COVID-19 and diabetes mellitus: An unholy interaction of two pandemics

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ABSTRACT

Background and aims: Diabetes mellitus is associated with poor prognosis in patients with COVID-19. On the other hand, COVID-19 contributes to worsening of dysglycemia in people with diabetes mellitus over and above that contributed by stress hyperglycemia. Herein, we have reviewed the two-way interactions between COVID-19 and diabetes mellitus.

Methods: We have performed an extensive literature search for articles in PubMed, EMBASE and Google Scholar databases till April 25, 2020, with the following keywords: "COVID-19", "SARS-CoV-2", "diabetes", "diabetes mellitus", "SARS", "infection" and "management of diabetes mellitus" with interposition of the Boolean operator "AND".

Results: Compromised innate immunity, pro-inflammatory cytokine milieu, reduced expression of ACE2 and use of renin-angiotensin-aldosterone system antagonists in people with diabetes mellitus contribute to poor prognosis in COVID-19. On the contrary, direct β-cell damage, cytokine-induced insulin resistance, hypokalemia and drugs used in the treatment of COVID-19 (like corticosteroids, lopinavir/ritonavir) can contribute to worsening of glucose control in people with diabetes mellitus.

Conclusions: The two-way interaction between COVID-19 and diabetes mellitus sets up a vicious cycle wherein COVID-19 leads to worsening of dysglycemia and diabetes mellitus, in turn, exacerbates the severity of COVID-19. Thus, it is imperative that people with diabetes mellitus take all necessary precautions and ensure good glycemic control amid the ongoing pandemic.

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1. Introduction

Ever since its outbreak in Wuhan, China, the novel coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected over 2.8 million people, claiming more than 198000 lives in over 200 nations all over the globe [1]. The overall mortality rate of COVID-19 is variable, ranging from as low as 0.7% in Germany to as high as 10.8% in Italy [2]; nevertheless, older adults and people with underlying comorbidities invariably have a poor prognosis [3]. Accordingly, diabetes mellitus (DM) has emerged as a distinct comorbidity that is associated with severe disease, acute respiratory distress syndrome (ARDS) and increased mortality in COVID-19 [4–6]. In the largest series reported from China comprising of 72,314 cases, patients with DM had higher mortality (7.3% in DM vs. 2.3% overall) [7]. DM was present in 20.3% of the patients with COVID-19 who died in Italy [8].

2. Diabetes mellitus and COVID-19: A two-way interaction

Coexistence of DM and COVID-19 is an unholy situation wherein one disease entity tends to compliment the other. Herein, we have summarized the possible interactions between the two raging pandemics.

2.1. How does diabetes mellitus affect COVID-19?

Available evidence does not support the notion that people with DM are at an increased risk of COVID-19 [9]. However, diabetes mellitus has been found to be an independent predictor of admission to intensive care unit or invasive ventilation or death in COVID-19 (Hazard Ratio 1.59, 95% CI: 1.03–2.45) [10]. No clear distinction has however been made between type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), but it is likely that both T1DM and T2DM are predictors of poor prognosis in COVID-19 [11].

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Multiple pathophysiological explanations can be put forward supporting the association between DM and COVID-19 severity. Innate immune system, the first line of defense against SARS-CoV-2, is compromised in patients with uncontrolled DM [12]. Moreover, DM is a pro-inflammatory state characterized by inappropriate and exaggerated cytokine response; this has been depicted in COVID-19 patients wherein serum levels of interleukin-6 (IL-6), C-reactive protein and ferritin were significantly higher in patients with DM than those without DM [13]. This suggests that people with diabetes are more susceptible to an inflammatory cytokine storm eventually leading to ARDS, shock and rapid deterioration of COVID-19. In addition, the aforementioned study also showed that COVID-19 patients with DM had higher D-dimer levels than those without DM [13]; perhaps signifying over-activation of the hemostatic system. Amid an already underlying pro-thrombotic hypercoagulable state predisposed by the mere presence of DM [14], over-activation of the coagulation cascade in COVID-19 can lead to fatal thromboembolic complications and eventual mortality [15].

Diabetes mellitus is associated with reduced expression of angiotensin-converting enzyme 2 (ACE2), an enzyme widely expressed in the lungs (specially type II pneumocytes), kidney, intestine and vascular endothelium. Under normal physiological conditions, ACE2 degrades angiotensin-II and to a little extent angiotensin-I to smaller peptides, namely angiotensin (1-7) and angiotensin (1-9), respectively. The pulmonary ACE2/Ang(1-7) system plays a potent anti-inflammatory and anti-oxidant role and ACE2 is known to be protective against lethal avian influenza A H5N1 infection [16]. Accordingly, low ACE2 expression in DM might explain the increased incidence of severe lung injury and ARDS with COVID-19 [4,17].

