Management of Diabetes Patients during COVID-19

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Bachelor of Pharmacy (Honors)

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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Approval

The thesis titled “Management of Diabetes Patients during COVID-19” submitted by G. M. Golam Mehebub Pantho (16346023) of Summer 2016 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelors of Pharmacy (Honors)

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Ethics Statement

This study does not involve any human and animal trial.

Abstract

During COVID-19 pandemic, people with diabetes are up to three times more prone to become seriously ill or die from COVID-19 than others, as they are more susceptible to infections, vascular complications, comorbidities such as hypertension, dyslipidemia, cardiovascular disease and particularly to impaired immune function. Based on current medical and scientific evidence the rational use of oral hypoglycemic agents, ketone level measurement, plasma glucose monitoring, electrolytes test are essential in case of managing diabetes in COVID-19 pandemic for both in-patients and out-patients. The contribution of pharmacists for confirming better adherence to the diabetes pharmacotherapy and positive clinical outcomes, as well as teleconferencing to bridge the gap between geographical locations, and the role of pharmacovigilance has been identified as extremely important in this pandemic. Therefore, this paper aims to explain an overview of COVID-19 disease and its interrelationship with diabetes, possible treatment strategies as well as proper guidelines to manage diabetes.

Keywords: Diabetes, COVID-19, Insulin, Teleconferencing, Pharmacovigilance, Comorbidity, Coronavirus.

Dedication

This project is dedicated to Dr. Eva Rahman Kabir ma’am.

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List of Acronyms

WHO	World Health Organization
COVID-19	Coronavirus disease-2019
SARS-CoV-2	Severe acute respiratory syndrome
CDC	Centers for Disease Control and Prevention
T1D	Type 1 diabetes
T2D	Type 2 diabetes
DM	Diabetes mellitus
CSII	Continuous Subcutaneous Insulin Infusion Therapy
TZDs	Thiazolidinediones
GLP-1	Glucagon-like peptide 1
MERS	Middle East Respiratory Syndrome
ACE2	Angiotensin-Converting Enzyme 2
RAAS	Renin Angiotensin Aldosterone System
FLD	Fatty liver disease
BMI	Body Mass Index

ARDS	Acute Respiratory Distress Syndrome
DPP-4	Dipeptidyl peptidase 4 inhibitor
DKA	Diabetes ketoacidosis
HHS	Hyperosmolar hyperglycemic state
SGLT2	Sodium-glucose like-transporter 2
PV	Pharmacovigilance
ARBs	Angiotensin II receptor blockers

Chapter 1

Introduction

Coronavirus disease-2019 (COVID-19) has spread rapidly over 222 countries due to severe acute respiratory syndrome (SARS-CoV-2) and 81,475,053 cases have been recorded including 1,798,050 deaths as reported by WHO (Erener, 2020). In the 2019 coronavirus disease (COVID-19) pandemic, 20-50 percent of COVID patients were diabetic, with variations observed due to geographical location, since diabetes is a major comorbidity related with the severity of all human pathogenic coronavirus infections that involves severe acute respiratory syndrome coronavirus 2 (Bornstein et al., 2020). As Centers for Disease Control and Prevention (CDC) is continuing to update new information about COVID-19, depending on their current report, there might be an elevated risk of severe illness from COVID-19 disease for patients with type 1 or gestational diabetes (American Diabetes Assosiation, 2020). People with diabetes-related health conditions are more likely to be affected by COVID-19 than healthy people who are otherwise associated with diabetes (American Diabetes Association, 2020).

Diabetes is a chronic illness and diabetic patients compare to healthy individuals are more susceptible to infections, vascular complications, comorbidities such as hypertension, dyslipidemia, cardiovascular disease and more importantly to impaired immune function. This impaired immune function is caused by decreased T cell–mediated immune response and compromised neutrophil function noticeable among diabetic patients (Muller et al., 2005) (Jeong et al., 2020). Clinical studies provide limited and ambiguous evidence for a strong correlation between diabetes and common infections. Some studies have shown that both common and rare

infections are more prevalent between patients with diabetes than non-diabetics, whereas other studies have not observed such an association (Muller et al., 2005).

1.1 Aim

The project is a study of the patients with comorbidities such as diabetes, prone to getting infected by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) (Bornstein et al., 2020). This project aims to suggest the management of diabetic patients during and post COVID-19. This study should be upgraded as more medical and scientific evidence becomes accessible.

1.2 Objectives

- To study COVID-19 disease and its relativism with diabetes.
- To discuss common anti diabetic medicines impact on COVID-19 patients having diabetes.
- To recommend possible treatment strategies and medication management.
- To summarize the overall health conditions of a diabetic patient.
- To suggest proper guidelines to follow in case of managing diabetes during a pandemic such as COVID-19.

1.3 Rationale:

Diabetic patients, specifically the elderly patients with macro vascular and micro vascular complications are more vulnerable to COVID-19. Rational use of oral hypoglycemic agents for diabetic patients during COVID-19 is a crucial decision to make for both in-patients and out-patients. Thus, following World Health organization (WHO) guidelines and clinical and medication management can decrease the chance of COVID-19 infection as well as result in speedy recovery from the disease.

Chapter 2

Methodology

To meet the aim, objective and rationale of the study secondary data was collected from several search engines such as PubMed, Elsevier, Nature, and Springer Link and other authentic and relevant articles and guidelines. The research was conducted by case study analysis, narrowing articles by fixing the focus and evaluating various health related websites. The information collected were precisely compiled and referenced to provide a comprehensive understanding of diabetes, management of diabetes, COVID-19 and management of diabetes during this pandemic. Most of the articles from which the information was collected are recent articles that include the up to date information. In addition, for further applicable research, reference lists were screened and systematic reviews were searched for suitable references.

Chapter 3

Management of diabetes

Diabetes is a metabolic and long-lasting disease recognized to cause elevated levels of blood glucose, leading to significant damage over time to the skin, kidneys, heart, nerves, and blood vessels (World Health Organization, 2020). In the National Diabetes Statistics Report for 2020, the Centers for Disease Control and Prevention (CDC) claimed that, 34.2 million cases of diabetes are found among the U.S. population, while in Bangladesh, the International Diabetes Federation evaluate 7.1 million people with diabetes (Mohiuddin, 2019) (Statistics, 2020). In the pancreas if autoimmune-mediated destruction occurs of insulin-producing β-cells then the condition is known as Type 1 diabetes (T1D). Type 2 diabetes (T2D) is a metabolic condition involving both insulin resistance and β-cell insulin secretory defect which eventually results in β-cell fatigue and destruction in the longer run (Erener, 2020).

