Chapter

COVID-19 and Type 2 Diabetes Mellitus

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Abstract

COVID-19 pandemic caused by SARS-COV-2 virus has evolved into a global crisis and is a major concern especially for the diabetes community. People with diabetes mellitus have increased morbidity and mortality associated with COVID-19 infection. Conversely, COVID-19 infection and treatment may predispose to hyperglycemia. Potentially modifiable risk factors have been discussed and urgent need to mitigate the risks is warranted. In this book chapter we summarize the available evidence on COVID-19 and type 2 diabetes mellitus including link between COVID-19 and type 2 diabetes, pathophysiology, clinical manifestations, management and complications.

Keywords: COVID-19, SARS-COV-2, diabetes mellitus, hyperglycaemia, type 2 diabetes

1. Introduction

From the offset of Coronavirus disease (COVID-19), groups that are more vulnerable to COVID-19 were identified. Presence of diabetes mellitus (DM), both type 1 (T1DM) and type 2 (T2DM) independently increases the adverse effects of COVID-19 [1]. A meta-analysis found that the proportion of diabetes in COVID-19 patients was 9.7% and that having cardiac disease and diabetes increased the risk of death by twice as much as the other risk factors [2]. The purpose of this chapter is to discuss in detail the current evidence available regarding type 2 diabetes mellitus and COVID-19.

2. Pathophysiology of T2D and COVID-19

There has been some insight into the pathophysiological mechanisms of COVID-19 infection and diabetes, but much remains to be investigated. The SARS-CoV2 utilizes angiotensin converting enzyme 2 (ACE2) to gain entry into infected cells and reduces expression of ACE2, and over activation of renin angiotensin aldosterone system (RAAS) is proposed to contribute to adverse effects in patients with diabetes (PWD) and COVID-19 infection [3].

Mechanisms accentuated in PWD include increased inflammatory cytokines, increased lipopolysaccharides, and increased RAAS (angiotensin 2) which results in vascular endothelial damage, increased ROS and IL-6 in increased insulin resistance (due to exaggerated angiotensin 2 activity) which results in hyperglycaemia [4]. There is increased blood viscosity due to increased fibrinogen and d-dimer [4].

The S1 spike protein of SARS-Cov2 is predicted to bind to DPP4 which may facilitate epithelial infection [1, 5].

It has been noted that infection with SARS-Cov-2 virus results in damage to pancreatic beta-cells [6]. Apart from COVID-19 related impaired insulin production [7], COVID-19 can cause insulin resistance due to activation of integrated stress response (ISR) initiating serine/threonine kinases which can induce IRS-1 serine phosphorylation. Hence, patients with COVID-19 infection can present with hyperglycaemia for the first time and may require insulin for insulin naïve patients or the one on insulin may have increased requirements [8].

Patients with type 2 diabetes (T2D) have a dysregulated immune response with higher ratio of lymphopenia, and increased levels of neutrophils, CRP and IL-6 have been noted in PWD with COVID-19 infections. T2D is associated with activation of the RAAS in different tissues [3]. In PWD pulmonary dysfunction has been reported involving changes in lung volume, lung diffusing capacity, ventilation, bronchomotor tone and neuroadrenergic bronchial innervation [3].

Increased metabolic rate, dysregulation of glucose metabolism, aggravation of inflammation and immune modulation result in increased oxidative stress, cytokine production, endothelial damage, increased glucotoxicity which ultimately can result in increased severity of COVID-19 and rapid progression of cardiorespiratory failure [4].

3. Clinical manifestations

The most common symptoms of COVID-19 infection are fever, cough [9], fatigue and shortness of breath [10]. Other symptoms such as sore throat, rhinorrhoea, ageusia, anosmia, vomiting and diarrhea have also been reported [11]. An observational study noted that male patients were more vulnerable than female patients to COVID-19 infection [9]. Common comorbidities include diabetes mellitus, hypertension obesity and cardiovascular disease [10].

