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RESEARCH

The Management of Diabetes Mellitus in Patients with COVID-19

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■ Abstract

Coronavirus disease 2019 (COVID-19), an infectious disease caused by novel coronavirus SARS-CoV-2, has spread rapidly worldwide and caused more than 110 million confirmed cases and approximately 2.6 million deaths. Diabetes mellitus remains as one of the risk factors of COVID-19 infection. As diabetic patients possess increased inflammatory responses to infection and heightened angiotensin II, it is associated with increased severity, morbidity, and mortality of COVID-19 infection. COVID-19 infection with acute respiratory syndrome itself can be a deteriorating cause for diabetes patients considering that infection may have immediate detrimental effects on the activity of ß-cells and precipitate the metabolic complications. The continuation of usual anti-hyperglycemic medications is suitable in most COVID-19 infected patients who are in good general condition with a normal oral intake. However, insulin is mainly recommended for optimal glucose control in hospitalized patients, especially those requiring intensive care. Pharmacists as healthcare professionals should actively participate in educating public about COVID-19 and diabetes management. Pharmacists also play an important role in the management of type 2 diabetes mellitus by giving diabetes self-care education and ensuring sufficient supply of anti-diabetic medications to their patients. This review summarizes the epidemiological trend, pathophysiology, prognosis, risk factors, diagnosis, complications, management and role of pharmacist in diabetes mellitus patient with COVID-19.

Keywords: COVID-19, Diabetes, Disease Management, Pathophysiology, Pharmacist.

1. Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a novel severe acute respiratory syndrome coronavirus (SARS-CoV-2), which was first reported in Wuhan, China since December 2019 [1-3]. Due to the rapid transmission and high infectivity of the virus, it has spread globally, and COVID-19 outbreak was declared as a pandemic by World Health Organization on 11th March 2020 [4]. As of 7th March 2021, the number of infected cases has reached a total of more than 110 million and causes approximately 2.6 million deaths worldwide [5]. It was found that patients with older age and with underlying diseases such as hypertension, diabetes and heart diseases have a poorer prognosis when being infected with COVID-19 [6, 7]. Diabetes mellitus, being one of the most common chronic diseases affecting 422 million people in the world [8], is one of the major risk factors of COVID-19 [9]. Studies have shown that diabetes mellitus leads to a greater severity of complications and is associated with higher mortality rate in COVID-19 patients [9, 10], similar to previous studies on association between diabetes and severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [11, 12]. This could cause deterioration in the clinical progression of both diseases, leading to a poorer clinical outcome. Hence, it is essential to discover optimal treatment approaches to manage diabetes mellitus in COVID-19 patients.

2. Diabetes and COVID-19

2.1. Epidemiology

Diabetes is associated with the increased severity, morbidity, and mortality of COVID-19 infection due to suppressed innate and humoral immune functions in the diabetic patient [13, 14]. Globally, there are 108 million COVID-19 cases as recorded in February and this pandemic burden has led to a total of 2 million deaths which reflects COVID-19 as one of the gravest global worries [15]. Plus, the high prevalence of diabetes is one of the comorbidities of COVID-19 infection, thus the management and the novel therapeutic approach of COVID-19 in diabetics patients is paramount.

In non-Western countries with a low calory diet and high calory output, type 2 diabetes mellitus (T2DM) is less prevalent, on the contrary, T2DM is becoming prevalent in the Western country as obesity and overweight are the

main issues [16]. According to the International Diabetes Federation, the number of diabetics predicted to increase from 366 million to 552 million by 2030. Besides, type 1 diabetes (T1DM) is mostly transpired during childhood and approximately 1 in every four to six hundred children and teenagers has T1DM [16-18].

2.2. Pathophysiology

The primary pathophysiology that engendered the increased infection severity in patients with diabetes mellitus is the heightened inflammatory mechanism by a virus that will elevate the synthesis of the inflammatory mediators such as cytokines, interferon γ, lipopolysaccharides which result in organ damage and multi-organ failure [13, 14]. On top of that, the other mechanisms in the diabetic patient which is deleterious in COVID-19 infection comprised of increased Furin which promotes viral replication, increased Interleukin-6 and compromised T-cell [14].

