International Journal of General Medicine and Pharmacy (IJGMP)
ISSN (P): 2319–3999; ISSN (E): 2319–4006
Vol. 10, Issue 2, Jul–Dec 2021; 7–14

International Academy of Science, Engineering and Technology
Connecting Researchers; Nurturing Innovations

BLOOD GLUCOSE TO PROGNOSIS OF COVID-19: THE SYSTEMATIC REVIEW

Daniel Setiawan Nathan & Hoo Yumilia

Research Scholar, Department of Internal Medicine, Division of Endocrine Metabolic Diabetes, Faculty of Medicine, Maranatha Christian University / Immanuel Hospital, Indonesia

ABSTRACT

Background: *Many studies have shown an association between high blood sugar levels, mortality and disease severity in COVID-19 patients.*

Objective and Methods: *This systematic review and meta-analysis sought data from Cochrane, PubMed, Googlescholar, and other journal databases. We searched for the keywords "blood glucose" and "COVID-19 prognosis". The inclusion criteria of the research to be included are research that examines the prognosis of COVID-19 based on glucose levels, research subjects are adults (not animal studies), and use primary data. The purpose of this study was to see the relationship between blood glucose levels and the prognosis of COVID-19.*

Result: *All the studies found showed a close relationship between blood sugar levels and the severity and risk of death of patients with COVID-19.*

Conclusion: *A bidirectional relationship between chronic inflammation and hyperglycemia has been described for both diabetic and nondiabetic chronic complications.*

KEYWORDS: *COVID-19, Hyperglycemia, Mortality*

Article History

Received: *09 Aug 2021* **|** ***Revised:*** *09 Aug 2021* **|** ***Accepted:*** *14 Aug 2021*

INTRODUCTION

The COVID-19 pandemic has already become a global health crisis with the number of confirmed cases worldwide. The number of COVID-19 cases in Indonesia has reached more than two million and continues to grow.[1,2] Signs and symptoms frequently reported in hospitalized patients include fever (77-98 %), cough (46 %-82 %), myalgia or fatigue (11-52 %), and shortness of breath (3-31 %) at the onset of the disease..[3,4]

Corona viruses are a large family of zoonotic respiratory viruses that can cause seasonal flu symptoms and respiratory failure associated with severe inflammation of the lower respiratory tract.[5] Co morbidities such as cardiovascular disease, diabetes, respiratory disease, hypertension and old age can exacerbate disease manifestations. Moderate and severe cases of COVID-19 infection can cause pneumonia with subtle cloudiness on a chest computer tomography scan, pulmonary edema and accumulation of pleural fluid in the lungs. Severe cases may require invasive oxygen supply.[6]

Many studies have shown that the virus will stimulate the patient's innate immune system and release a large number of cytokines into the body after being infected with COVID-19, thereby causing a cytokine storm and acute

inflammatory reactions that result in abnormal endothelial cell structure and function, impaired insulin delivery, and ultimately lead to resistance insulin and high blood glucose.[7]

An article showed that 43 out of 99 patients with COVID-19 had liver damage that reduced the ability of liver cells to use glucose to synthesize glycogen leading to increased insulin resistance and increased blood glucose. A study reported that Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) can attack cells by binding to the angiotensin converting enzyme 2 (ACE2) receptor.[7]

Hyperglycemia is common and multifactorial in critically ill patients. Severe hyperglycemia can cause endothelial dysfunction, cytokine release, platelet activation, mitochondrial dysfunction, and electrolyte and acid-base disturbances that are associated with worsening in patients with and without a history of diabetes.[8,9]

This association has not been demonstrated in diabetic patients. In patients with sepsis, hyperglycemia usually occurs and is associated with disease severity. Several studies have reported an association between high glucose levels during hospital or ICU stay and mortality in critically ill patients in general and in septic patients in particular.[8,9]

Previous studies have found that in addition to human lung and respiratory tissue, ACE2 is also expressed in pancreatic endocrine tissue. Therefore, there is speculation that the pancreas can also be a target organ for COVID-19 attacks. The disease factor for increasing blood glucose in COVID-19 patients is probably COVID-19 which strongly binds to the ACE2 receptor on islet cells, causing islet cell damage.[7] This review was made to analyze the relationship between blood glucose levels and the prognosis of patients with COVID-19.

