New Insights into the Effects of SARS-CoV-2 on Metabolic Organs: A Narrative Review of COVID-19 Induced Diabetes

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Abstract: Coronavirus disease 2019 (COVID-19)-induced new-onset diabetes has raised widespread concerns. Increased glucose concentration and insulin resistance levels were observed in the COVID-19 patients. COVID-19 patients with newly diagnosed diabetes may have worse clinical outcomes and can have serious consequences. The types and exact mechanisms of COVID-19-caused diabetes are not well understood. Understanding the direct effects of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on pancreatic beta cells and insulin target metabolism organs, such as the liver, muscle, and adipose tissues, will provide new ideas for preventing and treating the new-onset diabetes induced by COVID-19.

Keywords: COVID-19, SARS-CoV-2, new-onset diabetes, hyperglycemia

Introduction

Coronavirus disease 2019 (COVID-19) is a pandemic infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). To date, COVID-19 has infected more than 774 million people and caused 7.01 million deaths. 1 There is a bidirectional relationship between COVID-19 and diabetes. 2 It is well known that diabetes increases the risk of severe COVID-19. On the other hand, SARS-CoV-2 infections have been associated with increased rates of new-onset diabetes, and the diabetic effects may persist even after infection recovery. 3–7 The new-onset hyperglycemia caused by COVID-19 may result in long-term hyperglycemia, worse clinical outcomes, prolonged hospital stays, and a greater need for oxygen support or positive pressure ventilation. 4 COVID-19 patients with newly diagnosed diabetes had higher a risk of all-cause mortality compared with COVID-19 patients with known diabetes and normal glucose. 8, 9 Laurenzi et al found that the prevalence of glycemic abnormalities returned to the preadmission frequency when the SARS-CoV-2 infection diminished and speculated that diabetes caused by COVID-19 was not likely to become a lasting public health problem. 10 However, the available evidence has shown that such a possibility exists and needs to be alerted and investigated.

Although the infection can cause stress hyperglycemia, the available data suggests that stress hyperglycemia alone does not explain the new-onset diabetes caused by COVID-19. COVID-19 may have a diabetogenic effect independent of the stress response during a severe disease. Type 1 diabetes and type 2 diabetes are the most prevalent types of diabetes. They are different from their pathologic characteristics. The incidence of patients with type 1 or type 2 diabetes cases increased following the COVID-19 pandemic. 11 It appears that exposure to SARS-CoV-2 precipitates the onset of type 1 diabetes. 12 In patients with COVID-19 and those recovering from COVID-19, fasting insulin, C-peptide levels, homeostasis model assessment of β cell dysfunction (HOMA-β) and homeostasis model assessment of insulin resistance (HOMA-IR) level were higher, 4,13 indicating multiple effects of SARS-CoV-2 infection on insulin-secreting organs as well as insulin-targeting organs. These phenomena suggested that new-onset diabetes may be different from type 1 diabetes. A retrospective cohort
analysis found that COVID-19 increased the risk of type 2 diabetes, while the incidence rates of other types of diabetes did not increase. Genetic correlation and detection of Mendelian randomization showed a bidirectional causal relationship between type 2 diabetes and SARS-CoV-2 infections. New-onset diabetes caused by COVID-19 might not simply be classified as type 1 or type 2 diabetes in terms of symptoms and mechanisms because of the atypical glycemic parameters. The virus-induced β cell cytotoxicity, insulin resistance and immune dysfunction were assumed to contribute to new-onset diabetes. Here, we conducted a narrative review using an open search strategy on PubMed with the search terms (“COVID-19” [Mesh]) OR “SARS-CoV-2” [Mesh] AND (“Diabetes Mellitus” [Mesh]). We filtered the researches focusing on the effects of SARS-CoV-2 on metabolic organs, including pancreatic cells, liver, muscle and adipose tissues.

