also resulted in a faster recovery time and lower disease

severity.^(58,59) This medication may be beneficial to obese COVID-19 patients.

Targeting the metabolism and distribution of cholesterol and lipids has been proposed as a novel strategy for treating viral infections. When cholesterol levels rise as a result of metabolic disorders, such as obesity, this may aggravate the severity of COVID-19. First, inflammatory cytokines promote the formation of 25-hydroxycholesterol, which in turn promotes adipose tissue inflammation.⁽⁶⁰⁾ Second, there is evidence that lipid rafts are required for viral entry by group ACE2 and TMPRSS2. Statins may disrupt this lipid raft composition. Statins also have anticoagulant and anti-inflammatory properties.⁽⁶¹⁾

Mesenchymal stem cells are also considered to benefit obese COVID-19 patients via a variety of mechanisms. First, they provide an anti-inflammatory environment by reducing cytokine, chemokine and inflammatory cell infiltration. Second, they promote tissue remodeling and reduce fibrosis while improving pathological resolution. Third, they restore organ function and protein expression in cells of lungs, kidneys, cardiovascular system and nervous system.⁽⁶²⁾

CONCLUSION

Obesity endemic aggravates COVID-19 pandemic. Controlling obesity will reduce morbidity and mortality of COVID-19.

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