Multiple comorbidities are associated with more severe disease and higher mortality [9]. Patients with T2D are more likely to develop severe COVID-19 infection as compared with patients without diabetes [12]. An increased prevalence of chronic obstructive pulmonary disease (COPD) and chronic kidney disease (CKD) has been noted in patients with T2D and COVID-19 infection [11]. COVID-19 infection may result in severe insulin resistance and insulin deficiency precipitating diabetic ketoacidosis (DKA) in patients with T1DM and not commonly but still possible in T2DM, result in new onset diabetes, or in PWD result in new or increased insulin therapy at times with very high dose requirements. Dexamethasone therapy which has been found to be beneficial in COVID-19 infection, can result in further hyperglycaemia and has the potential of precipitating Hyperosmolar hyperglycaemic state (HHS) and DKA [7]. Regular monitoring of capillary blood glucose (CBGs) is warranted for inpatients. As hyperglycaemia with ketosis may occur in COVID-19 infection, ketones should be checked in all patients with diabetes initially or if CBG > 12 mmol/L [13].

Laboratory findings include lymphopenia, thrombocytopenia, raised CRP, raised ALT and other markers of inflammation such as ferritin [10]. Compared with patients without diabetes, patients with T2DM were found to have a higher ESR, CRP, IL-6, TNF-α and procalcitonin but lower lymphocyte and T lymphocyte subsets [12]. HbA1C, IL-6 and lymphocyte count have been proposed as risk factors for the severity of COVID-19 infection and T2DM [12]. CT scan changes are common and include ground glass abnormalities, lung lesions and enlargement of lymph nodes [10].

4. Management of type 2 diabetes and COVID-19 infection

Diabetes UK, a British-based patient, healthcare professional and research charity, has provided advice for healthcare professionals on COVID-19 and inpatient diabetes care on their website and topics include front door guidance, managing inpatient hyperglycaemia, dexamethasone therapy and safe discharge endorsed by the Joint British Diabetes Society (JBDS) and Association of British Clinical Diabetologists (ABCD) [14].

Front door guidance is available for inpatients [13]. An ABCDE (Airway, breathing, circulation, disability and exposure) approach is warranted initially if patient is unwell, CBG> 12 mmol/L or known diabetes. Aim is rule out DKA, HHS and watch out for new presentation of diabetes, sepsis, steroid use, uncontrolled diabetes or delayed and missed treatment of diabetes [13]. Be aware of the possibility of euglycaemic DKA. Stop Metformin and SGLT2 inhibitors on admission. Fluid requirements may differ in patients with COVID-19 infection and have to be tailored individually due to ARDS, cardiac involvement or AKI. Contact the diabetes specialist team and early involvement of critical care team where appropriate.

Target glucose levels are 6–10 mmol/L, and up to 12 mmol/L is acceptable. The guidance for managing inpatient hyperglycaemia should be used if glucose levels are >12 mmol/L and a corrective dose is appropriate and the patient is not in DKA or HHS [14]. It provides information for patients on insulin and insulin naïve patients too, regarding insulin dose adjustment as while recovering from COVID-19 related insulin resistance, doses may require rapid reduction to avoid hyperglycemia [14]. Initiation of IV insulin with monitoring of blood glucose, electrolytes, pH and ketones should be done as appropriate. Blood ketones <0.6 mmol/L is safe, blood ketones 1.5–2.9 mmol/L signifies increased risk of DKA [13], and if 3 mmol/L or greater, then check pH and bicarbonate for possibility of DKA [13].

If patients unable to manage insulin pump start on variable rate intravenous insulin infusion (VRII) or subcutaneous (S/C) insulin. For S/C insulin find out the total daily insulin dose and if not available can be calculated as 0.5 units multiplied by weight. Half this dose is given as basal and remaining half as bolus dose divided by 3 to give the meal time dose [13]. If patient is placed in prone position, feeding may be affected and that needs to be taken into account while dosing insulin.

