Heterogeneity in presentation of hyperglycaemia during COVID-19 pandemic: A proposed classification

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A B S T R A C T

Diabetes and hyperglycemia occurring during COVID-19 era have implications for COVID-19 related morbidity/mortality. In this brief review, we have attempted to categorise and classify such heterogenous hyperglycemic states. During COVID-19 pandemic broadly two types of hyperglycemia were seen: one in patients without COVID-19 infection and second in patients with COVID-19 infection. Patients not inflicted with COVID-19 infection and diagnosed with either type 2 diabetes mellitus (T2DM) or type 1 diabetes mellitus (T1DM) show more severe hyperglycemia and more ketoacidosis, respectively. In former, it could be attributed to weight gain, decreased exercise, stress and in both type of diabetes, due to delayed diagnosis during lockdown and pandemic. In patients with COVID-19 and associated pneumonia, altered glucose metabolism leading to hyperglycemia could be due to corticosteroids, cytokine storm, damage to pancreatic beta cells, or combination of these factors. Some of these patients present with diabetic ketoacidosis, hyperglycemic hyperosmolar state or both. We have provided a framework for categorisation of hyperglycemic states, which could be consolidated/revised in future based on new research data.

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Hyperglycemia has emerged as one of the risk factors for adverse outcomes and mortality of SARS-CoV-2 virus infection (COVID-19) [1–3]. Further, bidirectional relationship of hyperglycemia and COVID-19 has been well recognised [4]. It must be realised that any magnitude of hyperglycemia is associated with poor prognosis in COVID-19 [3,5,6]. However, the timing and extent of hyperglycemia varies according to several factors: pre-existing diabetes or pre-diabetes [1,2], age (5), presence of obesity [7], other co-morbidities and stress [8], severity of infection, type of treatment given, and beta cells capacity during times of COVID-19 infection. Many of these factors have been researched, while knowledge regarding others is limited. During the times of COVID-19, knowledge of presentation of hyperglycemia and its relationship with morbidity and mortality has increased [9]. Indeed, varied presentations of hyperglycemia have been reported. A synthesis of this knowledge and categorisation of types of hyperglycemia has not been done so far. Aim of this short review is to propose classification of various categories of hyperglycemia during times of COVID-19.

A literature search was performed with Medline (PubMed), Scopus, and Google Scholar electronic databases till January 2021, using relevant keywords; COVID-19 induced diabetes; COVID-19 and type 1 diabetes; COVID-19 and type 2 diabetes; COVID-19 induced diabetic ketoacidosis; new-onset diabetes after SARS-CoV-2 infection, to extract relevant studies describing relationship between COVID-19 and hyperglycemia.

Upon literature review and according to recently published data till now, we propose the following classification of hyperglycemia taking recourse to current literature. We hope that an enhanced understanding of hyperglycemia would be attained with this proposed classification.

1. Proposed categories of hyperglycemia during times of COVID-19

Fig. 1 lists a simplified classification. Discussion and further details have been provided below.

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| Hyperglycemic states during COVID-19 pandemic |

| Without COVID-19 infection | With COVID-19 infection |

New onset T2DM

Higher glycemia than new onset diabetes before COVID-19 pandemic?

T1DM

Higher number of patients have DKA than before COVID-19 pandemic?

Mild hyperglycemia

Mostly in patients with well controlled diabetes/prediabetes with mild infection.

Severe hyperglycemia with/without ketosis/DKA (includes new-onset diabetes)

Mostly due to severe disease (with pneumonia) due to following:

Common:

- Cytokine storm, stress, and corticosteroid therapy

Relatively rare:

- Direct damage to beta cells
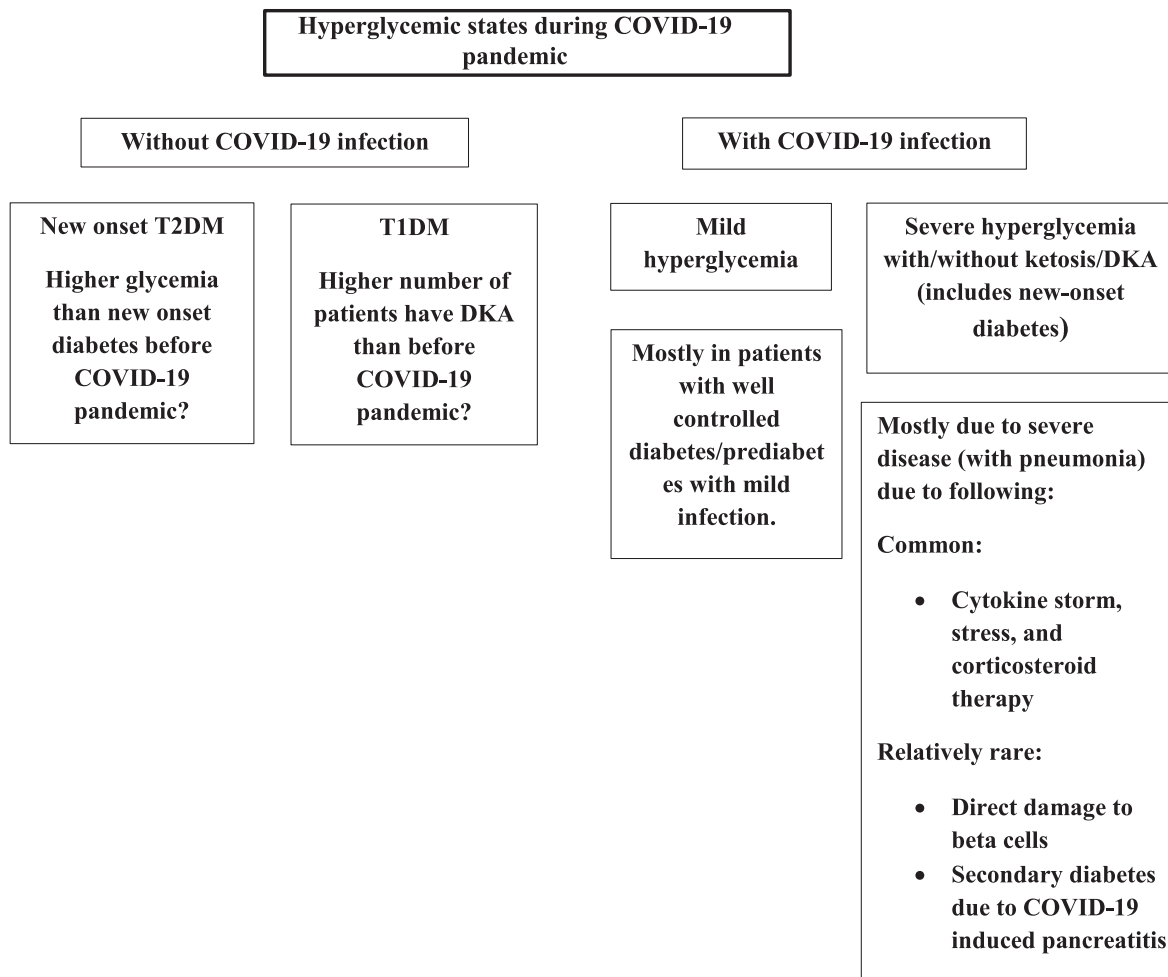- Secondary diabetes due to COVID-19 induced pancreatitis

Fig. 1. Proposed classification of hyperglycemic states during COVID-19 pandemic.

1. Mild Hyperglycemia:

Mild hyperglycemia could be seen in following category of patients;

a. *Patients of T2DM with previously controlled glycemia.* Subsequent to mild COVID-19 infection these patients may have minimal changes in their glycemic status. Upon mild COVID-19 infection, these patients can be managed at home. Mostly these patients are continued on their previous diabetes treatment.

b. *Patients with pre-existing prediabetes:* Upon mild COVID-19 infection, these patients either remain in prediabetes category or covert to diabetes. Most of these can be managed with oral anti-hyperglycemic drugs.

c. *Patients with mild hyperglycemia detected for the first time at admission for COVID -19 infections.* This category of patients have been researched. A retrospective analysis was done on 605 patients without known diabetes in two hospitals based in Wuhan, China. These authors showed that the odds ratio for 28-day in-hospital complications in those with fasting blood glucose $>/= 7.0$ mmol/l and 6.1–6.9 mmol/l vs. <6.1 mmol/l was 3.99 (95% CI 2.71, 5.88) and 2.61 (95% CI 1.64, 4.41), respectively [10]. Such mild hyperglycemia without previous history of diabetes could also occur during home quarantine with mild COVID-19 infections, however, it is detected only in those who have glucose meter at home or upon subsequent visit to laboratory [11].