The World Health Organization's (WHO) diagnostic procedure for diabetes mellitus includes a fasting plasma glucose level of 126 mg/dL (7.0 mmol/L) or a plasma glucose level of 200 mg/dL (11.1 mmol/L) after an oral glucose load of 75 g. However, WHO recently proposed one additional requirement as the cut-off point for diagnosing diabetes, such as a glycated hemoglobin level of 6.5 percent. If two hours plasma glucose level is 140 mg/dL (7.8 mmol/L) and less than 200 mg/dL (11.1 mmol/L) after a 75 g oral diabetes level then the condition is known as impaired glucose tolerance which is a state of intermediate hyperglycemia with an elevated risk of development to frank diabetes. A fasting glucose level of 110 mg/dL to 125 mg/dL (6.1-6.9 mmol/L) is characterized as impaired fasting glucose (Thomas & Philipson, 2015).

Table 1: Diagnostic protocol for diabetes mellitus

Blood sugar classification	Fasting	2 hours after eating	Glycated hemoglobin
Diabetic	(126-200 mg/dL) or (7.0-11.1 mmol/L)	126 mg/dL and above	≥ 6.5 %
Impaired glucose	(110-125 mg/dL) or (6.1-6.9 mmol / L)	(140-200 mg/dL) or (7.8-11.1 mmol/L)	6.5 %

Diabetes can lead to macro vascular complications such as peripheral arterial disease, coronary artery disease, stroke, as well as micro vascular complications including diabetic retinopathy, neuropathy, and nephropathy (Fowler, 2008). Early diagnosing of diabetes and ensuring efficient treatment is a must in order to avoiding life threatening complications. Firstly, diabetic along with non-diabetic patients require enough knowledge regarding this disease, otherwise it can be risky for them. For instance, delayed diagnosis and insufficient treatment of glycaemia and other risk factors often occur among the South Asians with type 2 diabetes, leading to micro-vascular and macro-vascular complications (Misra et al., 2018). Secondly, approximately 80% of type 2 diabetic patients are obese when diagnosed with insulin resistance, and drugs are required to manage blood glucose levels in such situation. Proper education regarding healthy and balanced diet as well as guidance on weight loss is required which can be done by increasing physical activity and calorie limitation. Most importantly, exercise and dietary measures are not sufficient enough to control glucose level and oral glycemic therapy is needed for more than 75% type 2 diabetic patients. They have other components of the metabolic syndrome, including hypertension

and dyslipidemia. Thus, an effective antihypertensive and lipid-lowering regimen is essential to proceed in these patients (Bornstein et al., 2020). Biguanide, Sulphonylureas, meglitinides, α-glucosidase inhibitor, thiazolidinedone are the common classes of ant diabetic drugs are available. Nevertheless insulin therapy is required for type 1 diabetic patients (Walker, 2012).

Treatment options for diabetic patients

Before the discovery of insulin, researchers noticed that carbohydrates intake raised glucose levels even though animal products consumption resulted in lowered the level of glucose (Blaslov et al., 2018). As a result, protein enriches diet along with low carbohydrate and high fat intake was the basis of Diabetes mellitus (DM) treatment. However, until 1900s there was no pharmacological treatment options available for type 2 DM. During the century, an enormous number of insulin and oral hypoglycemic agents witnessed rapid advance of their production (Blaslov et al., 2018).

3.1 Non pharmacological approaches

Despite several changes in the perception of diet and physical activity over past twenty years, they still characterize as two basic treatment strategies for type 2 DM alongside pharmacological treatment and possibly can remain so in the future (Blaslov et al., 2018). To reduce the risk of death of diabetic patients, fasting diet in combination with modest physical activity on a regular basis could be effective (Blaslov et al., 2018).

Dietary management is the cornerstone of type 2 diabetes and plays an essential role in type 1 dia betes management (Walker, 2012). In case of type 1 diabetes, if premeal regular insulin is adjusted to the carbohydrate content of the meals, raising the level of carbohydrate consumption does not affect glycemic control (Effects of Meal Carbohydrate, 1999). The guidelines for carbohydrate consumption are about to same for both type 2 diabetes and type 1 diabetes. Considering the total calories, around 60 to70 percent should be composed of monounsaturated fats and carbohydrates (Fowler, 2007). However, obese patients with type 2 diabetes are at risk to gain weight from excessive intake of unsaturated fat. Eventually this condition can reduce insulin sensitivity (Fowler, 2007).

Protein consumption can be the reason of hyperglycemia for type 1 diabetic patients who are treated with long term continuous subcutaneous insulin infusion (CSII) therapy as they are able to convert amino acids into glucose (Fowler, 2007). Protein requirements for type 2 diabetic patients may be greater to some extent than non-diabetic individuals because protein degradation seems to be worsened by hyperglycemia and they exhibit more negative nitrogen balance (Fowler, 2007).

Dietary fat consumption guidelines are same for both diabetic and coronary artery disease patients. The risk of myocardial infraction is higher in diabetic patients, so it is essential to balance trans fatty acids, saturated fatty acids, cholesterol intake. Considering the total calories, trans fat must be reduced, dietary cholesterol level must be restricted to less than 200 mg/day and saturated fat should be limited to less than 7% in order to reduce the risk of cardiovascular disease of individuals with diabetes (Association, 2007).

In case of physical activity, type 1 diabetic patients having good control of blood glucose and no complications, can carry out all forms of physical activity. Numerous studies suggest that, regular physical activity for 3-4 times a week with an intensity of 50–80% V_{o2max} (V_{o2max} = maximum

oxygen consumption rate measured throughout incremental exercise) for 30–60 minutes at a period, is effective for insulin sensitivity and carbohydrate metabolism (American Diabetes Association, 2004). Changes in HbA1c are normally 10-20 percent of the baseline also notable in moderate type 2 diabetic patients and who are more prone to insulin resistant (American Diabetes Association, 2004).