**SARS-CoV-2 and Pancreatic Endocrine and Exocrine Cells**

Infection with viruses such as enterovirus, hepatitis C, hepatitis B and coxsackie B have been reported to have a direct or indirect effect on the pancreatic islets. SARS-CoV-2 infected and reproduced in cultured human islets, reduced insulin-secretory granules in β-cells, and adversely affected glucose stimulated insulin secretion (GSIS) function.

A study revealed that COVID-19 patients had a higher area under the curve (AUC) for insulin or C-peptide in response to the arginine test, which suggested the hyperstimulation of β cells. However, several studies have shown that SARS-CoV-2 can directly infect β cells. Cats infected with a high dose of SARS-CoV-2 could develop hyperglycemia and the SARS-CoV-2 RNA could be detected in their pancreatic tissues. SARS-CoV-2 infected about 2.5% of the primary human pancreatic islets in vitro, and all of the islet cell types were targeted, while the β cells were preferentially targeted over the α cells. SARS-N protein could be found in 38.7% ± 4.9% of the β cells. Although direct infection of SARS-CoV-2 can cause widespread β cell destruction, many pathological reports have shown normal morphologies in postmortem pancreatic tissues.

The relatively common perception is that SARS-CoV-2 binds to the Angiotensin converting enzyme (ACE) receptors in islets, and then induces selective β cell inflammation or impairs β cell functions. The IHC detection showed that approximately 57% of the insulin positive β cells in non-T2D patients were ACE2 immunopositive. A general study has demonstrated that severe acute respiratory syndrome (SARS) coronavirus, binds to the ACE2 receptor, which is located in the endocrine portion of the pancreas, could damage islets and lead to acute diabetes. Moreover, the microarray and RNA-sequencing data showed that ACE2 expression was higher in pancreatic β cell than in other endocrine cells, and a single-cell analysis of infected islets showed that the productive but limited infection dependent strictly on ACE2. Descending regulation of ACE2 caused by viral entry into β cells increases angiotensin levels, and reduces insulin secretion. However, the expression of ACE2 in pancreatic islets is conflictual. ACE2 and Transmembrane serine protease 2 (TMPRSS2) are expressed in the human pancreatic microvasculature and ducts, but are not enriched in β cells or in the endocrine pancreas. Kusmartseva et al found the rare ACE2 expression in endocrine cells at the mRNA level, suggesting that ACE2 may not be the direct pathway by which SARS-CoV-2 damaged β cell function. In addition to individual differences, the inflammatory microenvironment can also lead to the variability of the ACE2 expression. Pro-inflammatory cytokines could improve the expression of ACE2 in the β cells and primary human pancreatic islets. Consequently, cytokines induced by SARS-CoV-2 infection may cause an increase in ACE2 expression in COVID-19 patients.

Besides ACE2, other SARS-CoV-2 entry factors may also participate in β cell infections. Wu et al found that ACE2 and TMPRSS2 were generally expressed within islet a and β cells at low mRNA and protein levels, while other entry factors Neuropilin 1 (NRP1) and Transferrin receptor (TFRC) are robust in β cells, but not in α cells. Tang et al also demonstrated that NRP1 was strongly expressed in islet β cells, but that the other two entry factors, FURIN and CTSL, were expressed in all types of pancreatic cells. This may explain why the endocrine cells in islet are widely infected, but the β cells are more susceptible. Moreover, NRP1 has been postulated to prevent β cell apoptosis and alter the GSIS dysfunction induced by SARS-CoV-2 infection.

