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Letter to Editors

Could a family history of type 2 diabetes be a risk factor to the endothelial damage in the patient with COVID-19?

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ABSTRACT

In December 2019, in China, a disease derived from a new beta coronavirus (SARS-CoV-2) was reported, which was termed coronavirus disease 2019 (COVID-19). Currently, it is known that endothelial cell dysfunction is a critical event in the infection by this virus. However, in a representative percentage of patients with COVID-19, neither cardiovascular disease nor diabetes mellitus, which could be linked with endothelial dysfunction, has been reported. Previous evidence has shown the presence of early endothelial dysfunction in healthy subjects but with a family history of type 2 diabetes (FH-DM2), where glucose metabolism, the synthesis of nitric oxide (NO), reactive oxygen species (ROS), as well as expression of genes involved with their synthesis are impaired. Besides, in subjects with an FH-DM2, the presence of hyperinsulinemia and high glucose levels are common events that could favor the infection of endothelial cells by the coronavirus. Interestingly, both events have been reported in patients with COVID-19, in whom hyperinsulinemia increases the surface expression of ACE2 through a diminution of ADAMTS17 activity; whereas hyperglycemia induces higher expression of ACE2 in different tissues, including microvascular endothelial cells from the pancreatic islets, favoring chronic hyperglycemia and affecting the release of insulin. Therefore, we hypothesized that an FH-DM2 should be considered an important risk factor, since the individuals with this background develop an early endothelial dysfunction, which would increase the susceptibility and severity of infection and damage to the endothelium, in the patient infected with the SARS-CoV-2.

Introduction

In December of 2019, a disease associated with a new beta coronavirus (SARS-CoV-2) was reported in China, and which was termed coronavirus disease 2019 (COVID-19) [1]. At the same time, some reports showed that cardiovascular disease or hypertension were important risk factors for developing COVID-19, especially in people above 65 years old [1]. Recent works have also shown that patients with diabetes mellitus have a worse prognosis if they get infected by the SARS-CoV-2 [2]. Type 2 diabetes mellitus (DM2) *per se* courses with high morbidity and mortality worldwide [3], and, although, it affects especially low- and middle-income countries of Latin America [4], the rest of the world is not free of this disease. In Europe, in 2019, about 59 million individuals were diagnosed with diabetes mellitus, a number that is anticipated to rise to about 68 million people in 2045 [5,6]. This higher susceptibility of patients with diabetes to infection by different infectious agents (including the SARS-CoV-2) has been associated with the numerous alterations of innate immunity observed in these patients [7].

Current reports show that the virus affects the lower respiratory tract, as well as the heart, kidney, gastrointestinal tract, and distal vasculature, using the angiotensin-converting enzyme 2 (ACE2) as its receptor [8]. The ACE2 is expressed higher in arterial and venous endothelial cells, as well as in smooth muscle cells of the heart; it is also present in kidneys, pancreas, adipose tissue, and lung epithelium [9]. Nowadays, it is accepted that the endothelial cell is one important entryway used by this coronavirus due to its high expression of ACE2 [9]. Recently, in patients with COVID-19, signals of inflammation and viral infection were observed, as well as evidence of endothelial cells death [10]. Furthermore, severe endothelial damage associated with the intracellular presence of the virus has been described in the lungs of patients who died due to COVID-19, as well as an increase in the growth of new vessels by intussusceptive angiogenesis [11].

The infection of endothelial cells by the SARS-CoV-2 induces their dysfunction [12]. The latter is of great relevance since the endothelium plays a central role in maintaining cell homeostasis, by regulating the synthesis of different molecules with an important biological activity [13]. For example, numerous evidences have shown the association between endothelial damage and pulmonary microvascular thrombosis, which is associated with a worse prognosis in patients with COVID-19 [14]. Likewise, the presence of SARS-CoV-2 induces the release of different pro-inflammatory molecules that favor the hypercoagulation state reported in the patient with COVID-19 [8]. Moreover, the presence of SARS-CoV-2 has negative effects in the synthesis of nitric oxide (NO), and in the anticoagulant factors synthesized by the endothelial cell. In addition, an increase in the expression of the von Willebrand factor (vWF), in leukocyte adhesion molecules (ICAM-1, P-selectin) has been reported, as well as in the synthesis of reactive oxygen species and of pro-inflammatory cytokines (IL-1α, -β, -6, -10, TNF-α, TGF-β), by the endothelium of the COVID-19 patient [14–17].

However, and in spite of all the new knowledge generated, there are still doubts about all the elements that intervene in the infection and evolution of the disease. For example, in a representative percentage of patients with COVID-19, pathologies such as cardiovascular disease or diabetes mellitus, which could be associated with an early endothelial

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dysfunction, have not been reported. Huang et al. [18] showed that only 27.2% of patients with COVID-19 had an underlying pathology, such as hypertension, diabetes mellitus, lung, liver, or cardiovascular diseases. Results shown by Li et al. [12] indicate that 33% of patients with COVID-19 had hypertension, while 5% had a diagnosis of coronary heart disease. On the other hand, Niu et al. [19], after evaluating the clinical characteristics of elderly patients with COVID-19, found that 15% had hypertension and 5% coronary heart disease, and only 3% of all patients had diabetes. On the other side, Ebinger et al. [20] reported in their study that of a total of 442 patients diagnosed with COVID-19, 16.1% had obesity and 36.4% hypertension, whereas 11.1% mentioned prior myocardial infarction, and 19% reported to have diabetes mellitus. In comparison, Goel et al. [21] found that diabetes mellitus was present in 30.9% of patients in America, in 16% in Europe, whereas it was present in 12.3% of Asian patients with COVID-19. Also, the authors showed that obesity was present in 37.6, 29.6, and 17.9% of patients positive to the virus in America, Europe, and Asia, respectively. Currently, it is known that the patient with COVID-19 shows different severity levels and variations in the immune response, facts that are associated with the age or gender of the patient [20,22,23]. Interestingly, and in spite of all still existing doubts, endothelial dysfunction is considered now a critical event for patients with COVID-19 [10–12].