One also needs to keep in mind the confounding role of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin-receptor blockers (ARB). ACEi/ARBs are commonly used in people with DM as anti-hypertensive and renoprotective drugs. The use of ACEi/ARBs is associated with increased expression of ACE2 as an adaptive response to counteract the elevated levels of angiotensin-II [4,18]. Unfortunately, SARS-CoV-2 uses ACE2 as a receptor for entry into the host pneumocytes, thus, ACE2 upregulation would facilitate entry and subsequent proliferation of the coronavirus. However, once the virus uses the enzyme to gain entry into the host tissue, ACE2 get downregulated and it is unable protect against lung injury [4].

A recent study (although presently in pre-print stage) has shown that non-structural proteins of SARS-CoV-2 attacks the β1-chain of hemoglobin leading to dissociation of iron from porphyrin, thereby impairing the ability of hemoglobin to carry oxygen [19]. Although just a hypothesis, SARS-CoV-2 might have a higher affinity to bind to glycated hemoglobin than non-glycated hemoglobin.

2.2. How does COVID-19 affect underlying diabetes mellitus?

Preclinical data and data derived from studies based on the prior SARS outbreak (2003) suggest that COVID-19 can lead to worsening of glycemic control in people with pre-existing DM over and above that caused by the stress of a critical illness (i.e., stress hyperglycemia). Yang et al. had reported that patients with SARS (caused by SARS-CoV, the 'cousin' of SARS-CoV-2) who had never received glucocorticoids had significantly higher fasting plasma glucose levels as compared to patients with non-SARS pneumonia [20]. This was explained on the basis of SARS-CoV mediated damage of the pancreatic β-cells as ACE2 is also expressed on the pancreatic islets [21]. Infact, immunohistochemistry and in-situ hybridization had identified SARS-CoV in the pancreas of patients who died of SARS [22]. This could partly explain the worsening of glucose control in

people with T2DM who do have some functional β-cells in reserve.

In addition, COVID-19 can lead to worsening of insulin resistance in people with T2DM and T1DM (specially those who are obese and have some component of insulin resistance apart from an absolute insulin deficiency). Even mild COVID-19 can induce a pro-inflammatory milieu, as evident by high amounts of IL-6, IL-1β, tumor-necrosis factor-α (TNFα), monocyte chemoattractant protein-1 (MCP-1) and inducible protein-10 that can further lead to lowering of insulin sensitivity. Moreover, obesity, commonly associated with T2DM is likely to further aggravate the cytokine response, thereby further worsening insulin resistance [23]. In addition, SARS-CoV increases serum levels of fetuin A, an α2-Heremans-Schmid glycoprotein that has been linked to impaired insulin sensitivity [24]; whether SARS-CoV-2 can lead to elevation of fetuin A needs exploration. Lastly, COVID-19 is often associated with hypokalemia; this has been attributed to downregulation of pulmonary ACE2, reduced angiotension-II degradation and subsequent increased aldosterone secretion [4]. Hypokalemia, in turn, can worsen glucose control in patients with T1DM and T2DM [25].

Amid the prevailing nationwide lockdowns, restriction in outdoor movements would limit the sunlight exposure leading to vitamin D deficiency [26]. Hypovitaminosis D has long been regarded as a risk factor for insulin resistance and vitamin D supplementation improves insulin sensitivity [27]. Thus, vitamin D deficiency can lead to worsening of glucose profile in patients subsequently getting infected with COVID-19.

The indirect role played by drugs used in the management of COVID-19 on worsening of glucose control also needs to be considered. Corticosteroids, used in patients with co-existing ARDS and sepsis can lead to glycemic excursions. Lopinavir-ritonavir could lead to lipodystrophy and subsequent insulin resistance, although short-term exposure as under the present clinical scenario might not be clinically significant. More importantly, ritonavir, being a potent enzyme inhibitor, can prolong the half-life of glucocorticoids and indirectly contribute to poor glucose profile [28]. Type 1 interferons (interferon-β1) have also been investigated as a potential treatment against COVID-19 [29] and interferon therapy has been associated with β-cell damage as well [30]. Azithromycin has also been used in combination with hydroxychloroquine in COVID-19 [31]; the macrolide antibiotic can increase the risk of dysglycemia in people with diabetes mellitus [32].