Table 2: Dietary management of two types of diabetes

Nutrients	**Current guidelines**	
	Type 1 diabetes	**Type 2 diabetes**
Carbohydrates (60-70 % of total calories)	If pre meal regular insulin is adjusted to the carbohydrate content of the meals, raising the level of carbohydrate consumption does not affect glycemic control.	Increased intake of unsaturated fat can encourage weight gain in obese patients and thus reduce insulin sensitivity (Fowler, 2007).
Proteins	Converting amino acids into glucose thus protein consumption may cause hyperglycemia because of long-term treatment of continuous subcutaneous insulin infusion (CSII) therapy (Fowler, 2007).	Protein requirements for type 2 diabetic patients may be greater than non-diabetic individuals as protein degradation seems to be worsened by hyperglycemia and they exhibit more negative nitrogen balance (Fowler, 2007).

Fats Reduce risk for cardiovascular disease (Association, 2007).	Considering the total calories, trans fat must be reduced and saturated fat should be limited to less than 7 %	Effective insulin sensitivity has been observed in case of replacing trans fatty acids and saturated fats with unsaturated fats (Risérus et al., 2009).

3.2 Pharmacological approaches

Insulin is known as the origin of pharmacological treatment for diabetes mellitus. After that the discovery and development of biguanides are recommended as first line treatment option as oral hypoglycemic agent. The next class of oral glycemic agents is sulfonylureas (SUs). In the midst of 1990, Thiazolidinediones (TZDs) class of drugs was launched to the market. This class of drugs are peroxisome proliferator-activated receptor-γ activators that activate this particular cell surface receptor and improves the sensitivity of skeletal muscle insulin and decreases the development of hepatic glucose. This makes TZDs longer lasting compared to metformin. It was a matter of concern for the researchers to develop dipeptidyl-peptidase inhibitors as these class of drugs had extended circulating half-life of endogenous incretine. Moreover, dipeptidyl-peptidase inhibitors could be taken orally. Noticeably, in post-marketing clinical trials, these medications showed promising performance, and they are now approved as second-line diabetes treatment. In accordance with dipeptidyl-peptidase inhibitor drugs Glucagon-like peptide 1 (GLP-1) analogues also have been established (Blaslov et al., 2018).

3.2.1 Type 1 Diabetes

Type 1 diabetes needs to be treated with insulin. The primary goal of insulin administration is to mimic usual insulin release of human body from pancreatic β-cells to prevent hyperglycemia and long term complications for type 1 diabetic patients. Such patients experience destruction of β-cells slowly than other patients. Otherwise cell mediated immune system eventually results progressive and complete lack of endogenous insulin (A.L. & L.S., 2013) (Jacques, 2015).

Table 3: Different Types of insulin(Bloomgarden, 2006)

Type	Onset of action	Duration of action	Examples
Rapid-acting	10 –20 minutes	2–5 hours	Insulin lispro, Insulin glulisine.
Short-acting	30–90 minutes	6–8 hours	Human sequence soluble insulin
Long-acting	1–2 hours	20–26 hours	Insulin glargine, Insulin detemir
Intermediate acting	30–90 minutes	11–24 hours	Human sequence isophane insulin
Biphasic	10–90 minutes	11–24 hours	Biphasic insulin aspart Biphasic insulin lispro

Every diabetic patients need to know how to monitor blood glucose levels as well as detecting symptoms of life threatening complication such as hypoglycemia (Jacques, 2015). To manage type 1 diabetes standard insulin dose differ from 2 to 5 injections per day (Walker, 2012). The starting dose should be kept low in patients who exercise frequently, to decrease the risk of significant hypoglycemia. A mealtime plus basal regimen can be used to obtain the best control for type 1 diabetes. This method aids to mimic insulin release like usual insulin release of human body than other regimens. It involves fast-acting insulin injections on the time of taking meal with an analogue, plus one or two basal insulin injections and the dose is up to five injections a day (Walker, 2012). In fact, few patients can get advantage by using a pump known as exogenous insulin delivery in which a continuous subcutaneous insulin infusion is administered. This pump system can be controlled according to patients need, for instance it can provide different basal rate of infusion at various times then boluses are delivered at meal time (Walker, 2012). In addition, meal time along with basal regimen provides more advantages like dose adjustment based on carbohydrate consumption, physical exercise and glucose level. Nevertheless, the downside of this combination is that they need multiple injections except the pump is in situ as well as continuous blood glucose checking which is uncomfortable for the patients.

To avoid multiple injections process, premixed insulin is a good solution as it is used in the easiest and most efficient twice-daily regimens. Premixed insulin contains a fast or rapid acting along with intermediate acting insulin. There are analogue mixes and daily mixes of human insulin available. Daily mixes of insulin must be administered thirty minutes prior to breakfast and thirty minutes prior to the dinner. On the other hand, analog mixes need to administer instantly before that two meals. Before breakfast, the portion of insulin mix which is long acting must cover the lunch and evening dose must cover the night. For the maintenance of type 1 diabetes management,

twice-daily regimens are not enough and this method sometimes used in new diabetic patients those that are not acutely sick, including, short acting preparation (Walker, 2012).

According to Svoren, amongst 299 children about 7 to 16 years old type 1 diabetes were tend to infuse higher than two insulin daily together with 0 in contrast with 23 percent by means of continuous subcutaneous insulin infusion (CSII) and 76 in contrast with 88 percent monitoring blood glucose more than twice a day which was compared in 1997 in contrast with 152 in 2002 (Bloomgarden, 2006). Several insulin doses or pump therapy and make use of more routine glucose monitoring, has increased glycemic regulation and lowered utilization of emergency rooms as well as hypoglycemia rates which indicates A1C was 8.7 contrast with 8.4 percent, the incident of hypoglycemic about 55 contrast with 29 and for emergency room the visits were 29 contrast with 22 (Bloomgarden, 2006).

3.2.2 Type 2 Diabetes

More than 75 percent patients having type 2 diabetes required oral hypoglycemic therapy as physical exercise, dietary measures cannot control blood glucose level for a long run.

