Article Review

Type 1 Diabetes Mellitus Due to COVID-19: Do We Need to Worry?

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Abstract—SARS-CoV-2, a Coronaviridae virus related to angiotensin-converting enzyme 2 (ACE2), is the virus that causes the COVID-19 pandemic. Diabetes mellitus is a condition that is reported to have a connection with the emergence of COVID-19. A diabetic patient has a higher risk of infection compared to other nondiabetic patients. In addition, some reports showed the possibility of infection that can stimulate diabetes in an individual without a hyperglycemia history. COVID-19 was also found to show a hyperglycemic conditions that may affect mortality. Therefore, a proper monitoring as well as management of glucose level is needed for COVID-19 patients regardless of their diabetes status, to minimize the risk of mortality and development of diabetes. The possibility of diabetes mellitus induced by COVID-19 infection is investigated in this paper, as well as the monitoring of COVID-19 patients with hyperglycemic conditions. Further investigation might be needed to confirm the relationship between COVID-19 and diabetes mellitus type 1.

Keywords: diabetes mellitus type 1, sars-cov-2, insulin

Abstrak—*SARS-CoV-2, virus Coronaviridae yang berkaitan dengan enzim pengubah angiotensin 2 (ACE2), adalah virus yang menyebabkan pandemi COVID-19. Diabetes mellitus adalah suatu kondisi yang diyakini memiliki hubungan dengan adanya COVID-19. Pasien dengan diabetes memiliki risiko infeksi yang tinggi dibandingkan dengan pasien nondiabetes lainnya. Meskipun demikian, beberapa laporan menunjukkan kemungkinan infeksi yang dapat merangsang diabetes pada individu tanpa riwayat hiperglikemia sebelumnya. COVID-19 juga ditemukan menunjukkan kondisi hiperglikemik yang dapat menyebabkan angka kematian yang cukup signifikan. Oleh karena itu, diperlukan pemantauan serta pengelolaan kadar glukosa yang tepat untuk pasien COVID-19. Kemungkinan diabetes mellitus yang disebabkan oleh infeksi COVID-19 akan diselidiki dalam makalah ini, serta pemantauan pasien COVID-19 dengan kondisi hiperglikemik. Penelitian lebih lanjut mungkin diperlukan untuk mengetahui hubungan antara COVID-19 dan diabetes melitus tipe 1.*

Kata Kunci: *diabetes mellitus tipe 1, sars-cov-2, insulin*

INTRODUCTION

A pneumonia case discovered in Wuhan, China in December 2019 sparked the COVID-19 pandemic caused by SARS-CoV-2. SARS-CoV-2 is a Coronaviridae virus that uses angiotensin-converting enzyme 2 (ACE2) as a receptor to pass through human body cells [1]. ACE2 is a part of the dipeptidyl-carboxypeptidase group that has a high affinity to angiotensin II receptors for types 1 and 2. As a result, ACE2 plays an important role in some physiological functions, such as inflammation, blood pressure, fluid balance, and cell proliferation. ACE2 is mostly expressed in nearly every body tissue, with its highest number found in the respiratory tract, digestive tract, kidney, testicles, and gallbladder [2,3].

Diabetes mellitus is a condition that is reported to have a connection with the emergence of COVID-19 itself. A study from the United States discovered that 38.5% of 1,112 patients suffered from diabetes or uncontrollable hyperglycemia. Patients with hyperglycemia were also reported to have a high periods of hospital stay as well as mortality [4]. Diabetic patients are at a high risk of infection compared to those nondiabetic patients. The infection may include bacterial infection, fungal virus, plus other infections that can attack the respiratory, urinary, and gastrointestinal system as well as systemic infection, such as HIV [5]. A higher risk was detected in type 1 diabetes patients when compared with type 2 diabetes

[6]. The increasing risk affected by hyperglycemia develops due to a dysfunctional immune system caused by the damaged neutrophil function and the decreasing of the antioxidant system as well as humoral immunity function [5]. On the other hand, in COVID-19 patients, a lot of severe hyperglycemia cases and other metabolic complications were discovered. Some diabetic ketoacidosis cases were found in patients without or with a diabetes mellitus history [7,8]. Diabetes mellitus was identified in a large number of people after SARS-CoV-2 infection, which was linked to a poorer result when compared to people who were not diabetic [9,10]. This literature review aimed to explore the association of diabetes mellitus type-1 after COVID-19 infection.

