



COVID-19 and diabetes cutaneous comorbidity



A B S T R A C T

Diabetes patients have a higher risk in morbidity and mortality with COVID-19. It should be considered as a risk factor for a rapid progression and bad prognosis of COVID-19. Additional, the research in the cutaneous complication of diabetes with COVID-19 need to be considered. Therefore, particular concern should be given to diabetes, and its cutaneous complications and SARS-CoV-2.

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On January 30, 2020, the WHO declared the outbreak of SARS-CoV-2 to be an international public health emergency. On March 11, it declared a global pandemic of SARS-CoV-2 and called on countries around the world to work together to deal with the virus. Up to date (April 20, 2020), 2,318,655 confirmed cases are officially reported in more than 210 countries with 157,956 deaths [1]. Currently, though some researches reveal the potential pathophysiological mechanism of SARS-CoV-2, it is not fully clear. Recently, some studies showed that older people, especially those with underlying diabetes, are more susceptible to COVID-19 and have a higher mortality [2,3]. One of the most common complications in elderly patients with diabetes is skin and soft tissue complications, such as diabetes, chronic ulcer, diabetic foot, etc. Therefore, understanding the damage and potential mechanism of SARS-CoV-2 to diabetic cutaneous comorbidity is of great clinical significance for the prevention and treatment of skin and soft tissue complications in patients with COVID 19 with diabetes.

1. Diabetes and SARS-CoV-2

It have shown that patients with diabetes and poor blood glucose control have a certain correlation between the severity of disease and the risk of death when they are infected with the virus including the SARS-CoV [4], pandemic influenza A (H1N1) [5], and MERS-CoV [6]. Previous studies should be considered and valued, because SARS-CoV, MERS-CoV and SARS-CoV-2 are all coronavirus [4–6]. It suggests that diabetic patients have a higher susceptibility to novel coronavirus and a higher mortality after infection [2–6]. Although some scholars have called for better blood glucose management in diabetes patient with COVID-19 patients [7], but there is little data on the glucose metabolism of covid-19 patients and its effect on diabetic complications. Similarly, diabetes is one of the comorbidities associated with adverse outcomes in hospitalized SARS-CoV-2 patients [2,3].

Diabetes mellitus is a chronic inflammation. Hyperglycemia and insulin resistance promote the synthesis of AGEs, pro-inflammatory cytokines and oxidative stress, and stimulate the production of cytokines that mediate tissue inflammation [8]. This inflammatory process may constitute the underlying mechanism leading to a higher susceptibility to infection, resulting in a worse prognosis for patients.

Diabetes inhibits the chemotaxis and phagocytosis of neutrophils, and restrains intracellular killing of microorganisms. Additionally, impaired adaptive immunity may result in initial delay in Th1 cell-mediated immune activation and subsequent hyper-inflammatory response. Diabetics infected with SARS-CoV-2 may trigger a higher stress condition, releasing more hyperglycemic hormones such as glucocorticoids and catecholamines, leading to elevated blood glucose levels and abnormal variations [9]. However, it is still not very clear how inflammation and immune responses exactly occur in these patients, and whether hyperglycemia or hypoglycemia will alter the virulence of SARS-CoV-2, and whether the virus itself will interfere with insulin secretion or blood glucose control.

It is worth to note that the interaction between COVID-19 and diabetes may be a mutual interference. SARS-CoV-2 might worsen existing diabetes, and sometimes might even induce normal patients to have diabetes, its mechanism might be: angiotensin converting enzyme 2 (ACE2) is the pathway that SARS-CoV-2 enter human body. It widely expressed in the pancreas and might play a role in while patient have the insulin resistance and insulin secretion disorders [10,11]. We suppose that the potential mechanism that diabetes is more susceptibility to COVID-19 may be: 1) The immune system dysfunction accompanied with impaired, neutrophils, macrophages, B cells, T cell. 2) Decreased virus clearance. 3) Disorder of inflammatory response process. 4) Abnormal pro-inflammatory response may enhance susceptibility to cytokine storm syndrome. 5) SARS-CoV-2 may damage the pancreas.

2. Hypothesis of potential influences of SARS-CoV-2 to diabetes cutaneous complications

Clinical studies have shown that patients with COVID-19 usually exhibit decreased lymphocytes, leukocytes and thrombocytes, which are more prominent in severe patients. Additional, exaggerated pro-inflammatory cytokines, including interleukin-6 (IL-6) and C-reactive protein, and increased coagulation activity, such as higher expression of D-dimer concentrations, are also associated with the severity of disease [12]. SARS-CoV-2 may aggravate the prognosis of diabetes, and may aggravate or induce diabetic skin and soft tissue complications, we speculate that the potential mechanism may be:

- 1) Poor blood glucose management. Previous studies have pointed out that the cutaneous features of diabetes mellitus have a certain correlation with blood glucose level [13], and the hyperglycemia caused by SARS-CoV-2 affects the stability of blood glucose, and the SARS-CoV-2 result in higher stress condition to influence the skin and soft tissue with diabetes.
- 2) Increased ACE2 expression. ACE2 is expressed in lung, skin and other tissues or organs. Recent studies have found a potential relationship between diabetes and the expression of ACE2 [10,11]. Though the significance of these observations is not clear at present, increased ACE2 expression might predispose people with diabetes to infection with SARS-CoV-2, even having some influence on the tissue, such as skin, which expressed ACE2.
- 3) Aggravation of cutaneous ischemia and hypoxia. SARS-CoV-2 induce thrombocytopenia and leukopenia, higher D-dimer levels. It observed that patient may occur ischemia changes in toes and fingers, this mechanism may cause by DIC [14]. The impaired angiogenesis is one of the pathological characteristics of diabetes, these abnormal features may exaggerate by SARS-CoV-2.
- 4) Abnormal immune response. The impaired neutrophils, monocytes/macrophages, T cells, B cells cytokines are existed in diabetes [9,12]. The inflammatory response and cytokine storm induced by SARS-CoV-2 may affect the inflammatory response in diabetes, interfering with the normal microenvironment of skin and soft tissues.

Currently, little is known about SARS-CoV-2, especially when diabetes is associated with COVID-19. Whatever may be the underlying etiology, patients with underlying diabetes and SARS-CoV-2 infection have an adverse prognosis. Future research needs to focus on the mutual pathogenesis between COVID-19 and diabetes, so as to: (1) reduce the susceptibility of diabetic patients with covid-19, (2) to reduce the mortality and the incidence of complications in COVID-19 patients with diabetes, (3) to improve the effective of diagnosis and treatment of diabetes mellitus with COVID-19.

Author contributions

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Declaration of competing interest

None. The authors declare that they have no conflicts of interest to disclose.

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