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Hypoglycemia at the time of Covid-19 pandemic

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ABSTRACT

Background: Hypoglycemia is the limiting factor in the glycemic management of diabetes, which need to be addressed critically to avoid complications. Lockdown because of new coronavirus strain (COVID-19) pandemic has further complicated the issue of hypoglycemia due to limitations in access to food, outpatient clinics, pathological services and medicines.
Aim: To assess the factors associated with the risk of hypoglycemia during April–May 2020 lockdown in people with type 2 diabetes mellitus.
Methodology: We analyzed the data retrospectively from 146 patients of type 2 diabetes mellitus (T2DM) reporting to the emergency department (ED) during lockdown period with symptoms suggestive of hypoglycemia.
Results: The majority of patients were male (90/146) with a mean age of 59.88 ± 10.09 years and a mean random blood glucose level of 57.67 ± 9.00 mg/dL. Two-third of patients (70.83%) had level 1 hypoglycemia, while level 2 hypoglycemia was reported in 29.16% of patients. A combination of Metformin and Sulfonylureas (SU) was most commonly associated with the risk of hypoglycemia (65.75%) followed by insulin (33.56%). Subjects who received insulin reported a lower blood glucose value (50.75 ± 8.20 mg/dL) as compared to those receiving a combination of metformin and SU (60.95 ± 7.10 mg/dl). 330.56% of patients who had received prophylaxis hydroxychloroquine (HCQ) 400 mg twice a day along with the routine anti-hyperglycemic agents without their dose adjustment reported hypoglycemia. Patients with hypertension, micro-vascular, macro-vascular complications, and coexistent with each other had a higher propensity to the risk of hypoglycemia (46.58%, 33.56%, 23.29%, and 32.88%) respectively.
Conclusion: The COVID-19 lockdown has shown to influence the risk of hypoglycemia in patients with T2DM, especially those receiving SU, insulin, HCQ especially in patients with associated co-morbidities. Patient education, support, and telemedicine plays a pivotal role to prevent hypoglycemia.

1. Introduction

Diabetes which cause unique microvascular complications, and a substantially increased risk of macrovascular atherosclerotic complications needing ongoing patient self-management, education, and support. Diabetes care is multifactorial and requires that many issues, beyond glycemic control, be addressed.

Glycemic goal, is limited by hypoglycemia [1–4]. Patients with uncontrolled diabetes and associated comorbidities are at a higher risk of developing acute complications. The risk of hypoglycemia is high in patients treated with sulfonylurea, glinide, and insulin. Interactions between these agents and other drugs including hydroxychloroquine can increase the risk of hypoglycemia [5–7].

The first case of the COVID-19 pandemic in India was reported

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on January 30, 2020, originating from China [8,9]. During the lockdown, all citizens were requested to "stay at home." [10] The COVID-19 pandemic increased morbidity and mortality among people with diabetes. Patients with diabetes will suffer the most from the prolonged lockdown due to limitations in access to food, outpatient clinics, pathological services, and medicines. Telemedicine provides us with an opportunity to judiciously manage patients with diabetes during the lockdown period in COVID- 19 epidemic, except emergencies where hospitalization becomes necessary [11].

Not having known the benefits of systematic, logical, and economical therapy in times of "national health crisis," treatments have experimented for the management of COVID-19 which also includes economical anti-malarial medicine chloroquine and its derivative hydroxychloroquine (HCQ). In India, its use has been approved in the management of type 2 diabetes as a third or fourth agent [12–14]. Close attention is warranted to avoid potential hypoglycemic episodes related to the use of HCQ in the management of COVID-19 in patients with type 2 diabetes.

Through this short report, we are trying to assess the factors associated with the risk of hypoglycemia during April–May 2020 lockdown in people with T2DM.

2. Methods

The data of the patients with T2DM reporting in the emergency department (ED) with symptoms suggestive of hypoglycemia (Sweating, feeling shaky, being nervous or anxious, chills and clamminess, Irritability or impatience, confusion, fast heartbeat, Feeling lightheaded or dizzy) was analyzed as a part of this retrospective observational study. During their visit to ED, demographics details, history of co-morbid condition/complications, and medication history were recorded. Random capillary blood glucose was measured using One Touch Verio Flex blood glucose monitor (Lifescan, Inc) and the same was also confirmed in venous plasma glucose sample (RBG) on an autoanalyzer at the time of admission. Blood glucose value of <70 mg/dL was defined as a case of hypoglycemia as per the 2020 American Diabetes Guidelines (ADA) [15]. The study was a retrospective data collection, and all patients provided written informed consent to the reuse of clinical data for research purposes. Data were expressed as mean ± SD (for demographics and RBG) and percentage (for medications and complications).

This was a retrospective data collection and consent from each patient was obtained for data collection as a part of regular patient registration process. Being a retrospective data analysis, ethics committee approval was not obtained.