METHOD

This literature review tried to combine kinds of literature related to COVID-19 and diabetes. Kinds of literature on diabetes, new onset hyperglycemia, in patients infected by COVID-19 or SARS-CoV-2 was observed from the PubMed database. The search of the literature was done using a combination of keywords: "hyperglycemia; diabetes; COVID-19; coronavirus". The kinds of literature used for this study were all in English. Since the literatures regarding COVID-19 and diabetes is still limited, the author did not restrict the years published and the design of the study. The title and abstract of each article were used as an evaluation by the reviewers. Those that did not fulfill the requirements were removed.

RESULTS

$CD4^+$ and $CD8^+$ lymphocytes are autoreactive to pancreatic cells in type 1 diabetes mellitus, which is an autoimmune disease. Virus infections, including enterovirus, mumps, rubella, and cytomegalovirus, are known to be linked to type 1 diabetes [11]. According to the study of TEDDY (The Environmental Determinants of Diabetes in the Young) in 2017 those who have had upper and lower respiratory tract infections are more likely to have pancreatic β autoimmune cells. Overall, 5.8% of 87,327 children suffered from pancreatic cells autoimmune, with single or multiple type 1 diabetes mellitus autoantibody on seroconversion for nine months post respiratory tract infections [12].

Some reports stated that type 1 diabetes mellitus with ketoacidosis cases were diagnosed at the onset of COVID-19 and in some cases appeared after recovering from COVID-19 [13,14]. Type 1 diabetes has also been linked to a greater rate of complications than type 2 diabetes. The odd ratio of mortality in COVID-19 at the hospital was 3.51 (95 %, CI 3.16-3.90) in the group with type 1 diabetes mellitus and 2.03 (1.97-2.09) in the group with type 2 diabetes, according to an analysis from England adjusted for age, gender, deprivation, ethnicity, and geographic region [15]. However, the data on the link between COVID-19 and type 1 diabetes are often left unreported due to the high number of infected patients and those being hospitalized [16,18].

The treatment of type 1 diabetes patients with COVID-19 must primarily focus on the patient's unstable glucose level. Risk of the complication must be observed closely, especially the hyperglycemia crisis that may happen with ketoacidosis diabetic (KAD) and hyperglycemia hyperosmolar nonketotic (HHS). Glucose level control is also an important thing to be noticed in diabetic patients with COVID-19. Previous studies reported that the hyperglycemia condition in COVID-19 patients was in line with poor outcome [24]. This situation relates to a functional system and regulation from cytokine which is linked to immune cells as a part of the host response [25].

Cox regression analysis was performed to obtain data that hyperglycemia patients treated with insulin therapy through infuse showed a lower risk of more serious disease due to COVID-19 when compared with patients without insulin therapy. This study was conducted on a sample of hyperglycemia diabetes patients. Until today, insulin given by infusion method is chosen to treat COVID-19 with hyperglycemia conditions to achieve the desired glucose level which will affect the outcome at the severity level that can appear in the previous COVID-19.

Administration of insulin can improve the prognosis of COVID-19 patients, especially those with hyperglycemia conditions [26]. The connection between type 1 diabetes and COVID-19 is caused by an exaggerated expression on lymphocyte T CD8^{+} that functions as protection. CD8^{+} functions increases, especially in apoptosis which leads to lymphocytopenia in COVID-19 infection linkages [19]. SARS-CoV-2 can be linked to the ACE2 receptor that is found in the pancreas and causes its damage [20].