Apart from worsening of hyperglycemia, a retrospective study from Wuhan reported that around 10% of the patients with T2DM and COVID-19 suffered at least one episode of hypoglycemia (<3.9 mmol/L) [33]. Hypoglycemia, in turn, contributes to higher number of cardiovascular events in patients with DM by undue activation of the sympathetic nervous system and by mobilizing pro-inflammatory mononuclear cells and increasing platelet reactivity [34].

Thus, COVID-19 in patients with underlying DM leads to worsening of glycemic profile that further compromises the innate immune response and promotes generation of pro-inflammatory cytokines, thereby setting up a vicious cycle (Fig. 1).

3. Management of diabetes mellitus amid COVID-19 pandemic

Considering the gravity of the pandemic and in the absence of a definitive therapy against COVID-19, it is imperative that people with DM be extra cautious and take all necessary precautions [3,4]. Stringent social distancing and hand hygiene should be the norm. Good glycemic control should be targeted as it would help boost the innate immune system [4,35]. However, widespread nationwide lockdowns would curtail their routine in-clinic visits, limit their physical activity, alter their food habits and adversely affect
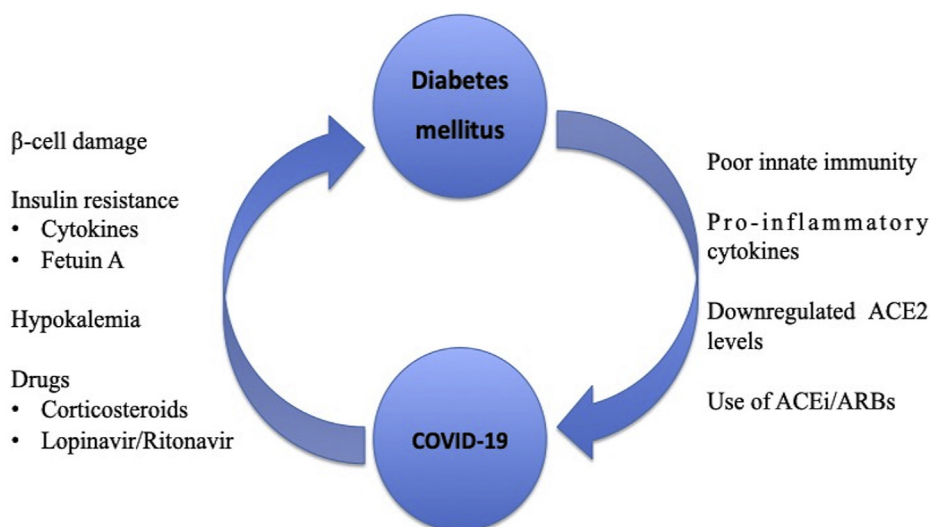
Fig. 1. Schematic diagram showing the two-way interaction between the novel coronavirus disease (COVID-19) and diabetes mellitus. Diabetes mellitus contributes to increased disease severity of COVID-19 via compromised innate immunity, exaggerated pro-inflammatory cytokine response and low expression of angiotensin-converting enzyme 2 (ACE2). In addition, use of angiotensin-converting enzyme inhibitors (ACEi)/angiotensin-receptor blockers (ARBs) in people with diabetes mellitus have widely been implicated in contributing to disease severity in COVID-19. On the other hand, COVID-19 leads to worsening of glucose control in people with diabetes mellitus perhaps by direct virus-mediated β-cell damage, augmentation of insulin resistance through cytokines and fetuin A and hypokalemia. In addition, drugs being used in the management of COVID-19 like corticosteroids and lopinavir/ritonavir can also contribute to dysglycemia.

Table 1
Table summarizing the potential effects of drugs/treatment options being used in the management of COVID-19 on glucose and lipid profiles.

