Austin Journal of Cardiovascular Disease and Atherosclerosis

Open Access

Austin Publishing Group

Review Article

Cardiovascular Disease Prevention in the COVID-19 Era

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Received: March 01, 2021; **Accepted:** March 25, 2021; **Published:** April 01, 2021

Abstract

Although the coronavirus disease 2019 (COVID-19) pandemic is still ongoing, the path towards a better future is finally becoming clear as a result of the initiation of COVID-19 vaccination. While pneumonia was initially emphasized as the only complication of COVID-19, it has become clear that fatal complications, such as a thromboembolism, are also likely to occur. In the era of recurring coronavirus infections, it is important to identify the causes and risk factors regarding exacerbations in patients who may develop severe COVID-19. This review describes how to prevent COVID-19 exacerbations in the context of cardiovascular disease, especially exacerbations related to the vascular endothelium.

Keywords: Vascular endothelium; COVID-19; Systemic Inflammatory-Reactive Microvascular Endotheliopathy (SIRME); Vascular endothelial glycocalyx

The COVID-19 Pandemic

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), has led to the emergence of a global pandemic. Three waves of the COVID-19 epidemic have already been observed in Japan (Figure 1) as well as in many other countries where the disease has killed many elderly people and patients with underlying diseases. Although the pandemic has not come to an end, progress is being made with COVID-19 vaccination.

While pneumonia was initially emphasized as the only complication of COVID-19, serious cardiovascular complications resulting from COVID-19, such as systemic thromboembolism, acute myocardial infarction, myocarditis, severe arrhythmias, and long-term dysfunction of the heart, have also been reported [1-3]. Moreover, studies have suggested that severe complications of COVID-19 are strongly related to a damaged vascular endothelium, the induced formation of thrombi, the release of inflammatory cytokines, and the production of excess Reactive Oxygen Species (ROS) [4,5]. Moreover, the vascular endothelium has been shown to be an important target of SARS-CoV-2 [6]. Here, we propose a new concept which we have termed the systemic inflammatory-reactive microvascular endotheliopathy (SIRME) [7] (Figure 2).

SARS-CoV-2 and Angiotensin-Converting Enzyme 2

Coronaviruses have a spike receptor-binding superfamily domain, which binds to the Angiotensin-Converting Enzyme 2 (ACE2) [8]. As more progress related to COVID-19 is being made and various findings become published, the approximate identity of COVID-19 and its resulting severe complications are becoming more apparent [9,10]. Based on the genomic sequence of SARS-CoV-2, researchers have found that the virus has a very high affinity for cells that strongly express ACE2, causing severe damage to such cells [11,12]. In addition, studies have shown that patients with cardiovascular disease, diabetes, and hypertension are more likely to experience severe COVID-19 and show a higher mortality rate than other groups of patients [4,6]. Moreover, obese people, smokers, and patients with chronic kidney disease are also more likely to become severely ill. In fact, scientists have long known that the ACE2 is expressed in vascular endothelial cells in such patients [13]. Based on these findings, researchers have concluded that SARS-CoV-2 uses ACE2 to invade vascular endothelial cells [14].

Vascular Endothelial Function

Arteriosclerosis progression, plaque rupture [15], and microvascular dysfunction in chronic heart failure are closely related to vascular endothelial dysfunction. Therefore, the evaluation of vascular endothelial function can be used as a screening method for high-risk patients with cardiovascular diseases to stratify the risk of developing cardiovascular diseases in the future. In Japan, evaluation of vascular endothelial function is covered by health insurance. For this evaluation, two measurement methods may be used: Flow-Mediated Dilation (FMD), which is performed by an ultrasonic device that evaluates blood flow-dependent vasodilatory reactions, and Reactive Hyperemia Peripheral Arterial Tonometry (RH-PAT), measured using an Endo-PAT™, which is a device that uses fingertip pulse waves. Vascular endothelial function measurements are useful as an index for primary and secondary prevention of cardiovascular diseases. Decreased vascular endothelial function is also related to heart failure, which is divided into cardiac systolic dysfunction (Heart Failure with Reduced Ejection Fraction, HFrEF) and diastolic dysfunction (Heart Failure with Preserved Ejection Fraction, HFpEF). Of those, HFpEF is known to be more common in elderly patients. Furthermore, HFpEF is more likely to occur when cardiac microvascular endothelial function declines.

Vascular Endothelial Glycocalyx Damage

As vascular endothelial cells hold various functions that help maintain homeostasis in the body, the state of intravascular dysfunction can be seen as a state in which the balance of biological functions is disturbed. Lifestyle-related diseases induce vascular

Citation: Yokoyama M, Kamide N, Tojo T and Yamaoka-Tojo M. Cardiovascular Disease Prevention in the COVID-19 Era. Austin J Cardiovasc Dis Atherosclerosis. 2021; 8(1): 1042.