3. Results

A total of 146 patients of T2DM (Male = 90, Female = 56) were included in this analysis. Mean RBG during admission was 57.67 ± 9.00 mg/dL while the HbA1c level was 8.5 ± 0.70%. The duration of diabetes of the patients included in this study was 10.05 ± 2.09 years (Table 1).

3.1. Documented symptomatic hypoglycemia

Glucose alert value level 1 of hypoglycemia (Glucose < 70 mg/dL and ≥54 mg/dL) was observed in 70.78% of patients, while 29.16% of patients had clinically significant level 2 of hypoglycemia (Glucose < 54 mg/dL). (Table 2).

Anti-hyperglycemic agents (AHA), Hydroxychloroquine (HCQ) and associated risk of hypoglycemia during lockdown:

A combination of Metformin and Sulfonylureas was most commonly associated with risk of hypoglycemia (65.75%) followed by insulin (33.56%). Patients who received insulin reported a lower blood glucose value (50.75 ± 8.20 mg/dL) as compared to those receiving a combination of metformin and sulfonylurea (60.95 ± 7.10 mg/dL). 33.56% patients who had received prophylaxis hydroxychloroquine 400 mg BD along with the routine anti-hyperglycemic agents without their dose adjustment reported hypoglycemia. In patients who had consumed hydroxychloroquine 400 mg BD and 400 mg OD the RBG was 52.95 ± 7.03 mg/dL and 54.82 ± 4.76 mg/dL respectively (Table 3).

3.2. Associated co-morbidities and risk of hypoglycemia during lockdown

Patients with hypertension, micro-vascular, macro-vascular complications, and coexistent with each other had a higher propensity to the risk of hypoglycemia (46.58%, 33.56%, 23.29%, and 32.88%) respectively (Table 4).

4. Discussion

Iatrogenic hypoglycemia is a limiting factor in the glycemic management of diabetes [16]. Our data showed the majority of patients (70.83%) had blood glucose values of <70 mg/dL to 54 mg/dL while blood glucose values of <54 mg/dL was observed in one third of patients. A blood glucose concentration of 70 mg/dL has been recognized as a threshold for neuroendocrine responses to falling glucose in people without diabetes [17]. Because many people with diabetes demonstrate impaired counter-regulatory responses to hypoglycemia and/or experience hypoglycemia unawareness, a measured glucose level, 70 mg/dL is considered clinically important, independent of the severity of acute hypoglycemic symptoms. Blood glucose concentration, < 54 mg/dL) is the threshold at which neuroglycopenic symptoms begin to occur and requires immediate action to resolve the hypoglycemic event [18]. Although it was difficult to recollect the causative history for hypoglycemia majority of patients reported reason behind the symptomatic hypoglycemia as stress related to lockdown, delay in availability of food, non-availability of food, fear psychosis of being infected with COVID-19 and the financial issues associated with loss of jobs.

Table 1
Demographics of patients with hypoglycemia

Sr. No	Characteristics	Observation (Mean ± SD)
1	Male: Female	90:56
2	Age, (Years)	59.88 ± 10.09 (40–82)
3	Duration of Diabetes, (Years)	10.05 ± 2.09 (06–13)
4	Random Blood glucose on admission, (mg/dL)	57.67.±9.00 (35–69)
5	HbA1c, (%)	8.5 ± 0.70 (7–9.8)
6	Serum creatinine, (mg/dL)	1.38 ± 0.60 (0.6–2.8)

Number of subjects (n) = 146, Values are expressed as Mean ± standard deviation (SD),HbA1c: Glycated hemoglobin.

Table 2
Classification of hypoglycemia.

Sr. No	Random blood glucose categories	Number of subjects (%)	RBG (mg/dL); Mean ± SD
1	Level 1 hypoglycemia Glucose < 70 to ≥ 54 mg/dL	102 (70.83)	62.53 ± 4.67 (54–69)
2	Level 2 hypoglycemia Glucose < 54 mg/dL	44 (29.16)	46.05 ± 4.84 (35–53)

Number of subjects (n) = 146, Values are expressed as Mean ± standard deviation (SD).

Table 3
Anti-hyperglycemic agents (AHA), Hydroxychloroquine and associated risk of hypoglycemia during lockdown.

Sr. No	Anti-diabetic drugs	N (%)	RBG (mg/dl), Mean ± SD
1	Metformin + SU	96 (65.75)	60.95 ± 7.10 (36–78)
2	Metformin + SU + TZD	16 (10.96)	61.68 ± 3.45 (54–66)
3	Metformin + SU + DPP-4i	25 (17.12)	60.24 ± 5.26 (43–67)
4	Metformin + SGLT-2 inhibitors	12 (8.33)	60.53 ± 8.12 (44–69)
5	Insulin	49 (33.56)	50.75 ± 8.20 (35–67)
6	Hydroxychloroquine 400 mg OD	28 (19.17)	54.82 ± 4.76 (36–61)
7	Hydroxychloroquine 400 mg BD	49 (33.56)	52.95 ± 7.03 (35–67)

n: Number of subjects; RBG: Random blood glucose; SU: Sulfonylureas; TZD: Thiazolidinediones; DPP-4i: Dipeptidyl peptidase-4 inhibitor; SGLT-2 inhibitors: Sodium-glucose co-transporter-2 inhibitors, OD: Once a day, BD: Twice a day.