Table 4: Classes of oral agents (Walker, 2012)

Therapeutic Class	Available drugs
Biguanide	Metformin
Sulphonylureas	glibenclamide, gliclazide, glimepiride, glipizide, tolbutamide

Meglitinides	repaglinide and nateglinide
Thiazolidinedione	pioglitazone
O-Glucosidase inhibitor	acarbose
Dipeptidyl peptidase-4 inhibitors	saxagliptin, sitagliptin and vildagliptin

Standard-release metformin is preferred as first line drug of choice to treat type 2 diabetic patients. The dose of metformin need to increase gradually over more than a few weeks to minimize gastrointestinal adverse reactions. Standard release metformin should be avoided and modified-release metformin is appropriate to prescribe the patient if gastrointestinal problems continue. In case of less than 45 ml/minute/1.73m^{2}glomerular filtration rates (eGFR), dose adjustment of metformin is required. Again, when less than 30 ml/minute/1.73m^2 eGFR is found of the patient then this medicine need to be stopped (Martyn, 2006). However, sulfonylurea or dipeptidyl peptidase-4 (DPP-4) inhibitor can be considered as initial therapy when metformin is contraindicated and intolerable. Pioglitazone can be considered as so but it cannot be given or continued to patients having history of heart failure, diabetic ketoacidosis, hepatic impairment, bladder cancer and haematuria (Martyn, 2006).

In order to controlling HbA1c to lower one's separately established threshold for amplification, a combination treatment by means of metformin and a DPP-4 inhibitor or metformin and pioglitazone or metformin and a sulfonylurea can be administered fundamentally, only if the primary drug treatment with metformin has not sustained (Martyn, 2006). Again, a combination therapy by means of DPP-4 inhibitor and a sulfonylurea or pioglitazone and a sulfonylurea or a DPP-4 inhibitor and pioglitazone should be administered, whether metformin is not used and unable to endure, as a result this primary drug treatment has stopped to manage HbA1c to lower

one's separately established threshold for amplification. Furthermore, a combination of trio treatment among metformin, DPP-4 inhibitor and a sulfonylurea or metformin, pioglitazone and a sulfonylurea or insulin-based therapy are supposed to be observed, in case a treatment combined with metformin along with other oral drug are unable to manage HbA1c to lower one's separately established threshold for amplification (Martyn, 2006).

Chapter 4

COVID-19 and its interrelationship with Diabetes

Coronaviruses are a huge group of viruses that cause respiratory infections varying from mild colds to more deadly illnesses, like Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). The most newly revealed coronavirus is responsible for coronavirus disease COVID-19 that was unidentified earlier the outbreak began in Wuhan, China, last year (World Health Organization, 2020). The usual signs and symptoms of COVID-19 are fever, dry cough and malaise. Other symptoms related with COVID-19 which are less frequent and can attack certain individuals that are included pains and cramps, rhinitis, inflammation, pharyngitis, dysentery, ageusia or loss of the sense of smell, hives, finger or toe staining. However, from this infection nearly 80 percent of patients get better without seeking any health treatment. In comparison; only 1 out of 5 patients become seriously ill and have trouble with breathing. People of all ages can be caught and become severely ill by COVID-19, but those who are already affected in hypertension, cardiac and lung disease, diabetes and cancer are most likely to develop COVID-19 (World Health Organization, 2020). As a consequence, everyone should seek medical attention immediately who experience fever and coughing in addition with difficulty in breathing or dyspnea, chest tightness, or laryngitis or motion. The reason of transmitting coronavirus disease is small droplets, typically from the nose or mouth and these droplets are being released by a COVID-19 affected person while coughing, sneezing, or speaking. Droplets are strong, do not move far and drop to the floor easily. Such droplets can drop on some materials like handle, table, railings, etc which we use on a regular basis. People may get contaminated with the virus by handling these objects or surfaces and then get infected by touching their eyes, nose or mouth with

their hands. Hand washing with soap and water on a regular basis or cleaning with alcohol-based hand rub is therefore necessary (World Health Organization, 2020).

People with diabetes as well as suffering from COVID-19 have shown greater death rate and morbidness, compared to people without diabetes (Obukhov et al., 2020). As a result, the rate of severely sickness and death are higher to diabetic people who are suffering from COVID-19. An assessment of U.S. national databases found that individuals infected with SARS-CoV-2 were more likely to have diabetes or chronic lung disorders than adults in the overall populace, including those who did not require hospital treatment, although the incidence of cardiovascular or renal disease was lower (Riddle, 2020).

Based on evidence that, the virus may enter the cells through angiotensin-converting enzyme 2 (ACE2) and it can act as a site for the virus and at the same time the probable function of the Renin Angiotensin Aldosterone System (RAAS) was briefly discussed in two mechanistic studies. In the first study, patients having type 2 diabetes were observed in abnormality of ACE2 as well as other types of RAS proteins in blood, however no modifications have occurred in these proteins, after gradual improvement in blood glucose control by means of insulin. In the second study, diabetes increases the chances of development to serious COVID-19 disease as increased liver expression of ACE2 and the presence of Fatty liver disease (FLD) have been found (Riddle, 2020). As a result, the level of ACE2 can be increased by various drugs for instance antihypertensive, incretin mimetics, lipid-lowering medicine, etc (Erener, 2020). Due to COVID-19, the consequences of diabetes may become more severe which leads to exacerbate the situation because of interruption caused by the pandemic which includes anxiety and routine treatment, physical exercise, lifestyle changes etc (Hartmann-Boyce et al., 2020).

4.1 Infection risk

Over 85,000 patients with diabetes from the United Kingdom show that impaired glucose levels are closely correlated with serious infections, based on epidemiological findings of the primary care database (Guo et al., 2020). It specifies strong correlations between bad diabetes and infection control.

Table 5: Laboratory parameter distinction between COVID-19 diabetic and non-diabetic patients (Guo et al., 2020)

	Normal range	**Median (IQR) Total (n = 174)**	**Non-diabetes (n = 137)**	**Diabetes (n = 37)**	***P*-value** [a]
HBDH (U/L)	72 to 182	190 (146–263)	190 (143.5-251.5)	210 (177-480)	.13
ALT (U/L)	5 to 35	26 (21-37)	25 (17-42)	28 (21-34)	.2
LDH (U/L)	109 to 245	248 (188-362)	241 (187-372.3)	252 (174.5-292.5)	.76
GGT (U/L)	11 to 50	25 (14-51.3)	24 (14-45)	32 (17.5-52)	.19
Lymphocytes ($\times 10^9$/L)	1.1 to 3.2	0.96 (0.7-1.3)	0.97 (0.74-1.3)	0.86 (0.5-1.3)	.04