Besides, there will be the elevation of angiotensin II which engender insulin resistance, hyperglycemia, beta-cell damage, vascular endothelial damage due to the association between ROS and renin-angiotensin-aldosterone system (RAAS) which activated by the virus [13, 14], plus diabetic patient with elevated angiotensin II will be more susceptible to COVID-19 infection [14]. There is also the risk of cardiovascular events, thromboembolism, and disseminated intravascular coagulation (DIC) due to increase clotting components and blood viscosity in infected persons [13].

2.3. Prognosis and Risk Factors

In people with diabetes, the multiple factors that lead to a poor prognosis are gender, age, race, and particularly comorbidities, for instance, respiratory disease, diabetes, hyperglycemia, high blood pressure,

Abbreviations:

COVID-19	Coronavirus disease 2019
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
MERS	Middle East respiratory syndrome (MERS)
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
OGTT	Oral glucose tolerance tests
HbA1c	Hemoglobin A1c
FPG	Fasting plasma glucose
NAAT	Nucleic Acid Amplification Test
RT–PCR	Real-time reverse transcriptase-polymerase chain reaction
SGLT-2	Sodium-Glucose Transport Protein 2
ACEI	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin receptor blocker
NSAID	Non-steroidal anti-inflammatory drug
DKA	Diabetic ketoacidosis
ICU	Intensive Care Unit
GLP-1	Glucagon-like peptide-1
GLP-1Ras	Glucagon-like peptide-1 receptor agonist
DDP4is	Dipeptidyl peptidase-4 inhibitors
SGLT2is	Sodium–glucose cotransporter-2 inhibitors
CDC	Centers for Disease Control and P revention
NICE	The National Institute for Health and Care Excellence
DASH	Dietary Approaches to Stop Hypertension