Hypothesis

Therefore, early endothelial dysfunction could be the reason why some apparently healthy (or asymptomatic) individuals are more susceptible to infection. Based on the above, we hypothesized that a family history of type 2 diabetes (FH-DM2) could be a risk factor for the severe endothelial damage observed in the patient infected with SARS-CoV-2. This hypothesis is supported by evidences of early endothelial dysfunction in subjects with FH-DM2 or in asymptomatic patients with type 2 diabetes [24,25], which could explain the greater susceptibility of these patients to infection by this virus. In relation to this, McSorley et al. [26] report a minor response to inducers of nitric oxide synthesis in young healthy adults with FH-DM2. Likewise, FH-DM2 has been associated with an impaired vascular function in healthy offspring, as well as with the development of DM2 in adult life [27]. Also, other authors have shown that endothelial cells from the umbilical cord from newborns of diabetic mothers had alterations in the cell membrane structure, a deficient glucose metabolism, and were less resistant to shear stress [28]. Additionally, the endothelial cells from newborns with an FH-DM2 had a diminished synthesis of reactive oxygen species (ROS), nitric oxide (NO), as well as an impaired expression of genes (eNOS, GLUT1, and p53) associated with the synthesis and metabolism of NO and glucose [29,30]. In comparison, the infection by the SARS-CoV-2 induced endothelial dysfunction, which was associated with pulmonary microvascular thrombosis and with impaired NO synthesis [12,14,16]. This has led to suggest the importance of increasing the synthesis and levels of NO in the patient with COVID-19, who has reduced levels of this mediator [31]. In young, healthy, insulin-sensitive women but with an FH-DM2, a reduced body metabolic rate and an impaired vascular endothelial function have been reported [32]. The above is similar to that observed in the COVID-19 patient, where both an impaired glucose metabolism and apoptosis have been described in the endothelial cells. In their work, Varga et al. [10] report the presence of apoptosis, viral elements within endothelial cells, and endotheliitis. In turn, Ackermann et al. [11] observed severe endothelial damage, intracellular presence of the virus, disturbance in the cell membrane, and variation in the expression of genes linked to the inflammatory process and cell metabolism.

These negative effects can be associated too with an impaired expression of molecules involved in the inflammatory response and with both glucose metabolism and NO synthesis, as has been reported in the subjects with FH-DM2; paralleling the recent findings in COVID-19 patients, in whom a total of 70 inflammation-related genes that influence cell metabolism has been reported [11,29,30,31,35]. Furthermore, here it is relevant to comment that the mitochondrion, which is associated with the origin of DM2, apoptosis, glucose metabolism, and NO synthesis in the endothelial cell, is affected in the patient with COVID-19 too [33]; similarly to the observations made in the endothelial cell from subjects with HF-DM2 [29]. It is also important to mention that several clinical features reported in patients infected with SARS-CoV-2 are similar to those observed in patients with metabolic syndrome or diabetes, such as hyperinsulinemia and hyperglycemia [34]. In relation to this, in subjects with an FH-DM2, the presence of hyperinsulinemia and high glucose levels are common events. Interestingly, both facts have been reported in patients with COVID-19 and favor the infection of endothelial cells by the coronavirus. The hyperinsulinemia induces an increase in the endothelial surface expression of ACE2 through a diminution of the protease ADAMTS17 activity (which normally diminishes the surface expression of ACE2) [35,36]; whereas hyperglycemia induces higher expression of ACE2 in different tissues, including microvascular endothelial cells from the pancreatic islets, favoring chronic hyperglycemia and affecting the release of insulin in the COVID-19 patient [35,37]. Moreover, the high glucose observed in the COVID-19 patient, consequence of impaired glucose metabolism, is associated too with the presence of “cytokines storm” [35,38]. In comparison, hyperinsulinemia and hyperglycemia have also been found in subjects with FH-DM2 [27,39]. Due to the aforementioned, the early treatment of endothelial cells as a new target has been suggested, aimed at reducing the vascular damage caused by the virus in the patient with COVID-19 [40].

Conclusion

Therefore, an FH-DM2 should be considered a relevant factor for the endothelial damage in the patient infected with the coronavirus because healthy individuals, but with a family history of diabetes, develop an early endothelial dysfunction. Nowadays, the presence of endothelial dysfunction is considered a critical event for the infection and severity of vascular damage in the patient infected with the SARS-CoV-2.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Noé Alvarado-Vasquez
Department of Biochemistry, National Institute of Respiratory Diseases, Mexico City 14080, Mexico
E-mail address: nnooee@gmail.com.