Thrombosis Mechanisms in Obese and Ischemic Stroke COVID-19 Patients: A Literature Review

Putri Winanda*, Natasya Putri**
* Langsa District Hospital, Aceh, Indonesia
** Banda Aceh Health Office, Aceh, Indonesia

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ABSTRACT

Coronavirus disease 2019 (COVID-19), despite being a respiratory infection, also causes neurological manifestations such as stroke due to thrombosis formation. Prior investigations have examined the correlation between COVID-19 and ischemic stroke, as well as COVID-19 and obesity. However, the mechanism of thrombosis in obese COVID-19 patients remains elusive. This review aims to examine the mechanism of thrombosis in COVID-19 patients with ischemic stroke and obesity. Chronic inflammation and impaired fibrinolysis are two major pathways responsible for thrombosis in people with obesity. Chronic inflammation activates prothrombic signaling pathways in vascular cells, resulting in procoagulant factors and adhesion molecules upregulation, anticoagulant proteins downregulation, platelet activation enhancement, and increased thrombin generation. SARS-CoV-2 enters human cells utilizing the angiotensin-converting enzyme 2 (ACE-2) receptors, which results in inflammation, which has been suggested as one of the factors contributing to thrombotic complications in COVID-19 patients. The infection also causes cytokine storm that induces atherosclerosis, plaque rupture, and superimposed thrombosis leading to brain damage. Together with endothelial injury, the cytokine storm might increase the expression of tissue factors and further promote a prothrombic state. In conclusion, the mechanisms of thrombosis in COVID-19 patients are related to direct infection of SARS-CoV-2 into the ACE-2 receptor and the cytokine storm that results in chronic inflammation and thrombosis formation. Obesity will further boost the inflammation process that leads to the formation of thrombosis and increase the risk of ischemic stroke among individuals with COVID-19 with obesity.

Keywords:
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Corresponding Author
Putri Winanda
Langsa District Hospital, Aceh, Indonesia
Email: putriwinanda93@gmail.com

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Further studies showed that the virus, which primarily affects respiratory organs, also impacts other organs, including the brain, leading to neurological manifestations like stroke, headache, and fogged brain. Early in the pandemic, there was a reduction in stroke admission. Still, later on, there was a rise in the incidence of acute cerebrovascular disease (CVD), including hemorrhagic and ischemic stroke in COVID-19 patients. The incidence of acute CVD in COVID-19 patients was 1.4%, with the highest rates reported in Asian population and ischemic stroke being the most common subtype. Despite the low incidence of stroke with COVID-19 (less than 2%), the magnitude of the ongoing pandemic means that thousands of people are at risk of having this complication.

A systematic review reported that people with COVID-19 who were older, had a higher risk of severe infection, and had preexisting cardiovascular comorbidities. However, compared to the strokes without COVID-19, strokes occurred at a younger age, manifested with severe symptoms, and were often caused by occlusion of large arteries. Studies suggested that artery occlusion in COVID-19 patients was more likely caused by cardioembolism or paradoxical embolism than artery atherosclerosis or plaque rupture, explaining the incidence of stroke among young COVID-19 patients without comorbid, patients with high D-dimer levels or in individuals with venous thrombosis and pulmonary embolism. Compared to other viral infections, SARS-CoV-2 infection is linked with a higher risk of thrombotic vascular diseases such as stroke due to endothelial dysfunction, hyperinflammatory state, platelet activation, obesity was implicated as a significant risk factor for poor outcomes after SARS-CoV-2 infection. BMI > 30 kg/m2 increased the risk of admission, ICU admission, and mortality in people with COVID-19. Patients with high BMI or obesity were more likely to experience COVID-19 outcomes due to metabolic organ dysfunction impairment that leads to insulin resistance and the pro-inflammatory state. Moreover, obesity enhances thrombosis, resulting in an increased risk of venous thromboembolism and prothrombotic disseminated intravascular coagulation.