Continuous glucose monitors (CGMs) and flash glucose monitoring (FGM) can be left on but capillary blood glucose monitoring must still continue. For magnetic imaging such as MRIs, these devices including pumps should be removed [13]. Always check the feet on admission to look for foot infection and rule out critical limb ischaemia.

4.1 Medications used in diabetes

As it was not feasible to conduct RCTs initially, expert opinion and observational studies regarding treatment with medication for T2D suggest the following [15]:

Regular monitoring blood glucose of patients on insulin should be encouraged [15]. A retrospective study in patients in China found that patients with T2D required more medical interventions and had a significantly higher mortality and multiple organ injury than the non-diabetic individuals [3]. Within PWD they found that well controlled BG (CBG 3.9–10 mmol/L) was associated with reduction in adverse outcomes including lower mortality as compared with poorly controlled BG while in hospital. Hence correlation of improved glycaemic control with better outcomes was made and aggressive blood glucose lowering treatment with tablets and insulin was advocated.

4.1.1 Insulin

Insulin therapy is the mainstay in acute unwell PWD admitted to hospital where oral tablets have been stopped or not enough to control the hyperglycaemia. However, there is some evidence that insulin treatment is associated with adverse clinical outcomes in patients with T2D and COVID-19, including increased mortality. Use of insulin was associated with enhanced inflammation (increased IL-1β-dependent CRP and IL-6) and injury of vital organs (acute cardiac injury and acute kidney injury) during the progression of COVID-19 in patients with T2D [16]. Hypoglycaemia was higher in patients on insulin and may have contributed to the increased mortality although a sub-group without hypoglycaemia still had increased mortality. Insulin has been the mainstay in ill PWD and if hyperglycaemia and insulin result in adverse outcomes, there is a difficult dilemma for clinicians [17]. A UK study of 2.85 million PWD, a higher risk of COVID-19 related mortality was seen in patients on insulin, but the higher risk was thought to be due to residual confounding factors rather than direct drug effects [18]. Currently guidelines continue to endorse insulin in unwell PWD. Caution and close monitoring is to be exerted while using insulin treatment in PWD and COVID-19.

4.1.2 Metformin

Metformin, a lipophilic biguanide, has been associated with reduced mortality in women with obesity or T2D admitted to hospital with COVID-19 infection [19]. Several explanations have been provided including decreased inflammatory factors. Retrospective studies evaluating use of Metformin in T2D and COVID-19 infection have mainly suggested some benefit or no harm or benefit whereas a single study has suggested some harm, but overall use of Metformin is considered to be safe [20]. The CORONADO study which was a prospective study noted that Metformin was associated with a lower risk of death in PWD hospitalized with COVID-19 infection [21]. Dehydration with Covid-19 may increase the risk of lactic acidosis in patients taking metformin, hence temporary cessation of the drug along with usual sick day rules should be followed. Renal function should be monitored closely [15]. As metformin may reduce progression to severe COVID-19 infection, after initial cessation and review of clinical parameters including hypoxic state, lactate and renal parameters, metformin may be re-introduced if appropriate [13]. The MET-Covid Trial is an RCT designed to evaluate use of Metformin versus placebo for outpatient treatment and post exposure prophylaxis of COVID-19 infection [22].

4.1.3 Sodium glucose co-transporter 2 inhibitors

Sodium glucose co-transporter 2 inhibitors (SGLT2i) primarily act on the proximal tubule to block sodium and glucose absorption. Given that the mechanisms that are attributed to the protective effects of SGLT2i overlap with the mechanisms that are activated in COVID-19 infection, SGLT2i seem to have the potential to protect against end organ damage through cardio-renal protection [23]. Initiation of this medication should not be done during any likely infection, and for patients with T2D with COVID-19 infection, on SGLT2I, risk of dehydration and euglycemic DKA remains and should temporarily stop this medication and follow sick day rules. Renal function should be monitored closely [15]. A retrospective study to evaluate SGLT2i and COVID19 infection in a large UK based primary care dataset concluded that as compared to DPP4i, SGLT2i did not confer an increased risk of COVID-19 infection [24]. They deemed that clinicians can safely use SGLT2i the everyday care of PWD during COVID-19. DARE-19, is the first randomized controlled multi-centre trial

investigating the use of Dapagliflozin, and the goals are to prevent COVID-19 related organ dysfunction or mortality and to improve clinical recovery [23].