Neutrophils ($\times 10^9$/L)	1.8 to 6.3	2.7 (1.8-4.6)	2.5 (1.6-3.7)	4.1 (2.8-6.9)	<.01
Red blood cells ($\times 10^{12}$/L)	3.8 to 5.1	4.14 (3.8-4.4)	4.17 (3.8-4.5)	3.9 (3.5-4.2)	<.01
Haemoglobin (g/dL)	115 to 150	124 (115-135)	127 (117-136)	117 (105-123.5)	<.01
C-reactive protein (mg/L)	<8	17.7 (7.34-51.8)	16.3 (7.17-43.9)	32.8 (11.3-93)	.06
Serum ferritin (ng/ml)	21.8 to 275	375.9 (169.5-746.9)	372.6 (185.8-685.8)	594.4 (164-1146.2)	.15
ESR (mm/h)	<15	28 (13-59)	23 (10-49)	67 (47.5-81)	<.01
IL-6 (pg/ml)	0.1 to 2.9	11.75 (5.1-28.2)	11.16 (4.5-25)	18.3 (7.3-37.6)	.07
D-dimer (µg/L)	<0.5	0.67 (0.3-1.4)	0.54 (0.25-1.1)	1.15 (0.83-2.11)	<.01
FIB (g/L)	2.0 to 4.0	4.78 (3.8-5.8)	4.58 (3.7-5.6)	5.1 (4.6-6.3)	.27

Table 5 indicate that diabetic patients having COVID-19 are at higher risk to develop impaired inflammatory responses as well as hyper coagulation, that leads worsen COVID-19 prognosis.

Table 6: Diabetic patients with impaired immune system and consequences

Abnormalities	Impact on diabetic patient	Consequences
Dysregulated Immune Response	overproduction of pro-inflammatory cytokines.	➢ In a feedback loop, more inflammation develops. The reasons are: ➢ exaggerated macrophage ➢ T cell recruitment ➢ Monocyte (Erener, 2020). ➢ Damages the lung infrastructure.
Alveolar Dysfunction	Augmented permeability of the vasculature. Pulmonary complications may be worsen.	➢ Aggravate pulmonary complications. ➢ An intensified requirement in patients with diabetes for mechanical ventilation.

Endothelial Dysfunction	Vasoconstriction is observed in diabetes patients. Basically, it is due to the change in vascular tone.	➢ Endothelial cells are consisting with ACE 2 receptors. SARS-COV2 can directly infect these endothelial cells by entering through these receptors (Erener, 2020). ➢ Hypercoagulable state ➢ Tissue edema ➢ Subsequent organ ischemia

Moreover, SARS-CoV-2 infection is responsible for hyper inflammatory conditions of diabetic patients. This condition is triggered by following factors:

1. Elevated platelet activity.
2. Adhesion to endothelial wall, providing a significant benefit for the occurrence of thromboembolic events.
3. Increasing significant response to stimulus of hyper coagulation and fibrinolysis markers.

It is now acknowledged that COVID-19 patients have a high mortality and morbidity rate if they are diabetic having aged as well as hypertension, and obesity of BMI ≥ 40 kg/m^2 (Muniyappa&

Gubbi, 2020). The vulnerability of Coronavirus disease of diabetes patients may increase due to following mechanisms (Muniyappa& Gubbi, 2020):

1. Impaired T cell activity.
2. Susceptible hyper inflammation.
3. Cardiovascular disease.
4. Reduced viral clearance.
5. Higher cellular binding affinity.
6. Virus entry is easier in human body.

4.2 Statistics and case studies regarding severity and mortality

A meta-analysis based on 27 published articles in current year, indicate that approximately 15 percent of COVID-19 patients are diabetic and they are at higher risk of mortality and intensity from Coronavirus disease (Abdi et al., 2020). Severe symptoms along with poor Acute Respiratory Distress Syndrome (ARDS) prognosis have been shown in these patients. Another revised and systematic comprehensive study and meta-analysis of 83 scattered numerical studies from Asia, Europe and the United States of almost 79,000 adult individuals observed that patients with laboratory-confirmed COVID-19, the combined incidence of conventional diabetes at hospital admission was nearly 15 percent (Mantovani et al., 2020). Most importantly, according to this study these patients with conventional diabetes are at doubly higher chance of serious illness needing admission to emergency unit and threefold increased risk of in-hospital mortality related with COVID-19 (Mantovani et al., 2020) (Sten Madsbad, 2020).

The first COVID-19 study to directly examine its effect in hospitalized diabetic patients observed that one in ten of them died within seven days after hospitalized and intubation, mechanical ventilation were required of one in five patients (Diabetologia, 2020). The research also pointed out that, 65% of hospitalized COVID-19 patients having diabetes were men, and their age usually around seventy years. In addition, increased age and body mass index as well as frequency of diabetes complications create the necessity of mechanical ventilation and death. In between 10 to 31 March 2020, another study of 53 hospitals in France revealed that, 89% patients were suffering from type 2 diabetes and 3% were type 1 diabetic among 1317 patients (Diabetologia, 2020). This study also discovered that, between those patients 47 percent individuals had micro vascular complications whereas 41 percent individuals were suffering from macro vascular complications. Chinese Centre for Disease Control researched on almost forty five thousands patients with COVID-19 and the found that, the mortality rate was 7.3 percent in diabetic patients versus 2.3 percent of non-diabetic patients. Moreover, another study of more than 1100 COVID-19 patients in many centers throughout the United States, diabetes was found to be associated with a more than fourfold rise in mortality (Gupta et al., 2020).

Chapter 5

Treatment options

5.1 Insulin

Studies suggest that, for type 1 diabetic patients insulin is an essential and the safest option which has no impact on Angiotensin-converting enzyme 2 (ACE2), also a good treatment option for type 2 diabetic patients with poor glucose control (Hartmann-Boyce et al., 2020) (Pal & Bhadada, 2020). The dose adjustment of insulin is important for the patients as improper dose can be the reason of life threatening condition like hypoglycemia. As a result, dose adjustment must be done by medical expert like doctors and pharmacists. It is a matter of concern that, medical professionals must not try to entirely stop insulin therapy for type 1 diabetic patients rather than they must prescribe supplementary doses of short-acting insulin for hyperglycemia.