DISCUSSION

Plausible Mechanism of New-Onset Diabetes Due to COVID-19

The ability of the infection to cause type 1 diabetes mellitus is widely established. Individuals with virus infections such as mumps, HHV6, coxsackievirus, hepatitis A, influenza, and parainfluenza have been found to have fulminant type 1 diabetes mellitus, which is characterized by insulin deficiency hyperglycemia symptoms that appear quickly (within a week), ketoacidosis without autoantibody detection, and ketoacidosis without autoantibody detection [21].
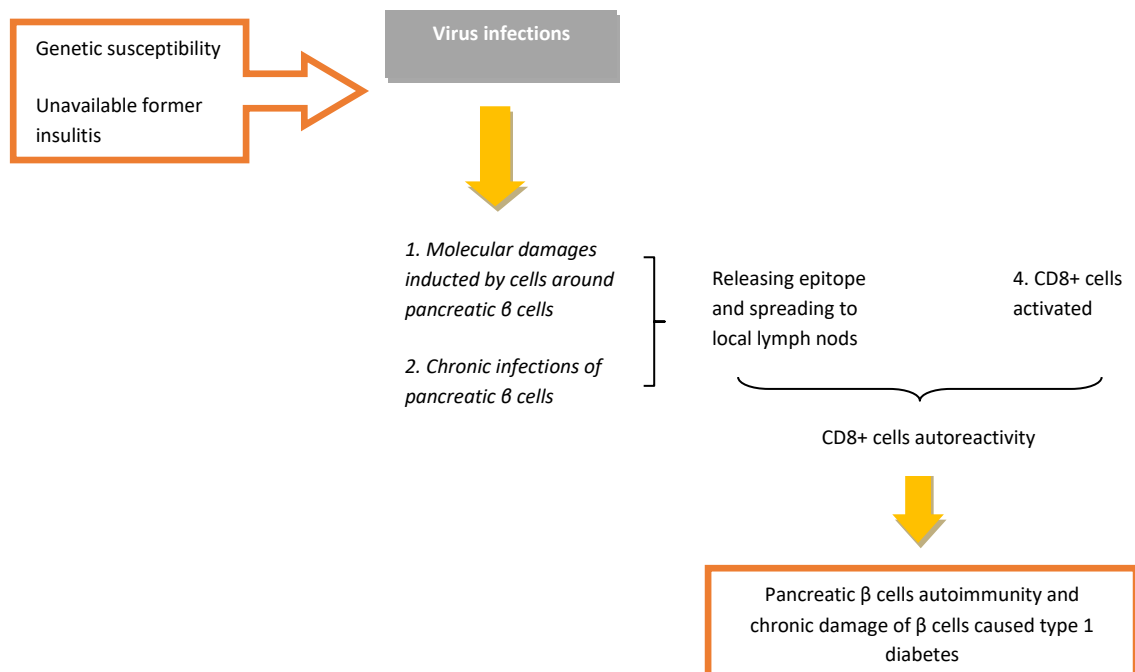

Figure 1. Pathogenesis damage of pancreatic β cells and type 1 diabetes [11].

Virus infection can lead to pancreatic β cell destruction and the development of autoimmune insulitis by several mechanisms. Virus amplification targeting pancreatic β cells triggers an immune response in infected cells, thereby triggering cell damage in the early stages of infection. Infection can also trigger the release of islet cells antigen to the circulation, presented to antigen-presenting cells on regional lymphatic nods. Pancreatic β cells were discovered to have the ability to clear moderate infections, which have the potential to become chronic infections. These chronic infections then activate excessive amounts of expression from major histocompatibility complex class I potentially leading to autoantibody formation caused by the spreading of the epitope to the immune system in the long run [11,22].

Epitope structures on viruses have homologs with autoantigen criteria that can cause antibodies to cross-react to be produced and cause damage to pancreatic β cells. This activity is often described as the molecular mimicry hypothesis. Nonetheless, this mimicry is expected to occur in recurrent infection and accelerate type 1 diabetes mellitus in individuals with pre-existing autoimmunity [22]. Another mechanism that is suspected to cause damage to

pancreatic β cells due to virus infection is the release of pro-inflammatory cytokine because of the infections around pancreatic β cells, such as an exocrine, endosteal, neuron, and α cells. Infection of these cells can also activate T cells in the pancreatic islet or lymphatic nodes, hastening the onset of type 1 diabetes in genetically susceptible people [11,22].

Glucose Management Approach in COVID-19 Patients

A hyperglycemia condition is known to have a relationship with the emergence of COVID-19, thus good management is needed to control the glucose level in COVID-19 patients, both for those who were previously diagnosed with diabetes and those who were not. Monitoring of glucose level can be done during fasting and 2 hours post-prandial right after the patient is diagnosed with COVID-19 regardless of the previous hyperglycemia history. Patients with a diabetes history have bad prognosis results when compared to those without a diabetes history. However, type 1 diabetes induced by COVID-19 needs to be detected promptly to prevent further damage. Ketoacidosis diabetic (KAD) can emerge when type 1 diabetes is being treated poorly. Because of late diagnosis and treatment, the new-onset of type 1 diabetes may develop into a powerful KAD. KAD is still the biggest factor in mortality due to type 1 diabetic complications [23].

Type 1 diabetes in both diagnosed patients and those with first-onset diabetes in COVID-19 require extra care since infection is linked to a worse outcomes. In addition, COVID-19 can also potentially trigger a new onset of diabetes that can affect the prognosis. Close monitoring of blood sugar levels is necessary to avoid complications that can occur from diabetic conditions. Further research is needed on the link between COVID-19 and types 1 diabetes mellitus, as well as the effects on the general population. Hyperglycemia condition is consistent with the rise of IL-6 levels in patients in comparison with the normoglycemia group of patients hospitalized. Further increase in blood glucose may cause inflammation that can lead to death and worse COVID-19 conditions. An intensity of IL-6 followed by D-dimer is found to have a significant rise (P<0.0001) when compared to the normoglycemia group. Hospitalized patients with standard COVID-19 treatment still experienced glucose parameters and D-dimer rise. Insulin given by infusion will have a good impact in the long run, as evidenced by hyperglycemia patients who can reach optimum blood glucose levels as well as IL-6 and D-dimer that return normal in hospitalized COVID-19 patients with hyperglycemia [26]. On the other hand, cytokine storm is suspected to occur in hyperglycemia conditions and this therapy will improve the condition by reducing cytokine levels and the risk of death [27,28].