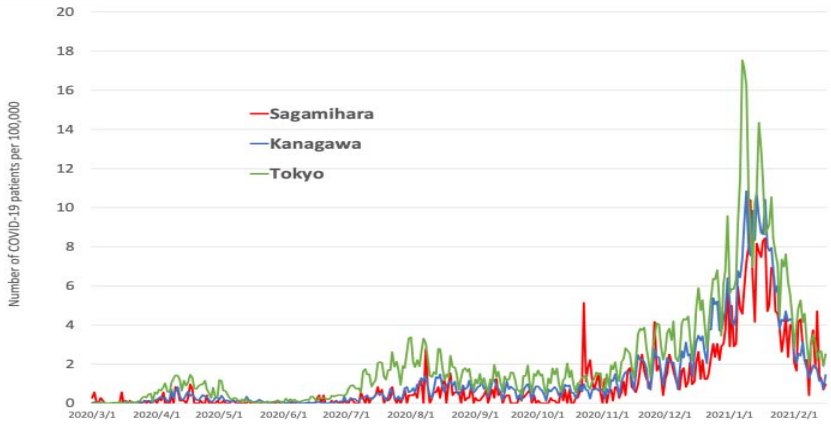

Figure 1: Changes in the number of COVID-19 patients in Tokyo and Kanagawa Prefecture. The changes in the number of COVID-19 patients per 100,000 in Tokyo and neighboring Kanagawa Prefecture from March 1, 2020 to February 16, 2021 is shown. In Sagamihara City, a government-designated city located in the northwestern part of Kanagawa Prefecture, the number of patients remained almost the same. On October 23, 2021, the number of COVID-19 patients in Sagamihara temporarily increased due to the occurrence of clusters in hospitals and related facilities.

endothelial dysfunction and damage the Vascular Endothelial Glycocalyx (VEGLX), which covers vascular endothelial cells. In acute inflammatory diseases, the VEGLX is peeled off and floats in large quantities in the blood [16]. The VEGLX is also impaired in patients with hypertension [17] and diabetes [18-21] as well as in patients with chronic diseases, such as bronchial asthma and chronic obstructive pulmonary disease, heart failure [22,23], ischemic heart disease [24], microvascular angina [25], kidney disease [26], atherosclerosis [27-29], hyperuricacidemia [30], or obesity, and elderly people [21] and smokers. Large amounts of VEGLX fragments have also been detected in the blood of a variety of acute and serious diseases, such as severe infections [31,32], sepsis [33-37], trauma [38,39], acute coronary syndrome [40,41], stroke [42], and multiple organ failure. Although the VEGLX is known to cover the inside of blood vessels and functions as a barrier for vascular endothelial cells, studies have recently shown that it also controls intracellular signals [43]. When the VEGLX becomes damaged, the function of the vascular endothelial cells deteriorates, resulting in many inflammatory substances as well as substances that promote blood clots being released into the circulating blood from the vascular wall.

Severe Complications of COVID-19

Many studies have reported that COVID-19 patients may experience severe disease as a result of decreased vitamin D concentration in the blood [44,45]. The relationship between vitamin K deficiency and severe COVID-19 has also been reported [46,47]. As insufficient vitamin K levels will result in an impaired vascular endothelial function, the virus is more likely to invade vascular endothelial cells with overexpressed ACE2 and impaired VEGLX.

Studies have highlighted that olfactory dysfunction, excessive hair loss, and prolonged general fatigue induced by COVID-19 are related to zinc deficiency [48-50]. Furthermore, in serious diseases, such as severe COVID-19, various minerals and vitamins are consumed in large amounts in the body [49]. The proper supplementation of these valuable nutrients may effectively prevent COVID-19 aggravation, thus accelerating recovery from various COVID-19 sequalae.

SIRME Could Explain Severe COVID-19 Complications

Various lifestyle-related diseases cause disorders of the VEGLX, arteriosclerosis progression, and other cardiovascular diseases. Contrastingly, serious COVID-19 complications, such as Acute Respiratory Distress Syndrome (ARDS), Disseminated Intravascular Coagulation Syndrome (DIC), Kawasaki disease shock syndrome [51-53], microvascular thrombosis, and arrhythmia, are known to be accompanied by VEGLX damage [54-56]. Based on their relationship with a damaged glycocalyx, we have termed these symptoms "Systemic Inflammatory-Reactive Microvascular Endotheliopathy" (SIRME) [5].