Obesity in children aged 6-11 years old has also significantly increased, from less than 5% to more than 20% over the last three decades. Obesity is correlated with metabolic homeostasis dysregulation that results in insulin resistance, dyslipidemia, and alteration of blood pressure regulation, all of which lead to increased non-communicable diseases like diabetes, cardiovascular disease, chronic kidney disease, and cancer. A high BMI has been suggested as a risk factor for thrombotic diseases e.g., cardiovascular disease, stroke, venous thromboembolism, diabetes mellitus, and one of the predictors of myocardial infarction independent of sex, age, and ethnicity. The increasing risk of mortality causes that. Moreover, obesity is also linked with an ischemic stroke, including thrombus or embolism, deep vein thrombosis, and pulmonary embolism.

Previous studies have shown the association between COVID-19 and ischemic stroke, as well as COVID-19 and obesity. However, the mechanism of thrombosis in COVID-19 patients with obesity might lead to ischemic stroke remains elusive. This review aims to elaborate on the mechanism of thrombosis in COVID-19 patients with ischemic stroke and obesity.

REVIEW

Mechanism of Thrombosis in Obesity

According to investigations, the prothrombic state of obesity was mainly driven by two major pathways: chronic inflammation and fibrinolysis impairment, which may cause endothelial dysfunction, rupture of atherosclerosis plaques, hypercoagulability, delayed clot lysis, and hyperactivation of platelets.

Thrombotic Pathways in Obesity

Based on the evidence, obesity is a chronic inflammatory disorder. Adipocytes secrete inflammatory cytokines that encourage macrophages to swarm to adipose tissue and accumulate as the fat mass grows, leading to chronic inflammation. The proinflammatory M1 phenotype macrophages produced by inflamed adipose tissue may further contribute to the pathogenesis of obesity-mediated metabolic disorders, as they cooperate with adipocytes and preadipocytes to boost inflammatory cytokines like tumor necrosis factor (TNF), interleukin-6 (IL-6), and IL-1.

The release of inflammatory cytokines further promotes thrombosis by inducing the accumulation of immune cells in adipose tissue and the expression of adhesion molecules that mediate endothelial–leukocyte and platelet–leukocyte interactions. Chronic inflammation also alters the mechanisms of endogenous anticoagulants such as tissue factor pathway inhibitors, antithrombin, and the protein C anticoagulant system, resulting in disturbed hemostasis
and higher thrombosis.\(^{32}\) Freedman et al. found a positive correlation between elevated BMI.\(^{33}\) It increased the expression of mRNA transcript in human platelets, supporting the theory that activated platelets can mediate inflammation-induced thrombosis and boost inflammatory response in people with obesity, atherosclerosis, rheumatoid arthritis, and sepsis. The platelet-monocyte aggregation also increased in patients with critically ill COVID-19.\(^{34}\) Last, inflammatory conditions found in people with obesity correlated with increased plasma levels of coagulation factors, e.g., fibrinogen, von Willebrand factor, and factor VIII, to induce further thrombosis.\(^{35}\)

Fibrinolysis is an essential process of fibrin clotting that degrades the fibrin clot. Plasminogen activator inhibitor-1 (PAI-1), a serine protease inhibitor secreted by vascular endothelium, the liver, and adipose tissue, severely inhibits fibrinolysis and significantly impacts this process. Studies showed that persons with insulin resistance and obesity had abundant PAI-1 found in visceral adipose tissue, which was associated with an increased cardiovascular risk of atherosclerosis.\(^{36}\) The circulating PAI-1 was elevated in people with central adiposity and major adipose, obesity and metabolic syndrome,\(^{37}\) as well as those with increased BMI and waist size.\(^{39}\) The study found that plasma levels of PAI-1 were higher in obese mice.\(^{40}\) Another invitro study suggested that PAI-1 might play a significant role in promoting prothrombotic effects of obesity, as it found that deficiency of PAI-1 in mouse models resulted in the dissolution of cerebral artery occlusion due to obesity.\(^{41}\)

**Thrombotic Pathways Modulators in Obesity**

Obesity induces dysregulation of hemostatic balance modulators such as adipokines and microRNAs for primary prothrombotic pathways (miRs). Adipokine, a bioactive substance secreted from adipocytes, plays an essential part in human metabolism as it regulates appetite and energy expenditure, modulates insulin sensitivity, oxidative capacity, lipid metabolism, and vascular cell function.\(^{20}\) One adipokine is Leptin, which has been identified in macrophages, endothelial cells, and platelets. The studies have revealed a strong relationship between leptin plasma levels and vascular thrombosis.