METHODS

This study is a systematic review. The source of this research data comes from literature obtained through the internet in the form of research results published on the internet, both in Cochrane, PubMed, Googlescholar, and other journal databases. We searched for the keywords “blood glucose” and “COVID-19 prognosis”. The research included in this article is a study that focuses on the prognosis of COVID-19 based on blood glucose levels. The inclusion criteria of the research to be included are research that examines the prognosis of COVID-19 based on glucose levels, research subjects are adults (not animal studies), and use primary data. The purpose of this study was to see the relationship between blood glucose levels and the prognosis of COVID-19.

RESULTS

There is still little study on COVID-19, mainly because COVID-19 is a newly discovered disease. The search results in the Pubmed journal database, we only found one journal that discussed the relationship between glucose levels and the prognosis of Covid-19. A Google scholar search shows three studies that are relevant to this study. Information on all the studies involved in this systematic review can be seen in Table 1.

DISCUSSIONS

The final products of the carbohydrate digestion in the alimentary tract are almost entirely glucose, fructose, and galactose, and the glucose comprises 80 % of the end product. After absorption from the alimentary canal, much of the fructose and almost all of the galactose is rapidly converted into glucose in the liver. Therefore only a small quantity of fructose and galactose is present in the circulating blood[8].

Glucose has become an inseparable part of our lives. This is because glucose is the main source of energy for humans. On the other hand, all studies found in this systematic review showed a close relationship between blood glucose levels and the severity and risk of death of patients with COVID-19.

A bidirectional relationship between chronic inflammation and hyperglycemia has been described for the chronic complications of diabetes. For example, some changes in the immune system include changes in certain cytokines and chemokines. Shifts in the number and activation of leukocytes and increased apoptosis and tissue fibrosis suggest that inflammation has an influence in the pathogenesis of hyperglycemia and chronic complications of acute infection.[14]

Wang (2020) showed that blood glucose levels are an important prognostic predictor factor in monitoring disease progression and risk of death from COVID-19. Wang showed that patients with elevated blood glucose levels >6.1 mmol/L had a 58 % higher risk of developing severe disease and an approximately 3.22-fold risk of death.[12]

Wu conducted a study involving 697 critical cases, of which one hundred and fifty-one of the 556 patients died. The 30-day hospital mortality for critical cases was 30.9 %. Univariate analysis showed that insulin treatment, blood glucose level at baseline, blood glucose level after critical diagnosis, maximum blood glucose level and minimum blood glucose level were significantly associated with hospital mortality ($p<0.05$).[13]

Blood glucose levels at the beginning of a critical diagnosis were significantly associated with hospital mortality (HR=1.84, 95 %CI 1.14-2.98, p=0.013). Multivariable analysis in this study showed that the maximum blood glucose levels (HR=1.09, 95 %CI 1.04 to 1.14) and minimum blood glucose levels (HR=1.14, 95 %CI 1.09 to 1.19) is a significant independent risk factor for in-hospital mortality in critically ill COVID-19 patients.[13]

This is consistent with previous reports that high glucose levels contribute to the development of acute respiratory distress syndrome in COVID-19 patients. Uncontrolled blood glucose levels also substantially contribute to other comorbidities, including atherosclerosis, diabetic nephropathy, peripheral arteriosclerosis, and diabetic ketoacidosis, which are also the leading causes of COVID-19-related deaths.[15]

A multicenter retrospective study of more than 7,000 cases of COVID-19 in Hubei Province of China showed a significant correlation between well-controlled blood glucose and serum levels of inflammatory markers (interleukin6 [IL-6], high sensitivity C-reactive protein [hsCRP], lactate dehydrogenase [LDH])) in patients with COVID-19. A study in patients with diabetes without advanced chronic complications or comorbidities at baseline supports a marked inflammatory process that develops rapidly in the presence of SARS-CoV-2 infection.[14]

Patients with hyperglycemia may initially present with mild symptoms and fever, then the clinical course deteriorates very rapidly with progressive dyspnea and pneumonia with higher CT scan imaging severity scores. Individuals with diabetes experienced higher concentrations of IL-6, ferritin, hsCRP, and D-dimer than those without diabetes. This condition signals a cytokine storm and a hypercoagulable state can cause rapid breakdown. Insulin requirements were very high even in patients who were insulin-naive prior to admission.[14]