2. Severe hyperglycemia with or without ketosis/ketoacidosis with COVID-19 or during COVID-19 era:

A. Severe hyperglycemia without ketosis/ketoacidosis in patient with T2DM:

a. *Patients with pre-existing diabetes without COVID-19 and with worsening of hyperglycemia:* This is ascribed to poor dietary habits, inadequate exercise and weight gain, stress and overall low testing for blood glucose [12–15].

b. *Patients with T2DM/prediabetes having moderate-severe COVID-19 infection requiring hospitalization:*

Patients with T2DM/prediabetes who receive corticosteroids for COVID-19 infection experience acute rise in blood glucose levels, which are difficult to control and need high doses of insulin. Even without steroids, infection and stress may increase blood glucose levels.

c. *Patients with no prior history of diabetes or pre-diabetes presenting with new-onset diabetes:*

i. With COVID-19 Infection: Mostly these patients have severe COVID-19 infection with pneumonia, cytokine storm and most are treated with corticosteroids [3,4,16]. Some patients acutely present with ketoacidosis suggesting acute insulinopenia, as described later (refer point c). In addition, we have also described patients with new-onset diabetes who are COVID-19 antibody positive but were asymptomatic [11]. In such

cases relationship of hyperglycemia with asymptomatic COVID-19 antibody positivity remains unclear.

  ii. Patients without COVID-19 Infection:

    1. Type 2DM: These patients develop hyperglycemia due to altered lifestyle during COVID19 era; change in food habits, decrease in exercise, weight gain [17,18], and excessive stress [11,18]. We have recently reported that glycemic parameters (fasting blood glucose, post prandial blood glucose, and glycosylated hemoglobin levels) in patients with new-onset diabetes during COVID-19 era were far more adverse than patients with new onset diabetes before COVID-19 era(11). It is possible that patients with new-onset diabetes during COVID-19 era delayed their visit to physician or for blood testing, causing delay in diagnosis and consequent inordinate rise of blood glucose levels. Such data have only been reported from India and should be researched in other countries.

    2. Type 1DM: Interestingly, presentation of patients of T1DM appears apperas to have changed during COVID-19 era. Data from several pediatric care centres in Italy showed that, as compared with 2019, there was a 23% reduction in new diabetes cases in 2020 (n,160; only 8 patients SARS-CoV-2 RT-PCR positive). Further, the authors show that among those newly diagnosed patients who presented in a state of DKA, the proportion with severe DKA was 44.3% in 2020 *vs.* 36.1% in 2019 (p = 0.03) [19]. Similarly, data from Australia shows that the number of new diagnoses of type 1 diabetes was comparable in the pandemic period and pre-pandemic periods, but the frequency of severe diabetic ketoacidosis was significantly higher in the pandemic period as compared to the pre-pandemic periods (45% vs 5%; P < 0.003), odds ratio 16.7 (95% CI 2.0, 194.7) [20].

B. Severe hyperglycemia with ketosis/ketoacidosis with/ without hyperglycemic hyperosmolar state (HHS) in patients with T2DM (includes new-onset diabetes):