The concept of SIRME could explain the mechanism behind COVID-19 aggravation in a unified manner (Figure 2). The definition of SIRME is the presence of a causative inflammation, a strong thrombotic tendency, and organ damage occurring simultaneously. In more severe SIRME, the fragility of fragmented glycocalyx is high and ground-glass shadows may be frequently observed in both lungs. Together, these should be recognized as an emergency condition preceding sudden COVID-19 aggravation. By evaluating the state of the VEGLX, the severity of COVID-19 can be determined at a very early stage of the disease. VEGLX damage in SIRME is considered to occur at an earlier and milder stage than the previously proposed shock-induced endothelial disease (SHINE) [57] and Systemic Inflammatory Response Syndrome (SIRS). Using the concept of SIRME to explain COVID-19 aggravation, it can be predicted that SARS-CoV-2 and other viruses, which mainly target vascular endothelial cells, will cause the same pathological condition.

Various Pathological Conditions Caused by SIRME

The presence of inflammation, strong thrombotic tendency, and organ damage as defined by SIRME cause microvascular damage, VEGLX loss, and increased vascular permeability [58]. As shown in Figure 2, if SIRME occurs in the brain, the condition will result in cerebral embolism, whereas if it occurs in the heart, it will result in myocardial infarction, heart failure, arrhythmia, and Kawasaki disease

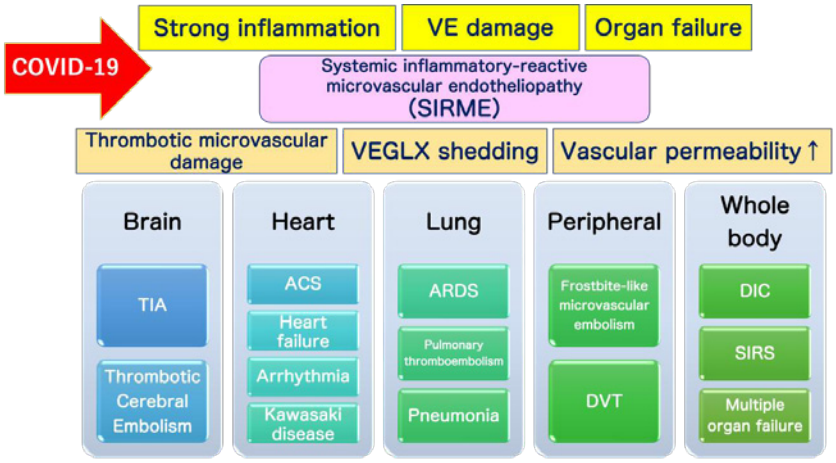

Figure 2: Definition of the Systemic Inflammatory-Reactive Microvascular Endotheliopathy (SIRME). SIRME results from damage to the Vascular Endothelial Glycocalyx (VEGLX), which is impaired in an inflammatory response. SIRME is defined as: 1) The presence of a strong causative inflammation; 2) Vascular endothelial damage with strong thrombogenic tendency and increased vascular permeability; 3) Organ failure. SIRME is presumed to be one of the major mechanisms causing diverse COVID-19 complications. VE: Vascular Endothelial; VEGLX: Vascular Endothelial Glycocalyx; TIA: Transient Ischemic Attack; ACS: Acute Coronary Syndrome; ARDS: Acute Respiratory Distress Syndrome; DVT: Deep Vein Thrombosis; DIC: Disseminated Intravascular Coagulation; SIRS: Systemic Inflammatory Response Syndrome.

shock syndrome [59]. Furthermore, if SIRME occurs in the lung, the condition will cause ARDS [60,61], pulmonary thromboembolism, and pneumonia. Finally, if systemic thrombosis is a consequence of SIRME, DIC, SIRS, and multi-organ failure will occur.

The Vascular Endothelial Glycocalyx and COVID-19

Recently, a number of studies on the aggravation of VEGLX and COVID-19 have been published [62-66]. Biomarkers related to the VEGLX and vascular endothelial damage are abnormally high in patients with severe COVID-19. Therefore, it is possible to identify patients who are at an increased risk of becoming severely ill and who may benefit greatly from prompt treatment. VEGLX is being increasingly considered as a new potential biomarker, especially in patients with severe COVID-19. Thus far, VEGLX damage has acted as an index for determining the effectiveness of screening for cardiovascular diseases, diabetes control, and cardiovascular protection measures. Proper disease management to prevent damage to the VEGLX will lead to the development of future atherosclerotic diseases and the prevention of cardiovascular events [67]. To prevent cardiovascular disease in the COVID-19 era, we should limit the intake of high amounts of sodium [68], oxidized lipoproteins [69], and sugar [18,19]. In addition, preventing obesity and smoking while encouraging increased physical activity is crucial in order to ensure the sufficient management of coronary risk factors. Whereas cardiovascular disease management is necessary to ensure a healthy VEGLX, a healthy VEGLX will in turn prevent the aggravation of COVID-19 and other emerging viral infections that target the vascular endothelium.

Acknowledgment

This work was partly supported by JSPS KAKENHI grant number JP19K11371.

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