In the meantime, insulin doses need to decrease by 10 to 20 percent and meal time insulin must be avoided if carbohydrate intake is low in case of hypoglycemia. On the other hand, type 2 diabetic patients having significant hyperglycemia, insulin dose should be increased by 10 to 20 percent. In addition, patients who take insulin therapy, should go for self-monitoring of blood-glucose for every 2 to 4 hours or they should take help from medical professionals to check glucose level frequently (Elnaem& Cheema, 2020) (Bornstein et al., 2020).

5.2 Metformin

Although metformin is used a first-line treatment option for type 2 patients with diabetes, it has following side effects (Barber, 2020):

1. Hypotension.
2. Lactic acidosis.
3. Renal impairment.
4. Liver impairment.
5. Acute illness.

Dehydration and lactic acidosis will likely to occur if patients are dehydrated. Moreover, COVID-19 patients having harsh symptoms have chance to develop episodes of acute metabolic decompensation (Bornstein et al., 2020). Therefore, current National Institute for Health and Care Excellence(NICE) guidance advices to discontinue metformin medication when suffering from any acute illness which includes COVID-19 infection (Barber, 2020).

5.3 Dipeptidyl peptidase 4 (DPP-4) inhibitor

In the current situation, using dipeptidyl peptidase 4 inhibitors (DPP4i) needs deep discussion. DPP4 inhibitor targets DPP4, which is a trans membrane glycoprotein type II, for enzymatic action and is ubiquitously expressed in immune cells and other tissues. DPP4 stimulates inflammation by following mechanisms:

1. Controlling CD86 expression.
2. T cell stimulation.
3. Controls nuclear factor kappa light chain enhancer of activated B cells (NF-κB)

Therefore, it has raised concerns about a potential increase in infection risk. Few meta-analyses identified the potential threat of urinary tract infection and nasopharyngitis (Pal & Bhadada, 2020). In addition, human DPP4 works like MERS-CoV (MERS-Coronavirus) functional receptor. Genetically modified diabetic mice expressing human DPP4 (DPP4H / M mice) developed a prolonged duration of serious illness and slow recovery following infection with MERS-CoV. DPP4 may help to nullify COVID-19 acute respiratory problems mediated by cytokine (Pal & Bhadada, 2020). There is also a need for detailed large-scale evidence to validate the conclusions that diabetic medicines with anti-inflammatory measures have a possible role in the particular outcomes or severity of COVID-19 infection although in general, these medications are well tolerated and can be continued COVID-19 positive patients with type 2 diabetes (Bornstein et al., 2020).

5.4 Sodium-glucose like-transporter 2 (SGLT2)

Over the last few years, the SGLT2 inhibitors such as canagliflozin, dapagliflozin, and empagliflozin have risen to popularity and considered as effective and beneficial choice of drug therapy to control blood glucose level. It has the complementary advantages of weight loss and systolic blood pressure reduction. Moreover, current clinical studies have observed the probability of cardiovascular events is reduced. On the other hand, SGLT2 inhibitor therapy has risen the

chance of diabetic ketoacidosis (DKA) and dehydration for older patients who are taking the medicines for a prolonged period. Dapagliflozin is recently being tested in COVID-19 hospitalized patients and being evaluated for emergence of serious complications for severe complications like hypertension, cardiac arrest, chronic kidney disease and atherosclerotic cardiovascular disease. Current National Institute for Health and Care Excellence guidance suggests to discontinue SGLT2 inhibitor medications as a safety precaution throughout any acute illness, including COVID-19 infection (Barber, 2020). It is important to ensure that good blood glucose level with alternative treatment options is maintained in these situations, specifically because glycemic control is likely to get worse throughout acute illness. Furthermore, patients should avoid initiating such class of drug during respiratory illness (Bornstein et al., 2020).

5.5 Glucagon-like peptide-1 (GLP1) receptor agonists

To treat type 2 diabetes, GLP1 therapies are commonly used as glycemic efficacy is typically excellent. The additional advantages of high blood pressure reduction and weight reduction are also produced by this class. In addition, certain medications of this class reduces the chance of cardiovascular complications. There is no comparable guidance from National Institute for Health and Care Excellence (NICE) to discontinue GLP1 therapies during acute illness, unlike metformin and SGLT2-inhibitors (Barber, 2020). Therefore, type 2 diabetic patients if found COVID-19 positive then they can continue GLP-1 therapies. However, continuation of GLP1 therapies is likely to lead to glycemic stability in such a scenario but in some clinical cases, temporary

withdrawal of GLP1 therapies may be needed if patient is critically ill having diabetes ketoacidosis and insufficient renal function (Elnaem& Cheema, 2020) (Barber, 2020).

Chapter 6

Clinical management

6.1 Out patients care

Stable non COVID-19 residents with diabetes, should continue usual diabetes treatment with continued monitoring of COVID-19 symptoms (Sinclair et al., 2020). In case of, COVID-19 positive and outpatient having diabetes should continue the usual treatment of diabetes despite losing of appetite, but checking blood glucose level on a regular basis is mandatory to avoid high blood glucose which is not less than 12 mmol/L or low blood glucose which is less than 4 mmol/L (Sinclair et al., 2020) (Gupta, Ghosh, et al., 2020). Protein consumption and balance diet are two important factors to notice in order to treat mineral and vitamin deficiencies. In addition, vaccines against influenza and pneumonia can be taken to minimize the possibility of subsequent bacterial pneumonia following respiratory viral infection, although such information is not available in the current viral outbreak (Gupta, Ghosh, et al., 2020).

In case of oral therapy, metformin should be stopped to minimize the risk of lactic acidosis in those with fever and acute disease. Moreover, SGLT-2 inhibitors need to be stopped due to an increased risk of dehydration, especially in those with diarrhea and vomiting and a different drug for example linagliptin can be incorporated if appropriate (Sinclair et al., 2020). If the level of sugar continues to increase and remains more than 12 mmol/L, insulin therapy possibly need at particular point.