This has also been shown in Ji's study who reported plasmin activation and increased fibrinolytic activity resulting in increased d-dimer in COVID-19 and reported that preexisting increased plasmin activity in hypertension, diabetes, and cardiovascular disease increases virulence and SARS-CoV-2 infectivity.[16]

The mechanisms underlying the impact of hyperglycemia on admission on COVID-19 outcomes remain to be investigated. There are several possible explanations that could explain the poor prognostic effect of hyperglycemia on

COVID-19. First, inflammatory cytokine and immune system dysfunction induced by hyperglycemia play a role in the predisposition to poor outcomes and mortality in COVID-19 patients.[11]

Hyperglycemia in patients with severe COVID-19 has been shown to reduce the proportion of immune cells, including CD4+ T cells, CD8+, and macrophages. Lymphocytopenia is common in MERS patients with severe disease. This condition resembles that of patients with severe COVID-19 who generally have lymphocytopenia. Low lymphocyte levels ($<0.6 \times 10^9$/l) at admission proved to be a risk factor for COVID-19 death.[11]

COVID-19 patients with hyperglycemia tend to have lower lymphocyte counts than normoglycemic COVID-19 patients. This led us to speculate that a low innate immune defense due to a reduced proportion of innate immune cells may also contribute to hyperglycemia-induced COVID-19 mortality and severity. Increased pro-inflammatory cytokines accompanied by low innate immune defenses may contribute to a hyperinflammatory state in COVID-19 patients with hyperglycemia.[11,17]

The CORONADO (Coronavirus SARS-CoV-2 and Diabetes Outcame) study aimed to identify clinical and biological features associated with disease severity and risk of death in diabetics hospitalized due to COVID-19. Hyperglycemia during hospitalization worsens the prognosis of COVID-19, which is generally more common in those without diabetes than in those with diabetes.[18–20]

Glucose variability during hospitalization, in both diabetics and non-diabetics also emerged as an independent risk factor for a poorer prognosis in COVID-19. Acute hyperglycemia has a key role as an independent risk factor in COVID-19. The specific and more relevant role of acute hyperglycemia is well recognized in the Intensive Care Unit (ICU), where an increased gap between admission glucose and HbA1 has been found to be a predictor of mortality in critically ill patients with diabetes.[18–20]

Acute hyperglycemia in the ICU is more dangerous for people without diabetes than for people with diabetes. Acute hyperglycemia induces inflammation, endothelial dysfunction and thrombosis, through the generation of oxidative stress. Chronic hyperglycemia in patients with diabetes can trigger increased antioxidant defenses in cells through oxidative stress, so that tissues remain protected during acute spikes of hyperglycemia.[18–20]

This does not occur in patients who do not have diabetes, making the tissue more susceptible to damage. In vitro experiments demonstrated the key role of several miRNAs in this phenomenon. SARS-CoV-2 can affect pancreatic cells which results in reduced insulin secretion and at the same time infection causes massive cytokine production, which can lead to insulin resistance. Decreased insulin secretion and insulin resistance occur in hyperglycemic patients.[18–20]

Increased ACE2 expression in alveolar, myocardium, renal, and pancreatic AT2 cells may also support increased cellular SARS-CoV-2 binding. Increased ACE2 expression has been demonstrated in the lung, kidney, heart, and pancreas in a rodent model of DM. Administration of insulin attenuates ACE2 expression, whereas hypoglycemic agents such as glucagon-like peptide-1 (GLP-1) agonists (liraglutide) and thiazolidinediones (TZDs; pioglitazone), antihypertensives such as ACE inhibitors, and statins increase ACE2 expression.[21]

Figure 1 shows Rao et al explored diseases or traits that might be associated with increased ACE2 expression in the lung. They found that DM was associated with increased pulmonary ACE2 expression. Circulating furin levels are elevated in patients with DM. This study supports the hypothesis that DM patients are susceptible to SARS-CoV-2 infection. A recent study reported that SARS-CoV-2 clearance was delayed in DM patients.[21]

ACE catalyzes the conversion of the prohormone, angiotensin (Ang) I to octapeptide (AngII), whereas ACE2 converts AngII to Ang1–7. AngII, through activation of the Ang II receptor type 1a induces vasoconstriction and proliferation, whereas Ang1–7 stimulates vasodilation and suppresses cell growth. An increase in the pulmonary ACE/ACE2 activity ratio as observed in patients with ARDS supports the formation of AngII. Upon binding to ACE2, SARS-CoV downregulates cellular expression of ACE2, and the unopposed action of AngII contributes to acute lung injury.[21]