Table 4
Associated co-morbidities and risk of hypoglycemia during lockdown.

Sr. No	Associated complications	N (%)	Random blood glucose, mg/dl (Mean ± SD)
1	Nephropathy	49 (33.56)	50.75 ± 8.20 (35–68)
2	Ischemic Heart Disease (IHD)	27 (18.49)	56.51 ± 8.98 (35–67)
3	Congestive Cardiac Failure (CCF)	17 (11.64)	50.71 ± 7.94 (39–68)
4	Cerebrovascular accident (CVA)	34 (23.29)	55.64 ± 8.62 (39–68)
5	Diabetic foot	37 (25.34)	58.54 ± 6.59 (42–67)
6	Hypertension (HTN)	68 (46.58)	53.94 ± 9.01 (35–68)
7	Nephropathy + Diabetic Foot	7 (4.80)	52.71 ± 7.64 (42–67)
8	IHD + CCF	4 (2.74)	54.25 ± 7.14 (44–60)
9	Nephropathy + IHD + CCF	48 (32.88)	52.31 ± 5.40 (44–61)

n = Number of subjects, IHD: Ischemic Heart Disease, CCF: Congestive cardiac failure, CVA: Cerebrovascular Disease, HTN: Hypertension.

The COVID-19 pandemic represents a huge burden to public health worldwide and healthcare services have faced severe challenges during outbreaks, resulting in major cutbacks in the care provided to people with chronic diseases, including diabetes [19,20]. Many outpatient clinics have had to change their routine interactions with the patient and use telemedicine to monitor patients at home. Diabetologists were concerned that glucose control could worsen during lockdown because of the limited possibility to exercise, the severe psychological stress imposed by social distancing in a cultural environment heavily reliant on direct interpersonal relationships and limited access to food supply and various other reasons especially in socio-economically weaker people in India [21].

In our study, sulfonylureas and insulin were the most commonly used anti-hyperglycemic agents associated with the risk of hypoglycemia. Dosage of oral anti-diabetic drugs may need to be re-adjusted based on the blood glucose parameters and the prevailing conditions. Patient's education, sick day guidelines and the need to more frequent monitoring of blood glucose are warranted to avoid hypoglycemia [21].

Many studies have reported that HCQ improves glycemic control in treatment-refractory patients with diabetes [22,23]. Inflammation has been said to be associated with impaired glucose control, the mechanism of HCQ hypoglycemic effect remains unclear. It has been described that patients on HCQ show a larger C peptide response, potentially reflecting an improved pancreatic β-cell function [23]. It has even been approved to treat T2DM in India as an add-on therapy for patients who do not achieve glycemic targets with two or more oral glucose-lowering drugs. Reduced intracellular insulin degradation and increased insulin accumulation have also been identified as possible effects of hydroxychloroquine in animals models [24]. Given the previously reported impact of hydroxychloroquine on glucose metabolism, caution should be taken when the drug is administered to patients with diabetes and COVID-19. A dose adjustment of the oral antidiabetic drugs and/or insulin is necessary to prevent potential hypoglycemic events.

Diabetes and its associated co-morbidities have a vicious relationship with hypoglycemia. Associated co-morbidities also increase the risk of hypoglycemia in patients with diabetes [25]. Diabetic kidney disease (DKD) is a significant risk factor for the development of hypoglycemia. Factors that predispose for risk of hypoglycemia in DKD are reduced renal insulin clearance, decreased degradation of insulin in peripheral tissues, reduced renal gluconeogenesis, and impaired renal excretion of commonly used AHA. The confluence of these factors may contribute to a greater risk for hypoglycemia among patients with CKD and may be an unintended consequence of therapy to treat hyperglycemia [26]. In our study, one-third patients of symptomatic hypoglycemia had diabetic kidney disease.

5. Conclusion

Hypoglycemia is a problem for many patients with diabetes, fundamentally iatrogenic, the result of therapeutic hyperinsulinemia. In the acute setting, hypoglycemia is deleterious, and clinical trials have demonstrated that a single episode of severe

hypoglycemia increases the risk of subsequent mortality and cardiovascular events. Patient education, support, and telemedicine plays a pivotal role to prevent hypoglycemia. The COVID-19 lockdown has shown to influence the risk of hypoglycemia in patients with T2DM, especially those receiving SU, insulin, HCQ especially in patients with associated co-morbidities.

Declaration of competing interest

None, Declared.

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