4.1.4 Glucagon like peptide receptor agonists

Glucagon like peptide receptor agonist (GLP-1 RA) in animal studies has shown to activate ACE-2 expression and there have been speculations if this accelerated virus entrance into host cells but also if this expression neutralizes the virus limiting infection [25]. There is support for the hypothesis that GLP-1 RA may mitigate a more adverse clinical course in PWD and COVID-19 infection [26]. GLP-1 RA also are beneficial with weight loss. There are a few studies on GLP1RA and COVID-19 infection and even the final report of the CORONADO study did not find any benefit or harm with its use [27]. Dehydration is likely to lead to serious illness so patients on GLP1RA with COVID-19 should be monitored [15]. Regular meals and adequate hydration should be encouraged [15].

4.1.5 Dipeptidyl peptidase-4 inhibitors

It has been proposed that SARS Cov-2 binds to Dipeptidyl peptidase-4 inhibitors (DPP4), but the clinical implications are not known. Dipeptidyl peptidase-4 inhibitors (DPP4i) are well tolerated in COVID-19 infection [15]. The majority of studies have shown either benefit with DPP4i in PWD and COVID-19, or no harm or benefit [20], Although DPP4 inhibitors appear to be safe in T2D and COVID-19 infection [4], in an observational study of 717 patients, in the diabetes sub-group, patients on DPP4I were at a higher risk of ICU admission [5]. As study that compared GLP-1 RA or DPP4i with SGLT2i did not note associated improved outcomes in patients with COVID-19 infection [28]. As DPP4 upregulation may be an indicator for severity of COVID-19 infection, there is interest regarding the use of DPP4i in COVID-19 infection and available information may form the path to discovering novel therapies [29]. RCTs involving Linagliptin versus placebo and Sitagliptin versus placebo have been registered [30, 31].

4.1.6 Sulphonylureas

The use of sulphonylureas with regard to COVID-19 infection has not shown any harm or benefit according to some retrospective studies [20]. If there is a risk of hypoglycaemia, they may be stopped. Sulphonylureas are not recommended in the context of dexamethasone induced hyperglycaemia as beta cell function maybe impaired with COVID-19 infection and there is insulin resistance too [7].

4.1.7 Thiazolidinediones

Several studies have shown a reduction in proinflammatory cytokines with pioglitazone, but no studies have reported outcomes in pioglitazone users with COVID-19 infection, and due to small numbers of users meaningful data is unlikely to be available soon [20].

4.1.8 Steroid induced hyperglycaemia

Dexamethasone has been proven to reduce mortality in patients dependent on oxygen therapy and ventilation. However, recommended dose of 6 mg orally or intravenously are bound to affect glucose metabolism and guidance for glucocorticoid therapy in patients with and without diabetes is provided by DUK [14].

4.2 Hypertension

Treatment with angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) could increase the expression of ACE2 and accelerate entry of the virus into the cells. However, in COVID-19 infection, impairment of the ACE2/Mas receptor pathway and increase in angiotensin-2 activity could occur, and RAAS blockade may protect against this serious lung injury. Thus it is recommended that ACEI and ARBs should continue [15].

4.3 Lipid medications

Reduction on ACE2 by hyperlipidemia is restored by statins. It is believed that statins should not be discontinued in patients with COVID-19 infection due to it pleiotropic effects and potential for a cytokine storm due to rebound increase in interleukins [15].

4.4 Renal transplant recipients

Potential effect of COVID-19 on pancreatic function of patients with solid organ transplants is not known. Monitoring is required for patients with PTDM and without diabetes at risk of PTDM [15].