Diabetes can inhibit neutrophil chemotaxis, phagocytosis, and destruction of intracellular microbes. Decreased adaptive immunity characterized by early delay in Th1 cell-mediated immune activation and delayed hyperinflammatory response is frequently observed in patients with diabetes. Kulcsar et al investigated the effect of DM in a humanized mouse model of MERS-CoV infection on a high-fat diet. After MERS-CoV infection became more severe and prolonged in diabetic male mice and was characterized by altered CD4+ T levels and abnormal cytokine responses.[21]

These findings were also found in patients with COVID-19 in whom peripheral CD4+ and CD8+ T cell levels were low, but with a higher proportion of highly proinflammatory Th17CD4+ T cells, as well as elevated cytokine levels. Thus, it is likely that patients with DM may have a blunted anti-viral response to IFN, and delayed Th1/Th17 activation may contribute to the prominent inflammatory response.[21]

Diabetes and hyperglycemia were previously known to cause structural changes in the lungs, leading to pulmonary remodeling and restrictive breathing patterns. Hyperglycemia is also known to produce reactive oxygen species (ROS) and induce oxidative stress. This can lead to endothelial dysfunction leading to hyperglycemic pulmonary microangiopathy in later life.[10,22]

Glycemic variability has been associated with a higher mortality rate than hyperglycemia in septic patients. Therefore, glycemic variability should be part of the management of hyperglycemia, even in ICU patients. Clinical guidelines recommend maintaining a glucose level between 140-180 mg/dL (7.8-10.0 mmol/L) for most critically ill patients and with a more stringent goal of 110–140 mg/dl (6, 1–7.8 mmol/L) is acceptable for certain patients, as long as these sugar levels are achievable without causing significant hypoglycemia.[23]

Table 1: Search Results

Author	Origin	Method	Sample Size	Population	Period	Blood Glucose	Outcome
Gilbert L (2020)[10]	Indonesia	Meta-analysis	14502 COVID-19 patient	COVID-19 patient	Up to 8 September 2020	The overall risk of severe/critical COVID-19 illness was higher in the hyperglycemia (>6.5 mmol/L) group than in the euglycemia group	High admission FBG level independently predicted poor COVID-19 prognosis.
Yang Y (2021)[11]	China	Meta-analysis	6396 COVID-19 patient	COVID-19 patients	2020	The overall risk of severe/critical COVID-19 illness was higher in the hyperglycemia (>6.5 mmol/L) group than in the euglycemia group	Hyperglycemia at admission in COVID-19 patients may be a strong predictor of mortality and complications.

Wang W (2021)[12]	China	Retrospective observational study cohort	2433 COVID-19 patient	COVID-19 patients	February 4 and April 15, 2020	The incidence of fatality at day 21 was four times higher in patients with blood glucose > 6.1 g/L (11.8 %) than blood glucose in range of 3.9–6.1 mmol/L	Elevated levels of blood glucose, fibrinogen and creatine kinase-MB, and low plateleta count were significant risk factors for fatality. Patients with elevated blood glucose level were 58 % more likely to progress and 3.22 times more likely to die of COVID-19.
Wu J (2020)[13]	China	Retrospective observational study cohort	2041 COVID-19 patient	COVID-19 patients	26 December 2019 and 15 March 2020	The overall risk of severe/critical COVID-19 illness was higher in the hyperglycemia (>6.1 mmol/L) group	Elevation of blood glucose level predicted worse outcomes in hospitalized patients with COVID-19.

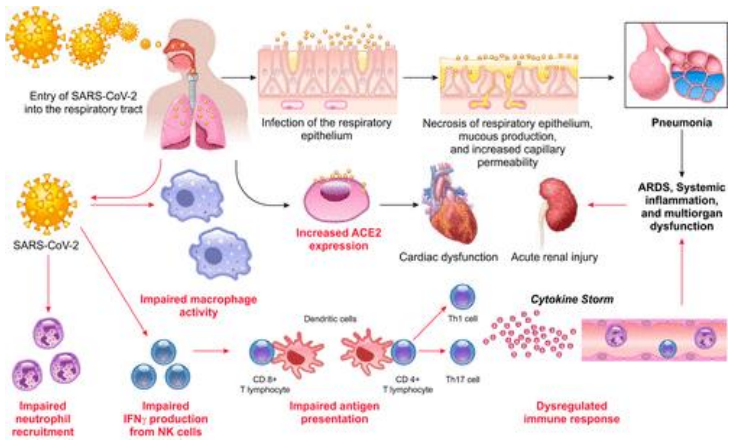

Figure 1: Mechanisms Thought to Contribute to Increased Susceptibility to COVID-19 In DM Patients[21].