Clinical scenarios and their initial action

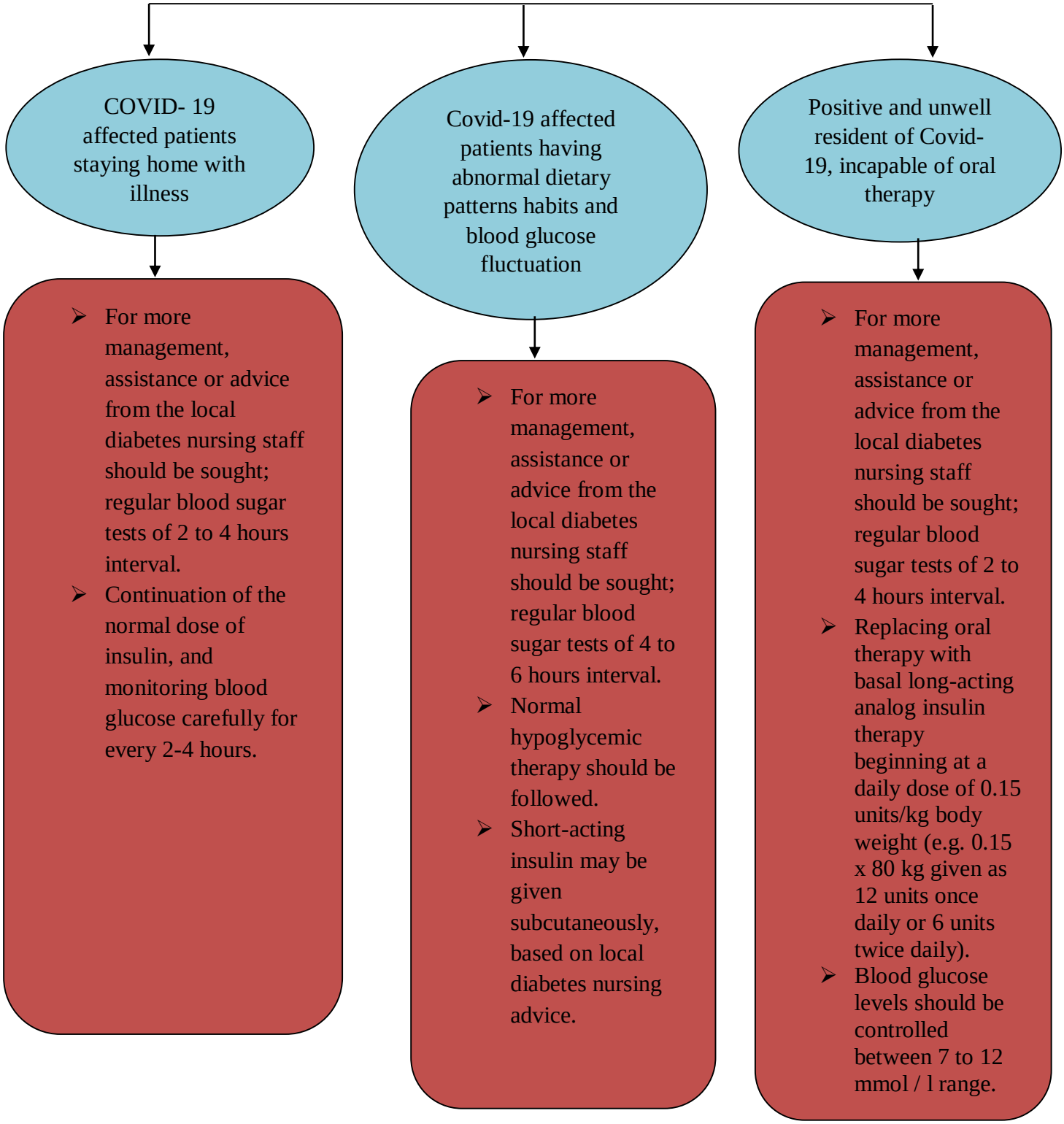

Figure 1: Recommended primary steps in multiple clinical situations

6.2 In patient care

Plasma glucose, electrolytes, pH, blood ketones, or β-hydroxybutyrate should be monitored for in patients having COVID 19. Metabolic surgery must be done for type 2 diabetic in patients when diabetic complications lead immediate threat to life, organs, or limbs (Halpern & Mancini, 2020). It also provides following advantages (Cefalu et al., 2016):

1. Enhance bile acid secretions.
2. Improved Glucagon-like peptide 1 (GLP1) circulation.
3. Stimulation of fibroblast growth factor 19.
4. Alternation of gut nutrient sensing, metabolism and absorption.

It is advisable to postpone elective metabolic surgery at this pandemic situation, in spite of issues about hospital facilities. Type 2 diabetes and obese patients have an elevated chance of COVID-19 complications, compounding the possible negative effect of recovery-period surgical stress. Metabolic surgery can, however, lead to nutritional deficiencies, including decreased absorption of vitamins and micronutrients, which are essential for proper immune function (Bornstein et al., 2020). Moreover, for COVID-19 patients or suspected COVID- 19 patients, the amount of IV fluid given to avoid exacerbating acute respiratory distress syndrome should be halved (ARDS) (NHS London, 2020).

Table 7: Concise advice on inpatient diabetes (UK, 2020).

Situations	**Main difference with COVID-19**	**Advised action**

Early in the admission process	People with COVID-19 infection tend to have a higher risk of ketone hyperglycemia including: ➢ Type 2 diabetic patients (risk even greater if SGLT-2 inhibitor is used) ➢ Newly diagnosed diabetic patient COVID-19 disease precipitates atypical diabetes emergency presentations (e.g. mixed DKA and hyperosmolar states)	· Every patient's blood glucose at admission should be monitored. · Ensuring ketones in: ➢ Anyone with diabetes being admitted. ➢ With a glucose intake over 12 mmol/L. · SGLT-2 inhibitors in all inpatient-admitted persons need to be stopped. · Metformin should be stopped but it is needed to check when data on blood lactate, renal and hypoxic status are available in all inpatient-admitted persons. · Using 10-20% glucose where ketosis persists should be considered.

Critical condition on admission	In those with DKA / HHS and evidence of "lung leak" or myocarditis, fluid requirements can differ.	· The rate of fluid replacement regimen will need to be changed after restoring the circulating volume where indication of "lung leak" or myocarditis is verified. · Early contact with the diabetes specialist team. · Early participation by the critical care team.
ICU	Important insulin resistance in ICU settings in patients with type 2 diabetes.	· IV insulin protocols (people seen needing up to 20 units/hr) will need to be modified. · Patients are also susceptible to nursing so that feeding

		may be unintentionally disrupted, a paradoxical hypoglycemic danger.

For fast acting insulin administration ketone level measurement is crucial for clinical decision.