Drug being used in the management of COVID-19	Mechanism of action in COVID-19	Effect on glucose profile	Effect on lipid profile
Corticosteroids	Anti-inflammatory, blocks cytokine storm	Hyperglycemia	Dyslipidemia (increase in TC, LDL, TG)
Lopinavir/Ritonavir	Protease inhibitors, blocks viral cellular entry	Lipodystrophy Hyperglycemia	Dyslipidemia (increase in TC, TG)
Darunavir/Cobicistat	Protease inhibitors, blocks viral cellular entry	Lipodystrophy Hyperglycemia (less likely compared to lopinavir/ritonavir)	Dyslipidemia (increase in TC, TG) (less likely compared to lopinavir/ritonavir)
Remdesivir	Adenosine analogue, inhibits viral replication	Increased blood glucose seen in 7% of patients in remdesivir vs. 8% in placebo group [45]	Increased blood lipids seen in 6% of patients in remdesivir vs. 10% in placebo group [45]
Interferon-β1 (and other Type 1 interferons)	Cytokine, stimulate innate antiviral immunity	Can lead to autoimmune β-cell damage, thereby, precipitating or worsening diabetes mellitus	Dyslipidemia (increase in TG mainly)
Chloroquine/ Hydroxychloroquine	Increases host cell endosomal pH, prevents viral entry and immunomodulator	Improves glucose profile and HbA1c in people with T2DM	Improves lipid profile in people with T2DM (reduced TC, LDL, TG, variable effect on HDL) [41]
Azithromycin	Macrolide antibiotic used with hydroxychloroquine, known to have *in-vitro* activity against Zika and Ebola virus, prevents severe respiratory tract infection in patients suffering from viral disease	Risk of dysglycemia in people with diabetes mellitus [32]	No robust data Being an enzyme inhibitor, may prolong half-life of statins
Camostat mesilate	Protease inhibitors, blocks viral maturation and entry into cells	Found to lower blood glucose levels in insulin-treated patients with diabetes mellitus [44]	Not known
Tocilizumab	Monoclonal antibody against IL-6, blocks cytokine storm	Improves glucose profile and reduces HbA1c in people with rheumatoid arthritis and diabetes mellitus [42]	Alters lipid profile in people with rheumatoid arthritis (increase in TC, HDL, TG, no change in LDL) [43]
Convalescent plasma	Provides anti-SARS-CoV-2 antibodies	Not known (probably no effects) [46]	Not known (probably no effects) [46]

COVID-19: Novel coronavirus disease; TC: Total cholesterol; LDL: Low-density lipoprotein; TG: Triglycerides; HDL: High-density lipoproteins; T2DM: Type 2 diabetes mellitus; IL-6: Interleukin-6; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

their psychological health; all these would ultimately lead to poor glycemic control [36]. Infact, a recent study from China had shown that elderly subjects with type 2 diabetes mellitus had higher fasting blood glucose during the COVID-19 pandemic [37]. Tele-consultations with registered medical practitioners would help people with DM circumvent a lot of problems imposed by

lockdowns [38]. Although certain anti-diabetic drugs like piogli-tazone and liraglutide have been shown to upregulate ACE2 in animal models, the current evidence does not support any change in the ongoing medications [39]. Similarly, international organiza-tions recommend patients on ACEi/ARBs to carry on with their medications. Although used rarely, hydroxychloroquine can be

good anti-diabetic medication in the present scenario as the drug has also been shown to inhibit SARS-CoV-2 infection *in-vitro* as well as reduce the viral load in COVID-19 patients. The drug has also been approved for prophylaxis against COVID-19 in many countries [40]. Considering the low-cost, widespread availability, modest HbA1c reduction, once-daily dosing and relatively good tolerability, hydroxychloroquine may be a good add-on drug during this outbreak for patients with poor glucose control, provided contra-indications like diabetic retinopathy and cardiomyopathy has been ruled out [39]. Similarly, tocilizumab, a monoclonal antibody against IL-6, is being tried in patients with COVID-19. Tocilizumab is known to improve insulin resistance and reduce HbA1c in patients with rheumatoid arthritis and diabetes mellitus [42]. In addition, camostat mesilate has been used as anti-viral drug against COVID-19; the drug was earlier pursued as an anti-diabetic drug as it was shown to lower blood glucose levels in insulin-treated patients with diabetes mellitus [44]. In addition, remdesivir, an adenosine analogue that inhibits viral replication, does not affect blood glucose and lipids when compared to placebo [45]. Convalescent plasma has been used in the management of COVID-19 and seems to be a safe alternative [46]. The effect of drugs being tried in the management of COVID-19 on glucose and lipid profiles has been summarized in Table 1.

4. Conclusions

The complex interaction between COVID-19 and diabetes mellitus places an individual at an extraordinarily high-risk of severe disease, acute respiratory distress syndrome and eventual mortality. In addition, the concurrent COVID-19 is likely to make glucose control difficult in people with diabetes mellitus. Nevertheless, people with DM need to be extra cautious and ensure strict social distancing, proper hand hygiene and good glycemic control amid the ongoing pandemic.

Limitations

We do respect the limitations of the manuscript. At this point of time, data pertaining to the effect of COVID-19 on glucose profile in people with diabetes mellitus seems more conjectural and theoretical. In the absence of robust clinical data, validated conclusions must not be drawn as much of the observations are based on prior experience with SARS and on recent literature derived from small-scale studies. However, the data do provide abundant scope for upcoming research.

Data availability

Not applicable.

Declaration of competing interest

None.

CRediT authorship contribution statement

Rimesh Pal: Writing - original draft, Data curation. **Sanjay K. Bhadada:** Writing - review & editing.

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