Increased adipose tissue associated with hypothalamic leptin insensitivity is considered to be responsible for elevated leptin levels in obese people,\(^{42,43}\) while a Vitro study found that leptin deficiency protects against arterial thrombosis.\(^{44}\) Beside leptin, adipose tissue releases other adipokines, including resistin, visfatin, and the anti-fibrinolytic serpin PAI-1. Resistin and visfatin activate endothelial cells, resulting in decreased expression of prothrombotic adhesion molecules, raising the leukocyte activation, adhesion molecule synthesis, and pro-inflammatory cytokine production.\(^{45-47}\) Elevated visfatin expression may also induce plaques break and following thrombosis in carotid and coronary arteries.\(^{48}\)

Adiponectin, the most abundant adipokines, is an antithrombotic factor that can reduce leukocyte-endothelial interactions and inhibit smooth muscle cell proliferation, which is associated with cardiovascular health.\(^{20,49}\) Moreover, it can also stimulate the production of nitric oxide that induces the anti-inflammatory cytokine IL-10 synthesis in macrophages and inhibits the expression of tissue factors in endothelial cells and macrophages.\(^{50,51}\) Unfortunately, plasma adiponectin levels can describe BMI increases,\(^{20}\) resulting in a higher risk of thrombosis in people with obesity.

Another important thrombotic pathway modulator in obesity is microRNAs. MicroRNAs, also known as miRs, are short (19–24 bp). RNA molecules govern physiological processes by ‘fine-tuning’ the posttranscriptional expression of a specific gene.\(^{52}\) According to reports, miRs have been implicated in the pathogenesis of obesity and its thrombotic complications. Obesity and diabetes were correlated with plasma and tissue miR expression, maintaining the role in insulin regulation.\(^{53,54}\) MicroRNA-126, which has antithrombotic effects by inhibiting the expression of endothelial adhesion molecules, was significantly lower in individuals with obesity.\(^{53}\) A study showed that miR-223 suppresses platelet receptors.\(^{55}\) However, the levels of miR-223 are lower in higher BMI individuals than in lean people,\(^{53}\) indicating the cause of obesity-induced platelet activation.

**Mechanism of Thrombosis in COVID-19 Patients**

According to investigations, stroke with COVID-19 may be associated with conventional mechanisms in which COVID-19 acts as a leader,\(^{56,57}\) or may be caused by SARS-CoV-2 infection through a particular pathway.\(^{6}\) COVID-19 is considered a prothrombotic disease with possible mechanisms including vascular endothelial dysfunction, altered blood flow dynamics due to hyperviscosity, and the hypercoagulable state as observed in COVID-19 patients.\(^{10}\) Vascular endothelial dysfunction causes fibrinolytic dysfunction that leads to thrombus formation in blood vessels.\(^{38}\) The formation of thrombus in individuals with COVID-19 is also aided by systemic inflammation or a cytokine storm caused by the infection.\(^{39}\) Hyperviscosity, associated with SARS-CoV-2 infection, is a prominent thrombogenic factor that might cause endothelial damage and dysfunction.\(^{10}\) Alteration in blood flow dynamics might also lead to aneurysmal rupture.\(^{60,61}\)

Sepsis-induced coagulopathy is characterized by coagulation pathway activation along with D-dimer and fibrinogen elevation in people with severe
COVID-19 symptoms. This mechanism is associated with a systematic inflammatory response induced by SARS-CoV-2 infection and might be responsible for the increased risk of stroke. Furthermore, hypercoagulation in people with COVID-19 might cause venous thromboembolism and paradoxical embolism that lead to ischemic stroke, explaining why stroke in COVID-19 patients could occur in younger people with no vascular risk factors.

