UNDERSTANDING THE DISEASE COURSE OF PATIENTS WITH COVID-19 AND TYPE 2 DIABETES: A SCOPING REVIEW

Ahmad Hasyim Wibisono[1], Ayu Nanda Lestari[2], Ahmad Jamaluddin[3]

Correspondensi e-mail: ahasyimw@gmail.com

[1]*Departemen Keperawatan, Fakultas Ilmu Kesehatan, Universitas Brawijaya*
[2]*Pedis Care Nursing Center, Malang, Jawa Timur*
[3]*Program Studi Keperawatan, Fakultas Kedkteran dan Ilmu Kesehatan, UIN Alauddin, Makassar*

ABSTRACT

Background: The outbreak of Covid-19 since it was first identified in Wuhan has a tremendous global effect on many aspects of human life and it affects both developed and developing countries. Meanwhile, the prevalence of diabetes is also increasing along with the viral infection, hence, a review needs to be developed that can serve as the basis for clinical care improvements. Design and methods: This scoping study review aims to explore the relationship between diabetes and Covid-19 condition using the latest relevant evidence. Results: The findings revealed that after hypertension and cardiovascular diseases, diabetes is a major comorbid among patients with the virus. Based on the existing evidence, the comorbid disease has deleterious effects on the treatment course, morbidity, and clinical outcomes of Covid-19. Furthermore, some unique changes in immune responses have been identified, which exhibit different manifestations and interactions with standard diabetes treatments. Interactions have also been discovered between blood glucose, body mass index, and several hematological parameters, which correspond to the progression of the infection among diabetic patients. Conclusion: Based on the results, Covid-19 triggered an exponential rise in the systemic inflammatory reaction, and patients with diabetes tend to have worse conditions, which were indicated by the increase in the ICU admission and mortality rate. Furthermore, the viral infection has various effects on the blood glucose stability of patients.

ARTICLE INFO

Keywords:
Type 2 Diabetes; Covid-19; Disease Course; Clinical Outcomes

MEMAHAMI PERJALANAN PENYAKIT PASIEN COVID-19 DAN DIABETES TIPE 2: TINJAUAN PENELITIAN

ABSTRAK

Latar Belakang: Wabah Covid-19 sejak pertama kali diidentifikasi di Wuhan memiliki efek global yang luar biasa pada banyak aspek kehidupan manusia baik negara maju maupun negara berkembang. Sementara itu, prevalensi diabetes juga meningkat seiring dengan infeksi virus, oleh karena itu perlu dikembangkan tinjauan yang dapat menjadi dasar perbaikan perawatan klinis. Desain dan metode: Kajian studi pemeriksaan ini bertujuan untuk mengeksplorasi hubungan antara diabetes dan kondisi Covid-19 dengan menggunakan bukti terbaru yang relevan. Hasil: Temuan mengungkapkan bahwa setelah hipertensi dan penyakit kardiovaskular, diabetes merupakan komorbid utama di antara pasien dengan virus. Berdasarkan bukti yang ada, penyakit komorbiditas memiliki efek buruk pada perjalanan pengobatan, morbiditas, dan hasil klinis Covid-19. Selain itu, beberapa perubahan unik dalam respons imun telah diidentifikasi, yang menunjukkan manifestasi dan interaksi yang berbeda dengan perawatan diabetes standar. Interaksi juga telah ditemukan antara glukosa darah, indeks massa tubuh, dan beberapa parameter hematologi, yang sesuai dengan perkembangan infeksi di antara pasien diabetes. Kesimpulan: Berdasarkan hasil tersebut, Covid-19 memicu peningkatan reaksi inflamasi sistemik secara eksponensial, dan pasien diabetes cenderung mengalami kondisi yang lebih buruk, yang ditandai dengan peningkatan angka rawat inap dan kematian di ICU. Selanjutnya, infeksi virus memiliki berbagai efek pada stabilitas glukosa darah pasien.