Viral replication requires an enormous supply of ATP, which would result in cellular depletion of ATP. Moreover, the untargeted metabolomic and lipidomic analysis demonstrated a disruption of the TCA cycle in non-severe COVID-19 patients, suggesting the impaired ATP generation. Glucose-dependent insulin secretion of β cells requires ATP, and consequently, ATP deficiency can impair the GSIS function. SARS-CoV-2 is associated with β cell failure. SARS-CoV-2 infection could increase the phosphorylated pseudokinase mixed lineage kinase domain like (pMLKL) protein, causing death...
of necrotic cells in islet cells. Phosphoproteomic mass spectrometry analysis demonstrated that the activation of the JNK/MAPK apoptosis signal could cause β-cell death after SARS-CoV-2 infection. However, a high level of C peptides in the serum suggested the hypersecretion of β cells, which is incongruous with the assumption of β cell failure. SARS-CoV-2-infected hormone-negative islet β cells were still positive for PDX1 or NKX6.1, suggesting the de-differentiation of mature β cells to progenitor cells. SARS-CoV-2 binding to ACE2 downregulated their expression. Loss of ACE2 resulted in impaired glucose homeostasis in mice, and β cells were dedifferentiated in ACE2 knockout mice. SARS-CoV-2 infection of the pancreatic islet may cause transdifferentiation of beta cells in α cells and acinar cells through eIF2 signaling, since the insulin expression decreased and a subgroup of the beta cells showed higher expression levels of α and acinar cell markers. However, single-cell analyses showed no significant difference in insulin-positive cell ratios in human islet cells infected with SARS-CoV-2.

COVID-19 infection can also indirectly affect islet β cells by an indirect way. ACE2 is expressed in the pancreas microvasculature and duct, which may cause may cause pancreatic inflammation. A prospective study estimated that 12.6% of COVID-19 patients suffered from acute pancreatitis. Pancreatic lesion is likely to damage β cells. In SARS-CoV-2 infected islets in vitro showed increased chemokines and cytokines, including CCL2, CXCL2, CXCL1, CCL4, CCL3, CXCL5, CCL8, IL1RN, and IL1B. Cytokine storm can play a role in facilitating hyperstimulation of β cells, ultimately leading to altered β cell function and death.

In general, SARS-CoV-2 could impair β cell insulin secretion by affecting pancreatic endocrine and exocrine cells (Figure 1).

**SARS-CoV-2 and Insulin Resistance**

Chronic inflammation caused by COVID-19 may exacerbate the insulin resistance. On the other hand, the binding of SARS-CoV-2 to ACE2 increased the level of Angiotensin II and led to insulin resistance. By activating PKR, SARS-CoV-2 viral RNA fragments can phosphorylate the serine residues of IRS-1 and lead to insulin resistance. The triglyceride and glucose (TyG) index is proposed as a reliable indicator of insulin resistance, and may predict the development of type 2 diabetes. In patients with severe COVID-19, the TyG was significantly higher than in patients with mild COVID-19 and was a predictor for the mortality of SARS-CoV-2 infections. Moreover, the serum cytokine profile of COVID-19 patients showed that 10 cytokines, including IL-1β, IL-4, IL-6, IL-7, IL-8, IL-10, IL-13, granulocyte-colony stimulating factor (G-CSF), macrophage inflammatory protein-1 β (MIP-1β) and tumor necrosis factor (TNF) were significantly upregulated in patients with COVID-19 as compared to healthy controls. The inflammatory score was in correlation with HOMA-IR, indicating the inflammatory origin of insulin resistance was associated with COVID-19. Hormonal control of glucose production by the liver and glucose uptake by muscle and adipose tissue is the main mechanism for maintaining glucose homeostasis. Insulin resistance results from the lack of insulin sensitivity in these target organs. In order to understand the COVID-19 induced new-onset diabetes, it is crucial to explore the relationship between viral effects on these organs and insulin resistance.
SARS-CoV-2 and Liver Function

A number of studies have shown that COVID-19 causes the liver injury. The large-scale plasma analysis revealed that Phosphatidylcholines, which are synthesized in the liver, were downregulated in COVID-19 patients, and were related to liver lesions. The loss of the mitochondrial matrix was observed in the liver of COVID-19 patients. As RNA viruses replicate, they upregulate glycolysis and glycogenolysis. This would provide their host cells with the TCA intermediates, and the aerobic glycolysis, which has been demonstrated to be triggered by most viruses. SARS-CoV-2 is also an RNA virus, which could cause the mitochondrial dysfunction of hepatocytes, and would increase aerobic glycolysis, thus contributing to the hyperglycemia.