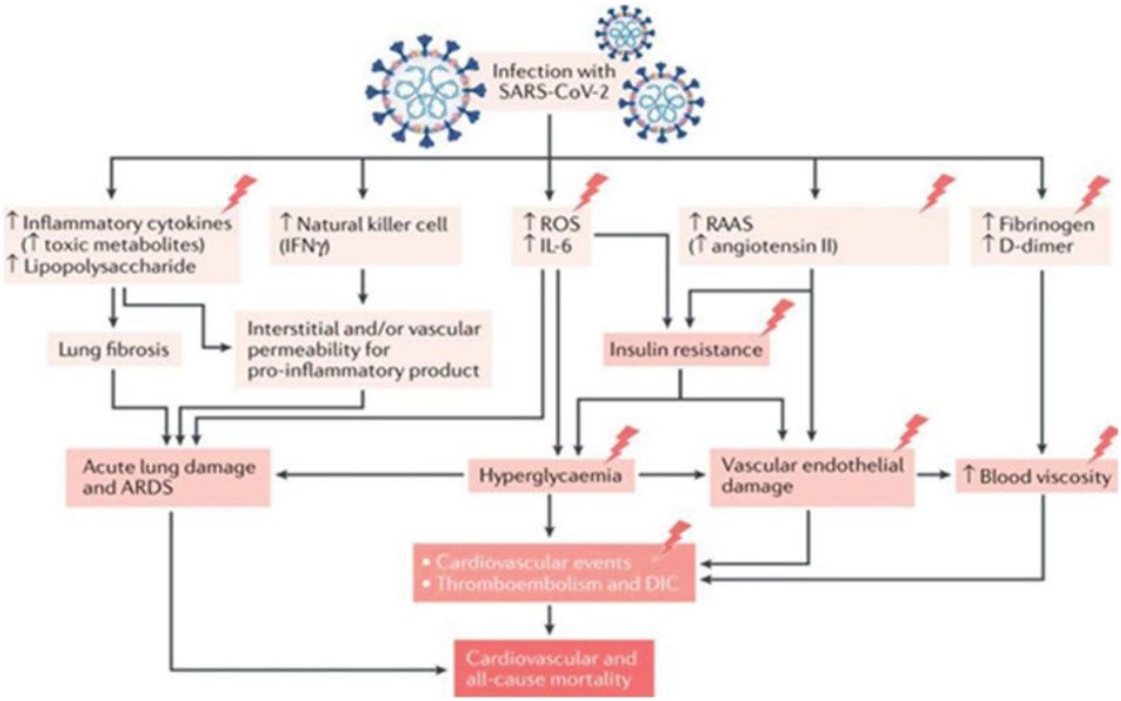

Figure 1: Pathophysiology of COVID-19 and Diabetes [13].

obesity, inflammation and coagulation disorder cardiovascular disease, and other chronic diseases [19-22].

Table 1: Different Age Group and the Risk of COVID-19 Infection [23].

Age (years)	Hospitalization	Death
18-29	Comparison Group	Comparison Group
30-39	2x higher	4x higher
40-49	3x higher	10x higher
50-64	4x higher	30x higher
65-74	5x higher	90x higher
75-84	8x higher	220x higher
>85	13x higher	630x higher

On the contrary, one of the risk factors of COVID-19 is older age. For instance, people with an age more than 85 years will have a 13 times higher risk of hospitalization and 630 times higher risk of death compared to those with 18 to 29 years [23].

Furthermore, people who are suffering from chronic diseases, medical conditions, comorbidities, or critical illness will have a higher risk of getting COVID-19 infection [24]. For instance, the medical condition comprised of T2DM, smoking, obesity with BMI >30 kg/m^2,

immunocompromised status, organ transplant, cardiovascular conditions (cardiac failure, coronary artery disease, cardiomyopathies), chronic obstructive pulmonary disease, cancer, chronic kidney disease, down syndrome, pregnancy, sickle cell disease, etc. [24]. Moreover, the patient who is more susceptible to COVID-19 infection also included those who is associated with hospitalization, ICU admission with mechanical ventilation or intubation [24].

2.4. Diagnosis and Symptoms

The diagnosis of the three main types of T1DM, T2DM, and gestational diabetes are random plasma glucose ≥200 mg/dl (11.1 mmol/l), 2-h plasma glucose OGTT ≥200 mg/dl (11.1 mmol/l), HbA1c≥6.5%, and FPG ≥126 mg/dl (7.0 mmol/l) [25]. The hyperglycemia symptoms are polydipsia, weight loss, polyuria, blurred vision, polyphagia, impaired growth, predisposition to infections, etc. [25].

Conversely, the symptoms of COVID-19 will appear within 14 days after coronavirus exposure and are comprised of fever or chills, fatigue, muscle or body aches, cough, shortness of breath or difficulty breathing, headache, the new loss of taste or smell, sore throat, congestion or runny nose, nausea, vomiting, diarrhea, etc. [26]. Furthermore, COVID-19 is diagnosed by several methods including nucleic acid amplification (NAAT), antibody-based immunoassay, antigen-based immunoassay, clinical tests, RT–PCR, etc. [27].

2.5. Complications

COVID-19 infection with acute respiratory syndrome itself can be a deteriorating cause for diabetes patients considering that infection may have immediate detrimental effects on the activity of β-cells and precipitate the metabolic complications [20]. This complication may engender diabetic ketoacidosis, hyperglycemia which may require hospital admission, and new onset of diabetes [20].

Besides, the type of complication that associated with long term diabetes is microvascular complications and macrovascular complications. Microvascular complications comprised of inflammation caused by high-sensitivity C-reactive protein, diabetic nephropathy caused by meprins are metalloproteinases, diabetic peripheral neuropathy, diabetic retinopathy which will lead to blindness [28]. On the contrary, macrovascular complications consisted of peripheral artery disease, diabetic foot ulcers, chronic ischemic pain, stroke [28]. Other complications such as severe hypoglycemia, hyperglycemia, diabetic ketoacidosis are also life-threatening in diabetes patients [28].