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Kata kunci:
Diabetes tipe 2; COVID-19; Kursus Penyakit; Hasil Klinis

Introduction

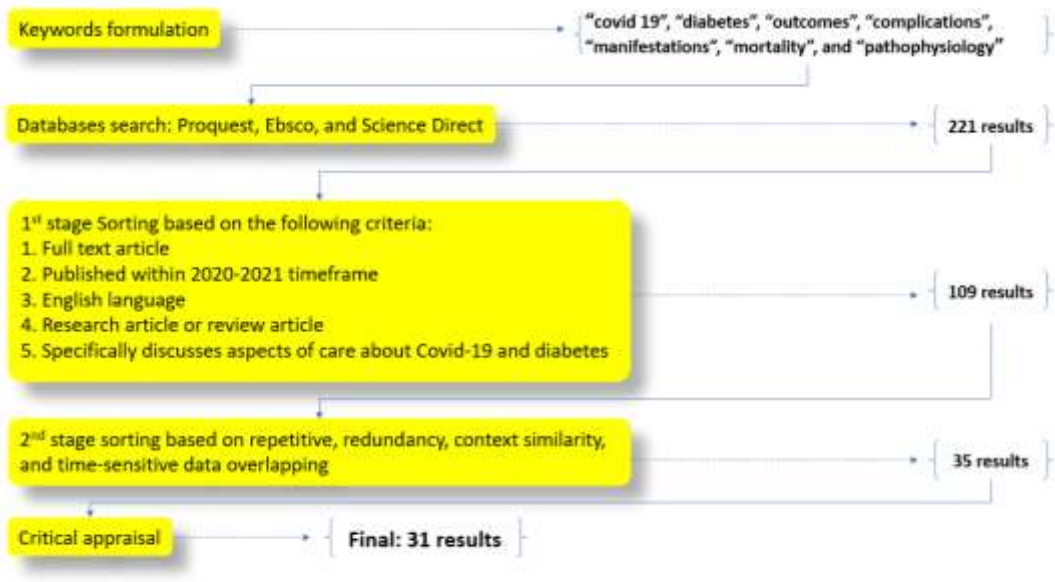
Globally, as of 3:36 pm CEST on 28 September 2021, WHO reported that there are 232,075,351 confirmed cases of COVID-19 with 4,752,988 deaths (World Health Organization, 2021). The SARS Cov-2 virus causes the infection, and it has been identified on the human angiotensin-converting enzyme 2 (ACE2) receptor, which is extensively expressed at the lung (Clerkin et al., 2020). Furthermore, another organ with large ACE2 receptor expression is the heart, and it is also present in other body parts, such as the intestinal epithelium, vascular endothelium, and kidneys where it is present in smaller numbers (Clerkin et al., 2020).

Among patients confirmed positive for Covid-19, a huge proportion was also diagnosed with diabetes mellitus. The disease was found in 20%3, 9-12% in general patients, and 16-20% in hospitalized patients (Lisco et al., 2020). Furthermore, (Angelidi et al., 2020) reported that approximately 21.2% of people infected with the virus were also diagnosed with diabetes 5. Several studies have confirmed that the comorbid disease is also strongly related to a higher fatality rate, increased demand for intensive care as well as higher mortality rate among people with the viral infection (Angelidi et al., 2020; Gregg et al., 2021).

Further studies are needed to explore the relationship between Covid-19 and comorbid diabetes. Various discussions and publications on this topic are still progressing, and there is a potential of gaining new knowledge on the particular aspects of diabetes that are affected by Covid-19. Therefore, this review aims to identify, compile, and articulate the latest evidence around diabetes mellitus and its relationship with the Covid-19 infection. The highlighted aspects are pathophysiology, clinical manifestations, and clinical outcomes of patients with the comorbidity (*italic)*.

Design and methods

Evidence was generated using scoping review approach due to the unique nature of the topic. Knowledge about the topic is still progressing and various studies have been developed to explore this aspect. Furthermore, the literatures used were obtained through online electronic sources including Proquest, Ebsco, and Science Direct. The keywords used were the combinations of “Covid-19”, “diabetes”, “outcomes”, “complications”, “manifestations”, “mortality”, and “pathophysiology”. The picture below illustrates the literature search and selection process.



The initial results of this step generated 221 articles, which were then sorted using the following criteria:

1. Full-text article
2. Published within 2020-2021
3. English language
4. Research article or review article
5. Specifically discusses aspects of care about Covid-19 and type 2 diabetes

After the selection process, which was based on the criteria, a total of 109 articles were obtained. They were then sorted to avoid repetitions, redundancy, context similarity, and time-sensitive data overlapping. Subsequently, the result of this process was appraised using the appraisal tools/worksheets developed by The Centre for Evidence-Based Medicine (CEBM), University of Oxford (Centre for Evidence-Based Medicine, 2020). A total of 31 articles were then obtained because they were considered to be reliable sources of information. Additional information was also extracted from highly respectable websites including the World Health Organization (WHO), Center for Disease Control (CDC), and International Diabetes Federation (IDF).