SARS-CoV-2 infection is more popular than other coronavirus and seasonal infectious pathogens to produce thrombotic vascular events such as ischemic stroke. SARS-CoV-2 infection induces human cells by using the angiotensin-converting enzyme 2 (ACE-2) expressed in the lungs, heart, kidneys, and vascular endothelium, causing inflammation that has been a suggested factor contributing to the thrombotic event of COVID-19. Furthermore, SARS-CoV-2 infection causes a reduction of ACE-2 receptor availability, results in the renin-angiotensin system (RAS) downregulation, and causes the unopposed generation of Angiotensin II that is accountable for brain endothelial dysfunction. This situation might lead to increased sympathetic nervous system activity, loss of blood pressure autoregulation, and organ ischemia due to vasoconstriction.

Continuous and uncontrolled immune system activation due to SARS-CoV-2 infection followed by excessive release of cytokine (called cytokine storm) induce atherosclerosis, plaque rupture, and superimposed thrombosis, leads to brain damage, together with endothelial injury increase the expression of tissue factor and further promote a prothrombic state. The cytokine storm was also associated with various types of myocardial injury such as viral myocarditis, myocardial dysfunction, coronary artery disease, and stress cardiomyopathy, all of which might lead to cardiac arrhythmias and the formation of intracardiac thrombus, leads to increased risk of cardioembolic stroke.

Another plausible explanation for cerebrovascular injury in COVID-19 patients was the result of hypoxemia, particularly in patients with intracranial stenosis. Hypoxemia might lead to infarction due to a mismatch between oxygen demand and supply. Similar to how cerebral hypoperfusion brought on by RAS downregulation may raise infarction risk.

Thrombosis in COVID-19 Patients with Ischemic Stroke and Obesity

Studies showed that SARS-CoV-2 infection might cause thrombosis in almost every part of the body due to endothelial dysfunction, hyperinflammatory state, platelet activation, and vascular stasis, resulting in thrombotic vascular diseases such as stroke. SARS-CoV-2 infects human cells by using the ACE-2 receptor to enter human cells, causes inflammation, and results in thrombotic complications of COVID-19. SARS-CoV-2 infection also causes cytokine storm, which is defined the excessive release of cytokines that induce atherosclerosis, plaque rupture, and superimposed thrombosis. The cytokine storm and endothelial injury increase the prothrombic state by increasing tissue factor expression.

High BMI has been associated with an increased risk of thrombotic-related diseases as it induces inflammation and oxidative stress that cause vascular damage and increased platelet activation. Moreover, the adipose tissue prevalent in obese people induces chronic inflammations and coagulation alterations by releasing inflammatory mediators, leading to insulin resistance, atherosclerosis, and thrombosis. These mechanisms explain the increased risk of vascular diseases in obese people, including stroke, diabetes, and heart disease. Both conditions, COVID-19 and obesity, can cause chronic inflammation leading to thrombosis formation, further increasing the risk of ischemic stroke. Thus, the risk of having ischemic stroke among individuals with COVID-19 and obesity is higher than those without obesity. Obesity will enhance the inflammation that has already been induced by SARS-CoV-2 infection.

CONCLUSION

In this case, a fusiform-type aneurysm was found to be > An increase in acute CVD incidence, including ischemic stroke in COVID-19 patients, has been a new concern in the ongoing pandemic. In COVID-19 patients, obesity has been associated with increased hospitalization risk, intensive care unit admission, and mortality. Obesity increases the consequence of thrombosis through inflammation and oxidative stress mechanisms, leading to damaged vascular endothelia and increased platelet activation, increasing the risk of thrombotic disorders such as myocardial infarction, venous thromboembolism, and stroke. SARS-CoV-2 infection also causes inflammation, therefore obesity will further increase the risk of people with COVID-19 having an ischemic stroke by inducing further inflammation. Thus, obese COVID-19 patients should be closely monitored for a high risk of ischemic stroke.

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