This type of presentation has been reported by many authors [3,21–26] [27] but its prevalence and features remain poorly researched. A retrospective cohort of 35 patients with COVID-19 (T2DM; 28, T1DM; 5, new presentation; 2), presenting with DKA (31·4%), mixed DKA and HHS (37·1%), HHS (5·7%), or hyperglycaemic ketosis (25·7%) were evaluated in a study reported from UK [21]. According to authors, acute insulinopenia in patients with COVID-19 and with type 2 diabetes, which persisted up until the time of discharge in 30% of patients previously not insulin-treated, was an uncommonly described feature. Further, in a study of 658 hospitalised patients from China, 42 (6.4%, one had T1DM) developed ketosis/ ketoacidosis. Interestingly, 27/42 patients had non-diabetic ketoacidosis [22]. A series of 3 cases who developed severe COVID-19 infection with acute onset diabetes, DKA and marked increase in cytokines [23,24] has been described from India. These patients responded well to treatment including intravenous fluids and insulin. The requirement of insulin gradually diminished after about 4–6 weeks of diagnosis and then hyperglycemia was controlled with oral anti-hyperglycemic drugs alone [23,24]. Another, albeit rarer variety of patients are those who present with new-onset marked hyperglycemia with ketonuria after very mild COVID-19 infection [25,26]. Such a patient, recently reported by us was managed on small doses of oral anti-hyperglycemic treatment [25]. Euglycemic ketoacidosis, due to Sodium- glucose Cotransporter-2 inhibitor drugs should also be considered in patients presenting with ketoacidosis.

"Diabetogenic effects' of COVID-19 infection have been debated but remain sparsely researched. Apart from 'stress', direct and possibly destructive effects of cytokine storm or SARS-CoV-19 virus itself (likely via attachment using ACE-2 receptors) on pancreatic beta cells have been speculated(4, 9). Nature (Type1, Type 2, or mixed) of diabetes in such patients and its course remains unclear.

C. *Patients of type 1 diabetes with COVID-19 infection presenting with diabetic ketoacidosis, or new onset T1DM.* A multicentre study from the UK showed an apparent increase in new-onset T1DM in children, with evidence of SARS-CoV-2 infection or exposure in some of these. Seventy per cent (21/30) children presented with DKA and 52% (11/21) had severe DKA. Of the five children with positive results (2 of 21 tested were SARS-CoV-2 PCR positive and 3 of 16 tested were SARS-CoV-2 IgG positive), three presented with severe DKA and refractory hypokalaemia, and one PCR positive child suffered a hypokalaemia-related cardiac arrest but recovered fully [28]. The series of patients presenting with DKA, described previously in UK based cohort (see point 2 (B)), comprised of a mixture of patients with T1DM and T2DM [22]. New onset diabetes with DKA has also been described in a child who was having COVID-19 antibody positive with multisystem inflammatory syndrome [29]. The natural history of such patients with T1DM remains unclear and required further follow up research.

3. Other Categories:

a. *Hyperglycemia with pancreatitis after COVID-19 infection.* Hyperglycemia following pancreatitis associated with COVID-19 infection (presumably due to direct effect of SARS-CoV-19 virus on pancreatic beta cells) has been described [30]. Pancreatitis after COVID-19 infection in an established case of diabetes has been described by us previously [31]. Overall, prevalence and natural course of such 'secondary diabetes' remains unknown.

b. *Gestational diabetes with/without COVID*-19 infection: This issue has been less researched. As shown for patients with type 2 diabetes, lockdown during COVID-19 could lead to worsening of glycemia [32]. In a meta-analysis 128176 non-pregnant patients (228 studies) and 10000 pregnant patients (121 studies) with confirmed COVID-19 were included. The most common complication in pregnant patients with COVID-19, as compared to general population was diabetes [33]. Euglycemic ketoacidosis in a case of GDM and COVID-19 has been reported [34]. Clearly, more research is needed.

2. Conclusions

There is considerable heterogeneity in the effect of COVID-19 on alteration of glucose metabolism, ranging from mild or no effect to severe hyperglycemia and ketoacidosis. These effects are because of the cytokine storm, steroids used in treatment and possibly the direct beta cell injury by virus. In addition, the psycho-socio-economic effects of the pandemic have resulted in altered glucose metabolism manifesting as worsening of glycemic control in people with pre-existing diabetes and in new onset diabetes. Importantly, association of altered glucose metabolism and severe COVID-19, as shown in many studies, indicate that SARS-CoV-2 infection involves an interplay with glucose metabolism. Exploration of heterogenous pathways by which SARS-CoV-2 dysregulates glucose metabolism

is important for understanding proper diagnosis, monitoring and therapy [3].

Recognition of these different clinical categories of hyperglycemia will lead to a better understanding of the effect of COVID-19 in patients with diabetes and will help in formulating appropriate treatment plans. Further research may lead to modification of these proposed categories.

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