Results

Globally, the Covid-19 pandemic has various effects on different aspects of human life. Aside from the healthcare sector that has been significantly disrupted, it also had destructive impacts on the economic, social, and public welfare. The latest evidence revealed that there are significant correlations between the viral infection and diabetes. Almost all aspects of diabetes produced significant changes due to the invasion of the virus including the course and progression, treatment course, and the clinical outcomes, such as morbidity, mortality, and emerging complications (Pérez-Belmonte et al., 2020; Sardu et al., 2020; Zhou et al., 2020). Among these changes, the profound impacts were found on:

1. Diabetes course, clinical conditions, treatment trajectory, and emerging complications.
2. The immune response of diabetic patients towards the infection
3. Glycemic responses and their interaction with diabetes therapies.

The discussion are presented based on the three items above.

Discussions

Diabetes course, clinical conditions, treatment trajectory, and emerging complications

As previously stated in the background, there are a large number of Covid-19 patients that have also been diagnosed with diabetes. For example, among hospitalized patients in the US, the prevalence of the disease ranged from 22.6% to 37.2% (Pugliese et al., 2020). A large-scale Spanish study, which involved 7 large hospitals, also reported that its average prevalence among coronavirus patients was 27.2%. Among the comorbidities of patients with the viral infection, it is the second most prevalent after hypertension (Dennis et al., 2021). Data from hospitals and international bodies do not reflect the overall prevalence when non-hospitalized patients were included. It was then assumed that the referral processes, which prioritized moderate to severely ill patients contributed significantly to the hospitalization of diabetic patients. It also implies that people with the disease are more likely to be admitted after they are infected with Covid-19.

The prevalence of diabetes among patients that died from the virus is very significant. Furthermore, among the comorbid patients, the ARDS-related deaths were 29.8% compared to 12.4% deaths without ARDS (Pugliese et al., 2020). In a China CDC report, the prevalence of diabetes has increased from 5.3% in the whole Covid-19 population to 19.7% among non survivors. Data from Italy also revealed a significantly higher proportion where its prevalence was 29.8% of the 3,857 hospital deaths that were recorded in July 2020. Meanwhile, in a total population study in the UK, 32.9% of hospital deaths were related to the disease. Another large-scale global study, which includes patients treated in HCU and ICU in England revealed that the mortality risk due to diabetes increased to 23% compared to cases without the disease (Dennis et al., 2021).

The number of deaths caused by obesity is in line with that of diabetes, and Seiglie et al., (2020) revealed that it also increases the risk of ICU administration by 2.2 folds as well as the odd for mechanical ventilation by 2.1 folds 13. Furthermore, this finding is consistent with Longmore et al., (2021), which discovered that overweight and obesity are related to a higher rate of ICU admission and ventilator support (Longmore et al., 2021). The condition was also found to be relatively independent of diabetes, which indicates that it can affect patients with/without diabetes, hence, attention must be paid to people with significant BMI.

Consistent evidence has shown a higher level of risk infection among patients with diabetes, mostly bacterial etiology, which involves respiratory, gastrointestinal, genitourinary, and skin and soft tissue (Lisco et al., 2020). Apart from infection, blood glucose control has also been identified as an important predictor of Covid-19 progression and mortality (Hussain et al., 2020; Lamptey et al., 2020; Pérez-Belmonte et al., 2020). Longmore et al (2021) also stated that overweight and obesity increase the risk for severe progression of coronavirus. The outcome worsens when the patient also has underlying hypertension and other cardiovascular diseases (Li et al., 2020) . Therefore, clinicians need to pay extra attention to coronavirus patients with diabetes, overweight, or obese, and they must also ensure that the target glucose level and body weight are achieved. Considerations also need to be given to certain glucose control medications that have impacts on the progression.

During inpatient care, patients with diabetes tend to have a higher possibility for ICU admissions (Lei et al., 2020). Similarly, the fatality rate has also increased from 2.3% to 7.3% among people with the disease. Several studies have reported that factors, such as age, CRP, myoglobin, ALT, AST, and tachypnea (RR>24/min) increased the risk of ICU admission18. A popular hypothesis believes that there is a higher expression of ACE2 receptors among patients with diabetes. Herman-Edelstein et al., (2021) also observed the expression in the heart, and it was significantly higher in patients with the disease. Furthermore, it was observed that the expression in the heart was strongly determined by glycosylated hemoglobin (HbA1c), body mass index (BMI), and activation of the renin-angiotensin system (RAS) (Herman-Edelstein et al., 2021). It is also interesting to note that Covid-19 tends to exaggerate the diabetic ketoacidosis condition by increasing the glucose and ketone level (Wallett et al., 2021). Another significant aspect is the immune reactions among people with diabetes when they are infected with the virus. These reactions tend to be different from "normal", and this matter is further discussed in the following section.