Table 8: Fast acting of insulin administration (NHS London, 2020)

Ketones + to + + for urine testing and 1.5-3mmol/L for blood testing	10 % of the total daily dose should be given every 2 hours as fast acting insulin plus the normal insulin-carbohydrate ratio if eating. Also basal insulin dose need to be increased by 10-20 %.
Ketones +++ to ++++ for urine testing and over 3mmol/L for blood testing	20 % of the total daily dose should be given every 2 hours as fast acting insulin plus the normal insulin-carbohydrate ratio if eating. Also basal insulin dose need to be increased by more than 10-20 %.

Chapter 7

Teleconferencing

Telehealth promotes coordination and quality of care throughout infectious disease occurrences as observed during COVID-19 in many developed countries like USA, Singapore and Portugal providing information that is effortlessly available through technology. As social distancing is a main aspect in reducing the spread of Coronavirus, teleconferencing is an ideal option to avoid person to person contact (Smith et al., 2020). Most importantly, this approach is essential to bridge the gap between two geographic locations during this pandemic which eventually, enable effective medical diagnosis (Smith et al., 2020). Telephone and video conferencing solutions are used worldwide, creating a platform of connection between patients and healthcare experts and allowing appointments specifically for continuing chronic disease and outpatient care. Refero, an online UK site, is providing free video conferencing platforms to pharmacies, primary healthcare clinics, and other regional and national authorities during the COVID-19 outbreak to assist with this initiative (Smith et al., 2020).

Portugal quickly rearranged facilities to ensure smooth diabetes care during the epidemic, in anticipation of national closures and movement restrictions, even as the COVID-19 pandemic was in its early stages (World Health Organization, 2020). Among other steps, the central government has expedited the authorization of reforms in clinical practice to allow the delivery of teleconsultation and prescription drugs to patient's homes (World Health Organization, 2020). The Portuguese Diabetes Association clinic has already reorganized entire scheduled appointments to

teleconsultation through telephone or videoconference. Physicians and nurses received equipment, remote access to electronic medical records and other resources to work from home. Patients were, however, contacted in advance to ask about the preferred teleconsultation format and whether they would agree to exchange images or videos, such as for the assessment of possible retinopathy or foot ulcers, or to download information such as prescriptions. Mobile devices were used for information sharing for patients who did not have access or knowledge to communicate via email and webinars that were available to patients and the public were coordinated by the clinic. Priority was given to areas where self-management is problematic for patients, along with particular questions relevant to the use of insulin pumps, the care of diabetic children and the preventative measures of COVID-19 infection (World Health Organization, 2020).

Chapter 8

Role of pharmacovigilance and pharmacists

Science that comprehends, evaluates, prevents and detects all kinds of drug related adverse reactions and it's any other problems are defined as Pharmacovigilance (PV) (World Health Organization, 2015). During this pandemic, numerous therapies are listed for consideration to treat coronavirus infections. These therapies are identified and arranged in many countries (Chandler et al., 2020). It is significantly important to monitor their adverse effects to avoid life threatening condition of patients. It is a matter of fact that, many adverse drug related reactions of these therapies have been doubted and these reports have already reached Vigibase. As a result, clinicians get an opportunity for treatment decisions in case of insufficient randomized controlled trials data. They also can use real life available observational data on treatment considering pros and cons (Chandler et al., 2020). Real-time signal detection as well as appropriate evaluation of incoming data confirms the assembly of high-quality data from adverse drug reaction reports throughout all countries which is important in this situation.

Both Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARBs) have nephroprotective effects and protect patients from renal damage. For Diabetic patients these two class of drugs are used as first-line agents. On the other hand, use of these medications can contribute to up regulation of the angiotensin-converting enzyme 2 (ACE2). It is also responsible for the viral entry of coronavirus 2 (SARS) syndrome of extreme acute respiratory distress (Stafford et al., 2020). But exactly what pulmonary effects ACEIs or ARBs exhibit for patients with diabetes is yet to identify because of inadequate evidence. This lack of data is disadvantageous for managing SARS-CoV-2 infected patients. Compared to other ACEIs and

ARBs, Captopril was shown to have a substantially higher occurrence of pulmonary ADEs on the basis of data mining methodology. Other particular drugs also showed significant pulmonary ADEs with their use. These evidences may encourage doctors and pharmacists to understand the impact of these drugs, whether they could get worse or influence diabetic patients to infections affecting the respiratory system (Stafford et al., 2020). As a result, these studies emphasize the importance of pharmacovigilance and point out that pharmacists and clinicians may need to take into account the adverse effect profile of the specific drug, particularly captopril, on how infections and acute disease conditions impairs pulmonary function, like COVID-19, are affected by the use of this drug.

At present many potential medications are being trialed for their potential efficacy against corona virus. Meanwhile, a number of drugs are being rejected for its ineffectiveness against the virus from the termination of new trials although they seemed effective initially (Elnaem & Cheema, 2020). Pharmacists are responsible to know that up to date information and incorporate these into patient care in this pandemic. They must follow and assess the updated guidelines regarding COVID-19 disease and implement into pharmaceutical care for patients. During the COVID-19 pandemic, pharmacists must maximize rational use of medication, enhance their services and support to patients. Based on research, participation of pharmacists in the management of diabetes creates beneficial impact on clinical outcomes. For instance, patient with high adherence shows a decline HbA1c level and vice versa (Kharjul et al., 2018). As a result, the role of pharmacists are vital for more patient adherence and to obtain balance glucose level of diabetic patients having COVID-19. In addition, pharmacists can contribute to the maximization of diabetes care by providing proper clinical services, as well as through teleconferencing, optimizing drug supply and use, improving patient care, isolated monitoring etc (Elnaem & Cheema, 2020).

Chapter 9

Conclusion

For the period of the COVID-19 pandemic, because of the severity of infection and death, diabetic patients are at risk and consisted of more than 15 percent of total COVID-19 patients, although the pathophysiological and molecular mechanisms behind this link are not fully understood yet (Katulanda et al., 2020). Medication management, blood glucose monitoring, limiting use of ACEI drugs by consulting with physicians, managing proper nutrition, telemedicine, consideration of the country's health and COVID-19 related recommendations for infection prevention is mandatory for diabetic patients during this pandemic. However, in the management of COVID-19, there are some unresolved clinical problems and dilemmas. In genetic inclinations over populations, a better perception of potential differences along with further research is desperately required for the fundamental pathophysiological processes of the interaction between COVID-19 and diabetes, and its medical care.

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Diabetes and Covid

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