3. Management of T2DM in COVID-19 Patients

3.1. Treatment Algorithm During Admission

There is a higher risk of hyperglycemia with ketones in a diabetic with COVID-19 infection especially those on an SGLT-2 inhibitor, plus the clinical presentation such as mixed diabetes ketoacidosis and hyperosmolar states will also exacerbate. Thus, the suggested action for early admission is glucose and ketones level monitoring, SGLT-2 inhibitors and metformin cessation, ACEI, ARB and NSAID used to review, 10-20% glucose use where ketosis persists despite treatment in line with usual protocols [29, 30].

If the patient with diabetic ketoacidosis or hyperosmolar states is severely ill on admission and have "lung leak" or myocarditis, the circulating volume should restore and the fluid replacement rate should change, diabetes specialist and critical care team should involve early [29]. In the case where insufficient infusion pumps in inpatient settings, alternative subcutaneous regimens with basal insulin support are used in the management of hyperglycemia and mild DKA [29, 30]. In the ICU setting, there will be higher insulin resistance in people with T2DM and a higher dose of insulin is needed [29, 30]. There is a need in changing IV insulin protocols for people who need up to twenty units/hr. Plus, the interrupted feeding in patients with prone position will heighten hypoglycemia risk [29, 30].

3.2. Use of Anti-diabetic Drugs in Patients with COVID-19

***Insulin*:** Insulin is a safe choice under most circumstances and is considered as a superior alternative in people with T2DM having poor glycemic control [31]. Insulin has beneficial effect by suppression of pro-inflammatory cytokines as it was found to exert anti-inflammatory action in humans and reduces biomarkers of inflammation in hospitalized individuals with critical illness [32]. Sardu et al. showed that insulin use achieved better glycemic control in 25 diabetic patients with COVID-19 as post-treatment plasma glucose was significantly lower in the insulin-treated group [32]. Moreover, in a study of whom 203 patients admitted at ICU were affected by diabetes, intensive insulin therapy significantly reduced the rate of morbidities, including newly acquired kidney

injury and the need of mechanical ventilation, with accelerated discharge from the ICU and the hospital [33]. Thus, insulin should be used in diabetic patients with COVID-19 to improve glycemic control, especially hospitalized patients. An intensive regimen with basal and prandial insulin analogues is recommended for non-critically ill hospitalized patients with good or poor nutritional oral intake [34]. In general, the use of insulin associated with continuous glucose monitoring should be the first-choice treatment for hyperglycemia in hospitalized patients to reduce exposure of health-care workers to coronavirus [33, 34].

Metformin: Metformin remains the first-line pharmacological treatment for management of hyperglycaemia in T2DM. As metformin exerts anti-inflammatory effects beyond its glucose-lowering action, it is hypothesized that metformin may positively influence the prognosis of patients with T2DM hospitalized for COVID-19 and reduce the risk of severe COVID-19 [35]. Furthermore, metformin can achieve the phosphorylation of ACE2 receptor which is vital in SARS-CoV-2 entry into the cells [32]. Consequently, the binding capacity of the virus is reduced due to steric hindrance by incorporation of phosphate molecule [32]. Thus, metformin may be considered beneficial in COVID-19 infection as it inhibits the viral entry into the cell [32]. Despite these beneficial mechanisms, metformin is not recommended in the clinical management of critically ill patients with COVID-19 infection [13, 32]. This is due to the risk of lactic acidosis particularly with organ dysfunction, which may ensue in diabetic patients with dehydration from acute viral infection and worsen hyperglycemic emergencies in hospitalized patients [32, 36]. Worsening dehydration may also result in prerenal acute kidney injury [32]. In brief, metformin requires close monitoring for lactic acidosis in the presence of respiratory illness, hypoxia and acute kidney injury [37].