Immune reactions among diabetes patients towards Covid-19 infection

Diabetic patients with Covid-19 were admitted and they have a wide range of clinical manifestations from mild to severe, and from stable to severe life-threatening conditions. Some centers reported that their condition worsened during admission, such as Yan et al., (2020) which observed that patients had more chronic underlying diseases and more serious conditions after they were hospitalized. Considering the referral system and the development

of a new community center, which vary among countries, these data can be unique and only represent the area where it was collected.

There are several mechanisms with which diabetes accelerates Covid-19 progression and worsens patients' outcomes. Furthermore, the chronic-uncontrolled level of the disease impairs their immune system (Fauci et al., 2014), which then suppresses the ability to adequately respond to the virus. Patients are also more prone to bacterial infections during coronavirus propagation (Peric & Stulnig, 2020). Since diabetes involves chronic inflammation and procoagulant state, an enhanced innate immune system is triggered to develop inflammatory reactions (Pugliese et al., 2020). Therefore, it is normal for diabetic patients with Covid-19 to demonstrate increased inflammatory signs in many different organs. Yan et al (2020) reported that there was an increase in the inflammatory index along with the disorders of glucose and lipid metabolism21. Mirsoleymani et al., (2021) also revealed that an increased neutrophil count during admission as well as decreased lymphocyte, initial C reactive protein, and serum creatinine are predictors of mortality among the patients (Zhao et al., 2020). Several studies have reported that an increase of 1,000 blood neutrophils per microliter increases the risk of developing severe coronavirus conditions by 1.23 folds (Zhao et al., 2020).

The hyperinflammatory conditions of the patients are facilitated by the overproduction of several proinflammatory cytokines, which lead to an increased level that is also called "cytokine storm" (Zhao et al., 2020; Zheng et al., 2021). Furthermore, this condition can be expressed along with an advanced degree of pneumonia, and Yan et al (2020) reported that Covid-19 patients with the comorbid tend to have more significant pulmonary inflammation, lesions, and their pulmonary lobes are greatly affected. This finding is consistent with several hematological studies, which also support the hyperinflammatory condition. The white blood cells level, procalcitonin, C reactive protein, and erythrocyte sedimentation rate are some inflammatory parameters that increase among patients with the comorbidity (Yan et al., 2020).

The immunosuppressive effect of chronic diabetes is related to lymphopenia, which also correlates with lymphocyte dysfunction and disease severity (Lisco et al., 2020; Sun et al., 2020). However, aside from the exaggerated inflammation, it was also observed that the expression of antibodies towards the virus has not been significantly affected by diabetes. As initially investigated by Pal et al., (2020) and further study by Lampasona et al., (2020), it was reported that there was a marginal and negligible difference in the antibodies expression among people with/without the comorbid (Lampasona et al., 2020; Pal et al., 2020). Furthermore, this suggests that an exaggerated inflammation is the key mechanism of worse clinical outcomes and increased mortality. People with diabetes have the same advantage of receiving Covid-19 vaccination with nondiabetics.

The comorbid has also been strongly linked to poor outcomes, hence, affected patients are very likely to benefit more from the vaccination. However, the humoral responses among people with diabetes towards the infection remain underexplored. Lampasona et al (2020) stated that most of the response-related studies were based on observations and they also used laboratory findings to identify the correlations between variables. Therefore, there is an urgent need for a direct study on humoral immunity responses parameters, which is expected to serve as fundamental underpinnings for future vaccination improvement among comorbid patients.

A study of 509 patients using a novel assay that is based on the luciferase immunoprecipitation system (LIPS) discovered that people with diabetes showed no significant difference in humoral response compared to patients without the disease (Lampasona et al., 2020). No profound difference was observed in terms of timing and antibody tits, and there was also no significant correlation between the response and

hyperglycemia. However, the authors were certain that hyperglycemia is a strong determinant for poor outcomes and increased mortality rate in diabetic and non-diabetic patients (Lampasona et al., 2020). This phenomenon was further described by Lisco et al., (2020), which stated that it weakens NK cells activity, and decreases the activation of macrophage and phagocytosis.