In addition, the upregulation of gluconeogenesis accompanied by a dramatic decrease in glucogenic amino acids has been observed patients with COVID-19, suggesting a disorder of glucose metabolism in liver. A study showed that SARS-CoV-2 increased the GP73, and then stimulated hepatic gluconeogenesis through the cAMP/PKA signaling pathway. Plasma GP73 concentrations were elevated in patients with COVID-19 and were positively correlated with blood glucose levels. Infection with SARS-CoV-2 enhanced gluconeogenic metabolism, primarily by GP73.

SARS-CoV-2 and Muscle

Muscle is another important target of insulin, and the insulin desensitization of muscle results in insulin resistance and may contribute to the development of diabetes. SARS-CoV-2 virus may directly infiltrate into skeletal muscle. Although the muscular insulin resistance has not been reported in COVID-19 patients, myalgia, myopathy and myositis and other musculoskeletal symptoms secondary to SARS-CoV-2 infection have been reported. Patients with severe COVID-19 may have a decrease in the number of skeletal muscle, and histological slices have shown atrophy of muscle fibers and may have a decrease in the number of infiltration of immune cells. The muscle-specific Thymidine kinase 2 knockout mouse had muscular mitochondrial dysfunction and lipid metabolic disorder associated with increased ACE2 expression. Mitochondrial dysfunction in the skeletal muscle has been shown to be related to insulin resistance in type 2 diabetes.

SARS-CoV-2 and Adipose Tissues

SARS-CoV-2 might infect the adipose tissues and drive the insulin resistance in patients with COVID-19. A study looking at autopsy reports found that 62.5% postmortem adipose tissue was positive for SARS-CoV-2, and the lipid droplets were surrounded by nucleocapsid protein. Nucleocapsid transcripts could be detected in adipose tissue of SARS-CoV-2-infected mice, as well as the decreased adiponectin levels. The study supports the assumption that SARS-CoV-2 may infect adipose tissue.

Figure 2 Potential mechanisms of SARS-CoV-2 induced insulin resistance.
Abbreviations: Ang II, Angiotensin II; ACE2, angiotensin receptor 2; NRP1, Neuropilin 1.
tissues, and lipolysis can result in increased serum-free fatty acids and elevated triacylglycerol levels in patients with COVID-19. The ACE2 expression level in adipose tissues is also controversial. Metwally et al suggested that adipose tissues strongly express ACE2, and can predispose to SARS-CoV-2. Adipose ACE-2 expression related to insulin sensitivity. Gene expression profiles from 1471 donors in three human datasets indicated a lower ACE2 expression in the subcutaneous white adipose tissues of obese or T2D individuals compared to control. Therefore, ACE2 might not be the direct way through which SARS-CoV-2 infects adipose tissue. NRP-1 was highly expressed in adipose tissues, and was related to insulin sensitivity in adipose tissues. SARS-CoV-2 may enter the adipose cells through ACE2 or NRP-1. Overall, SARS-CoV-2 could induce insulin resistance by affecting liver, muscle and adipose tissues (Figure 2).

Conclusion
The COVID-19 pandemic is ongoing and the sequelae of COVID-19 is having a growing impact on people’s health. It is of particular concern that COVID-19 would cause new-onset diabetes. SARS-CoV-2 can infect pancreatic β-cells, liver, muscle and adipose tissue, which in turn affects insulin secretion and induces insulin resistance. In spite of the many studies, there is still controversy about how SARS-CoV-2 causes β cell damage and insulin resistance. More precise experiments and long-term clinical observations will help to understand, prevent and treat COVID-19 induced new-onset diabetes.

Ethical Statement
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