CONCLUSIONS

The conclusion of this study is that there are three main mechanisms linking hyperglycemia and death from COVID-19. First, regarding the activity of the immune system that is too reactive, causing a process that resembles a cytokine storm. Second, blunting of several types of leukocytes that causes an inadequate immune system. Third, direct organ damage caused by viral infiltration into certain people or due to hypercoagulation.

REFERENCES

1. *World Health Organization (WHO). Naming the coronavirus disease (COVID-19) and the virus that causes it. Geneva; 2020.*
2. *SATGAS. Peta Sebaran Covid-19. 2020.*
3. *Huang C; Wang Y; Li X; et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10334):497–506.*

4. *Centers for Disease Control and Prevention. 2019 Novel Coronavirus (2019-nCoV). Washington DC; 2020.*
5. *Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol. 2020;215(April).*
6. *Gubernatorova EO, GOrshkova EA, Polinova AI, et al. IL-6: Relevance for immunopathology of SARS-CoV-2. Cytokine Growth Factor Rev. 2020;53:13–24.*
7. *Yan L, Yan Y, Yalin C, et al. The relationship between hyperglycemia and the infection of COVID-19 in diabetic patients A protocol for systematic review and meta-analysis. Medicine (Baltimore). 2020;99(36):210–8.*
8. *Kasper; Denis L; et al. Harrison's Principles of Internal Medicine 19th Edition. New York: McGraw-Hill Education; 2018.*
9. *Fishman JA, Grippi MA, Kotloff RM, et al. Fishman's Pulmonary Disease and Disorders Fifth Edition. New York: Elsevier Saunder; 2016.*
10. *Lazarus G, Audrey J, Wangsaputra VK, et al. High admission blood glucose independently predicts poor prognosis in COVID-19 patients: A systematic review and dose-response meta-analysis. Diabetes Res Clin Pract. 2020;171.*
11. *Yang Y, Cai Z, Zhang J. Hyperglycemia at admission is a strong predictor of mortality and severe/critical complications in COVID-19 patients: a meta-analysis. Biosci Rep. 2021;41(2):2020–35.*
12. *Wang W, Shen M, Tao Y, et al. Elevated glucose level leads to rapid COVID-19 progression and high fatality. BMC Pulm Med. 2021;21(64):78–82.*
13. *Wu J, Huang J, Zhu G, et al. Elevation of blood glucose level predicts worse outcomes in hospitalized patients with COVID-19: a retrospective cohort study. Epidemiol Serv Res. 2020;8(1).*
14. *Gianchandani R, Esfandiari NH, Ang L, et al. Managing Hyperglycemia in the COVID-19 Inflammatory Storm. Diabetes. 2020;*
15. *Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan. JAMA Intern Med. 2020;180(7):1–11.*
16. *Leentjens J, Haaps TF, Wessels PF, et al. COVID-19-associated coagulopathy and antithrombotic agents—lessons after 1 year. Lancet Haematol. 2021;*
17. *Zhang C, Wu Z, Li JW, et al. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int J Antimicrob Agents. 2020;55(4):105–9.*
18. *Sing A. Hyperglycemia without diabetes and new-onset diabetes are both associated with poorer outcomes in COVID-19. Diab Res Clin Pr. 2020;167.*
19. *Zhu L, She ZG, Cheng X. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing Type 2 diabetes. Cell Metab. 2020;31:1068–77.*
20. *Ceriello A. Hyperglycemia and COVID-19: What was known and what is really new? Diabetes Res Clin Pr. 2020;167.*

21. *Muniyappa R, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. Am J Physiol. 2020;318(5):736–41.*
22. *Caruso I, Giorgino F. The diabetic lung: an easy target for SARS-CoV-2? Diabetes Metab Res Rev. 2020;*