4.5 Fatty liver disease

Should be considered at an increased risk of cytokine storm and should be considered at risk of severe disease. Hence patients at risk of a cytokine storm and are to be considered at an increased risk of severe disease. There may be some benefit of screening and monitoring tests for hyperinflammation [15].

4.6 Discharge

Advice regarding safe and supported discharge is available [14]. Patients using insulin pumps or wearable diabetes technology should have them returned to the patient if not being used and ensure enough consumables are available at home. If a patient has had DKA, SGLT2i should not be used. Metformin can be re-started once the patient is well, eGFR>30 ml/min and lactate is normal. Sulphonylureas may have been withheld due to risk of hypoglycaemia, and assessment should be made if re-starting it is appropriate.

4.7 Outpatient management

It is suggested that patients with diabetes (PWD) not yet infected with the SARS-CoV-2 virus should intensify their treatment to prevent COVID-19 infection including glycaemic control, management of hypertension and raised cholesterol. Tele medicine and virtual appointments should continue to ensure adequate follow up [15]. The priority was to contain spread of COVID-19 but health care services need to ensure that the needs of PWD are met is imperative which includes continuous supply of medications and available healthcare services in the primary care [32].

4.8 Prevention

Patients with COVID-19 infection without diabetes should be monitored for new onset diabetes especially if on steroids. PWD and COVID-19 infection should have good glycaemic control [15].

4.9 Lifestyle management

While lockdown was the best armamentarium we had while the vaccination program was established and rolled out, it lead to potential for more sedentary activity, unhealthy diet, mental health related issues and possible delay in seeking care due to fear of contracting COVID-19 especially for patients with chronic conditions. Maintaining a healthy lifestyle is important now more than ever [32]. Adoption of dietary advice and restriction of dietary carbohydrates has been proposed for people with metabolic syndrome [33]. Smoking was associated with a higher mortality rate in hospitalized patients and advice regarding smoking cessation should be given [9].

4.10 Prediabetes

Prediabetes is associated with increased CRP and IL-6, and hospitalized patients with moderate to severe COVID-19 infection have been noted to have prediabetes, hence it has been proposed that pre-diabetes be treated as a comorbidity for COVID-19 infection [34]. Whether screening of all COVID-19 infected patients for prediabetes to improve patient care is feasible or beneficial remains to be seen as there is currently no therapeutic drug approved for prediabetes.

5. Complications

Apart from the known pulmonary complications, extra pulmonary complications from COVID-19 include neurological, cardiovascular, gastro-intestinal, renal, endocrine and dermatological complications are being reported [35]. Due to COVID-19 infection, there have been increased risk of hyperglycaemia, euglycaemic ketosis and diabetic ketoacidosis (DKA) [35]. With COVID-19 infection, there is a risk of atypical presentations of complications such as DKA or mixed hyperosmolar states with associated increased mortality. A retrospective case series confirmed that PWD are at a risk of combined DKA and HHs with COVID-19 infection [36]. Data from our own centre has shown that DKA in T2DM is increased significantly and that the frequency of HHS increased seven fold during the first Covid pandemic in the UK [37]. Fluid management is a challenge in such patients especially in case of renal impairment and ARDS should be avoided. Guidelines for management of DKA is available on the Diabetes UK website and it is worth remembering that euglycaemic DKA can occur in patients taking SGLT2i or in pregnancy [14]. In a whole population study assessing risks of in-hospital death in England, people with T1DM were found to be three-and-a-half times more at risk of dying from COVID-19 infection, while people with T2D are at twice the risk of dying than people without diabetes [38]. Hence, continued measures to mitigate the risks of people with diabetes of becoming seriously ill or dying due to COVID-19 infection is warranted.

6. Conclusion

COVID-19 infection and diabetes mellitus have important and clinically relevant interactions. It is important for all physicians to be aware of these, particularly in view of likely further COVID-19 pandemics.

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