The blood sugar target that must be met in the event of hyperglycemia is separated into two parts. The goal for critical patients is about 140-180 mg/dL (7.8-10.0 mmol/L) [29]. When the glucose level is below 180 mg/dL, it can escalate the severity level due to complications in hospitalized patients. The risk of hyperglycemia must be watched carefully [30]. Administration of insulin to critical patients aims to achieve the optimum blood sugar desired. Glucose level control in critical patients can vary and needs to be monitored because the majority of critical patients are equipped with a ventilator to assist breathing and nasogastric tube to provide nutrition which poses a high risk of hyperglycemia, balanced with some other factors such as administration of a high dose of corticosteroid that can cause hyperglycemia [31]. Administration of insulin in critical patients can be done by infusion. However, in hemodynamically unstable patients, insulin administered subcutaneously is much more recommended. Blood glucose monitoring can be done every 4 times a day. In hemodynamically unstable patients, insulin administered by infusion will be gradually replaced subcutaneously followed by a stable condition of the patient [32,33]. The duration of double insulin administration both intravenously and subcutaneously needs to be done during the transition period in line with hemodynamic changes to be stable to prevent lesser hyperglycemia at the end of the transition period. The supply of short-acting insulin is mostly used in the first 1-2 period (hours), while long-acting insulin is given in the 2-3 periods,

depending on the method used in insulin administration. In noncritical patients, insulin is targeted to be given at 140-180 mg/dL [34]. A good clinical outcome report can be achieved by controlling blood glucose at 70 and 180 mg/dL [35]. A review of hyperglycemia management in COVID-19 patients with or without critical status can be seen in Table 1 (appendix).

CONCLUSION

Type 1 diabetes, both on diagnosed previously and those having onset diabetes first time in COVID-19 patients need to have extra care due to the infection linked to a worse outcomes. On the other hand, COVID-19 also potentially provokes a new onset diabetes that can affect prognosis. Close control of blood glucose levels is necessary to avoid possible complications due to diabetic conditions. Blood glucose monitoring is important in COVID-19 patients, regardless of their history of diabetes. Insulin might be considered in patients with elevated blood glucose, with or without a history of diabetes. More research on the relationship between COVID-19 and type 1 diabetes mellitus, as well as the effects on the general population, is needed. Furthermore, type 1 diabetes necessitated more research on a group of individuals who were more susceptible to infection than others who were not, as well as ballast variables.

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Appendix

Table 1
Hyperglycemia Therapy Management in COVID-19 Patients.[36]

	Glucose level targeted	Clinical condition	Insulin regimens	Glucose level measurement
Critical patient	140-180 mg/dL*	Hemodynamic instability Parenteral nutrition Insulin need that is not consistent Treatment with corticosteroids	Insulin is infused continuously.	Every hour
		Hemodynamic stability Stable insulin demand	Subcutaneous insulin The basal correction, also known as the basal-bolus correction, is a type of correction that is used to correct	Every 4-6 hours
Non-critical patient	110-180 mg/dL**	Type 1 diabetes (no oral intake)	Basal correction	Every 4-6 hours ##
		Type 2 diabetes with oral drugs (with oral intake) ∓ insulin	Bolus basal correction	Before eating and when asleep ##
		Type 2 diabetes with diet (glucose level when admitted <180 mg/dL)	Insulin correction before eating or every 6 hours	Before eating or every 6 hours ##
		Unknown DM (glucose level when admitted >180 mg/dL)	Basal bolus correction	Before eating and when asleep ##

*Several people can be evaluated for 110-140 mg/dL if it can be achieved without causing severe hyperglycemia.
**On stable patients with little illness and a history of good glycemic management, 110-140 mg/dL can be evaluated. Patients with a high risk of hyperglycemia or a short life expectancy might get glucose levels >180 mg/dL.
#After counting insulin needs for the first 24 hours, basal correction or bolus-basal regimens are used.
##When a blood sugar sample from the finger may be utilized instead, consider utilizing a continuous glucose level control.