***Sulfonylureas*:** Sulfonylureas are not ideal in the management of hyperglycemia in patients with severe COVID-19 [34]. Due to poor caloric intake in acute infections, the use of sulfonylureas should be held as it may induce hypoglycemia for at-risk patients especially in ICU admissions [32, 36, 38].

***Glucagon-like peptide-1 receptor agonist*:** Glucagon-like peptide-1 receptor agonist (GLP-1RAs) are effective glucose-lowering injective drugs [34]. Physiologically, glucagon-like peptide-1 (GLP-1) release is increased in response to enteral nutrients to stimulate insulin secretion and contributes to glucose homeostasis [34]. GLP-1 is also released in response to inflammatory stimuli to attenuate inflammatory response [34]. Preclinical studies demonstrated that GLP-1RAs attenuate pulmonary inflammation, reduce cytokine production, and preserve lung function in mice and rats with experimental lung injury [38]. It is also well established that GLP-1RAs are associated with the beneficial effect in prevention of cardiovascular and kidney disease in diabetic population [13]. Therefore, GLP-1RAs could be ideal for the treatment of T2DM patients affected by COVID-19 at risk of cardiovascular and kidney disease [13]. Furthermore, GLP-1RAs therapy in the ICU setting is associated with a reduction of hypoglycemia, glucose variability and catabolism by suppressing glucagon which can be protective in critically ill patients [37]. GLP-1RAs are suitable for patients with obesity because they have weight-reducing properties [13]. However, delayed gastric emptying which is common in the critically ill might affect glycemic control [39]. Exenatide-based formulations should be stopped in patients with deteriorating kidney function [38]. Currently, there is insufficient evidence to support or against the use of GLP-1RAs in COVID-19 infection. However, initiating or maintaining GLP-1RAs in severe COVID-19 is not recommended as they take time to be effective and might provoke nausea and vomiting [13].

***Thiazolidinediones*:** The thiazolidinediones are agonists of the peroxisome proliferator-activated receptor-γ, that regulates the transcription of various genes involved in glucose and lipid metabolism [13]. Thiazolidinediones have the potential to mediate protective effects on the cardiovascular system. In a review of RCTs that compared thiazolidinediones with placebo for the secondary prevention of stroke and related vascular events in people who experienced stroke or transient ischemic attack, thiazolidinedione treatment reduced the recurrence of stroke compared with placebo [13]. However, thiazolidinedione therapy has the potential to induce weight gain and oedema and was associated with aggravation of heart failure [13]. Clearly, the tendency to cause fluid retention and worsen heart failure do not support the use of thiazolidinedione in patients with COVID-19 [32].

Dipeptidyl peptidase-4 inhibitors: Dipeptidyl peptidase-4 inhibitors (DDP4is) are one of the most frequently prescribed medications without serious adverse events [13]. Current evidence does not suggest safety issues associated with the use of DPP4is in patients with T2DM and COVID-19. In a retrospective case-control study, sitagliptin treatment during hospitalization was associated with reduced mortality and improved clinical outcomes in such patients [40]. In a meta-analysis of multiple DDP4is trials encompassing 23456 study participants with T2DM treated with a DPP4 inhibitor compared with 15300 control, no increased risk of infection was detected in subjects treated with DPP4 is [38]. Additionally, results of large trials examining the safety of saxagliptin, alogliptin, sitagliptin and linagliptin in humans with T2DM at risk for cardiovascular or renal disease did not reveal clinically relevant safety concerns related to infections, immune, or inflammatory disorder [38]. Therefore, DDP4is can be recommended for use in most patients with a broad spectrum of severity of COVID-19 [13]. In individuals with active COVID-19 infection and clinically significant volume depletion or systemic sepsis, a reduction in renal function may require dose adjustment for some DDP4is [38].