Glycemic response and the interaction of Covid-19 towards diabetes therapies

Until now, it remains unclear whether poor glycemic control is a risk factor for worsening of Covid-19 among patients with comorbid diabetes. As contemplated by Pugliese et al (2020), large-scale studies also obtained inconsistent results. Some studies suggested that the comorbid with better blood glucose control had lower mortality rate. Meanwhile, a large-multi center study in France showed that glycemic control was not associated with the composite outcomes including the death rate, and mechanical ventilation needs (Pugliese et al., 2020).

It is worth noticing that Covid-19 has a diabetogenic effect due to its direct effect on metabolic organs including the β cells of the pancreas where it produced emerging hyperglycemia or deterioration of pre-existing diabetes (Angelidi et al., 2020; Lisco et al., 2020). In regards to the virus propagation in the pancreas, clinicians need to be aware that diabetes has been proven to (Lamptey et al., 2020):

- Increase expression of ACE2 receptors
- Reduce T lymphocyte response

A study in China obtained a strong result on immunostaining of ACE2 in the pancreatic islets, and the result describes the diabetogenic effect of coronavirus and explains the occurrence of acute hyperglycemia events (Hussain et al., 2020).

Within the context of Covid-19 patients with diabetics, the primary source of blood glucose instability was the stress response towards the exaggerated inflammatory condition. Furthermore, this situation created a hypermetabolic state, which triggered the release of stress hormones, increased insulin resistance, and accelerated gluconeogenesis. The combination of these pathologic events makes achieving blood glucose targets and maintaining glucose level stability a very challenging process due to variations in the interfering mechanisms.

Apart from the immunologic and metabolic effect of Covid 19 on diabetes, several interactions with medications have also been identified. The first interaction is with chloroquine and its hydroxy analog hydroxychloroquine that has been reported to have potential as a broad-spectrum antiviral drug through its immune modulation and anti-inflammatory effect (Hussain et al., 2020). Several studies also stated that it interferes with glycosylation of cellular receptors of SARS Cov, thereby inhibiting the viral infection. The favorable effect of the drug on diabetes is achieved through the increment of C peptide response, which indicates an improved β cell function. An animal study also observed that it decreases the rate of intracellular insulin degradation, thereby increasing the deposition of the hormone. Furthermore, in clinical trials, the drug was proven to improve glycemic control in decompensated and refractory diabetes patients with Covid 19 (Hussain et al., 2020). It has also been used widely in India to help patients that failed to achieve their glycemic target with two oral agents.

Metformin is another important medication for patients with type 2 diabetes as it serves as the first line of oral intervention30. However, Gao et al., (2020) reported that it produced life-threatening events, increased the risk of disease progression during hospitalization, and ICU

admission rate. Peric & Stulnig, (2020) also stated that the use of the drug must be carefully considered due to its potential life- threatening adverse effects.

Implications to health practice

With the existing evidence, which demonstrated that there are certain connections between Covid-19 and diabetes, several adjustments need to be developed to improve clinical outcomes. These include early screening for significant risk factors, development of evidence-based management protocol for patients at risk, as well as creating planning protocol to optimize patient care after they are discharged. Furthermore, clinical pathways must be adjusted along with certain administration procedures, personnel allocation, and other physical resources, but the process is challenging and demands the creation of new improvisations. This effort is expected to provide optimal care for each unique patient condition, and in this case, Covid-19 patients with diabetes.

It is also important for clinicians, especially nurses to be sufficiently knowledgeable about all risk factors, but this can be overwhelming. Therefore, a job and knowledge division is essential to ensure that the right person is in charge of treating the patient. The sudden and forceful nature of the pandemic made it impossible for hospitals to develop new and specialized units where patients with their unique comorbidities can be treated. However, improvising more on the human resource and software sectors can solve this challenge. Appreciating the preexisting skills of nursing staffs and updating them with Covid-19 skills as well as its interaction with certain diseases relevant to their expertise can improve the treatment given. These steps can help hospitals to create a group of nursing staff that is knowledgeable in treating patients and can work together with respective specialist physicians.

Hospitals are the primary source of data collection, analysis, and knowledge development. Therefore, thorough and precise documentation is essential as a cornerstone of care improvements. Every center also needs to be familiar with the "research data collection" mindset, which implies that every step of the treatment process must be well documented. The data must also be recorded in a way that is suitable for data analysis and inferential purposes

Conclusions

This article has provided valuable information about the existing relationship between Covid-19 and diabetes with the highlights on (1) Covid-19 triggers an exponential rise in the systemic inflammatory reaction, (2) patients with diabetes tend to have worse conditions, which is indicated by the increase in ICU admission and mortality rate, and (3) the virus influences the patients' blood glucose stability.

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