Sodium-glucose cotransporter-2 inhibitors: Sodium–glucose cotransporter-2 inhibitors (SGLT2is) act on the

kidney to reduce blood levels of glucose [13]. SGLT2is have profound effects on urinary glucose and sodium excretion, resulting in osmotic diuresis and potentially worsen dehydration, and increased urinary uric acid excretion, which has been suggested to be a risk factor for acute kidney injury [13]. Although SGLT2is are generally well tolerated in the outpatient setting, the use of SGLT2is may be difficult in patients under critical care, who need meticulous control of their fluid balance [13]. Holding of SGLT-2is should be considered in patients at risk of dehydration, especially those who cannot maintain adequate fluid intake [36]. In addition, these drugs must be discontinued during reduction of estimated glomerular filtration rate, which limits their glucose-lowering effects and will be a risk in critically ill patients [13]. Furthermore, SGLT2is treatment can cause euglycemic ketoacidosis, especially in critically ill patients [13]. As such, the use of SGLT2is is not recommended in patients under critical care as euglycemic diabetic ketoacidosis and genitourinary infections would be impractical during the COVID-19 pandemic [37].

4. Role of Pharmacist

In this pandemic, pharmacist as a healthcare professional plays an important role in managing the disease. Due to the sedentary lifestyle following restrictions on outdoor activity, there is expected increase trend of uncontrolled blood sugar level among diabetes patients [41]. To add, social distancing gives a negative effect on the self-management of diabetes. In this situation, pharmacist should actively participate in educating public about COVID-19 and diabetes management. As a healthcare provider who understands how COVID-19 can spread, pharmacist should encourage public to do social distancing and wear mask in crowded area to prevent the spread of the virus. This is recommended by many healthcare organisation like CDC and NICE [42].

Besides, pharmacist also can educate and give support on the self-management of diabetes. The accessibility of pharmacist compared to other healthcare professional provides an opportunity to enhance the patient care in managing diabetes [43]. Pharmacist can advise diabetic patient to do physical exercise at home and adhere to DASH diet to control the blood sugar level. Pharmacist can also monitor the blood sugar level and counsel patients on the therapy change if needed. If face-to-face visit is not possible, these activities can be done by telehealth services such as video conference. This will provide more flexibility and convenience for patient to receive continuous care and reminder from the pharmacist [42]. With an increase of pharmacist involvement in self-care, there will be increase in the adherence to the diabetes pharmacotherapy [41].

Another role of pharmacist is to manage drug shortage. Pharmacist should make sure the medication stock and other medical device in pharmacy is enough to supply the demand. In the diabetes patient situation, pharmacist need to make sure their prescription refilled and prepared with testing supplies to monitor blood glucose level [44]. To reach these objectives, pharmacists are expected to extend the scope of medication service such as home delivery service and drive-through pharmacy. These new services open the opportunity to expand the pharmacy business as well as improving the existing service. Pharmacist also need to assess and follow and integrate the updated information and emerging evidence regarding COVID-19 and diabetes into the clinical practice [41]. In clinical setting, pharmacist can continue to ensure the patient receiving safe and effective medication and recommend appropriate pharmaceutical care plan to other healthcare professionals [42]. Therefore, in this pandemic situation, pharmacist plays an important role in educating the public and involvement in diabetic patient care.

4.1. Conclusion

In conclusion, T2DM remains one of the challenging risk factors of COVID-19 exposure and severity. Proper management of T2DM in COVID-19 patients could reduce the risk of mortality and prevent further complications of T2DM. As the COVID-19 infection crisis has not been successfully halted, self-care is the utmost importance for diabetic patients in reducing the risk of COVID-19 exposure. Pharmacists play an important role in giving diabetes self-care education and ensuring sufficient supply of anti-diabetic medications to their patients. To date, vaccines of COVID-19 have been successfully developed and distributed out to the whole world population. Vulnerable population such as frontliners and patients with comorbidities are at the highest priority to accept vaccination. It is hoped that the development of vaccines could give protection to the people and bring this enraging pandemic to a halt.

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