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New-Onset Hyperglycemia in Adult COVID-19 Patients

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Abstract: BACKGROUND: Adults without diabetes mellitus may experience transient hyperglycemia during a severe illness, and it is caused by a variety of circumstances. **AIM:** Assess the incidence of hyperglycemia in newly diagnosed COVID-19-infected patients without previous history of diabetic. Study the correlation between various risk factors of diabetics with the incidence of hyperglycemia. **PATIENTS AND METHODS:** A prospective cohort study which involved a recently newly diagnosed COVID-19-infected patient. Each patient was followed up prospectively for the duration of admission (two weeks), and random plasma glucose was recorded for each patient at diagnosis, during the active infection, and 14 days after remission. Patients with elevated blood glucose are treated with insulin therapy. The study was carried out in the Baghdad Teaching Medical City complex outpatient clinic. The study started in January 2021 and was completed in March 2021 (about three months). **RESULTS:** The study of 96 patients, with a mean age of 47.7 ± 15.1 years with a similar male-to-female ratio, 27.1% of the patients had hypertension, followed by asthma and ischemic heart disease (IHD). 41.7% of the patients had a positive family history of DM, and 68.8% used steroids during admission. There was a significant change in blood glucose from its baseline value to during infections (33.3% had levels above 200 mg/dl and reduced to 10.4%, whoever its value was not significantly elevated during remission (similar to baseline value). In Univariate analysis, the following factors were associate with the increased risk of hyperglycemia: increased age, male gender, hypertension, IHD, family history of diabetics, and use of steroid therapy. While in multivariate analysis, only age and steroid remain significant, which indicates both are independent predictors of hyperglycemia. **CONCLUSIONS**: The development of hyperglycemia is common in non-diabetics newly diagnosed with COVID-19.

Keywords: Hyperglycemia; Adult Covid-19 Patients; Infection; Family History; And Steroid Therapy.

INTRODUCTION

Severe sickness in persons without a known history of diabetes mellitus can lead to temporary high blood sugar levels, known as transient hyperglycemia. This condition is known as stress hyperglycemia and occurs due to several variables, such as elevated levels of cortisol, catecholamine, glucagon, and the growth hormone in the bloodstream [Marik, P. E. *et al*., 2020; Marik, P. E. *et al*., 2009]. These factors result in increased production of glucose, breakdown of glycogen, and reduced responsiveness to insulin. While not all people experience diabetes, stress hyperglycemia can serve as an indicator of poor glucose tolerance and an elevated likelihood of acquiring diabetes. In the context of critical care, the management of high blood sugar levels often necessitates the use of insulin infusions along with intermittent administration of short-acting insulin. Establishing the prevalence of stress-related hyperglycemia on critical illness is challenging due to insufficient data and differences in the definition for hyperglycemia. Stress hyperglycemia is characterized by a plasma glucose level that exceeds 200 mg/dL [van den Berghe, G. *et al*., 2001 – Abdul-Ghani, M. A. *et al*., 2010]. Considering the findings from the Leuven Intensive Insulin Therapy Trial, it is now important to take into account stress hyperglycemia in any critically sick patient whose blood glucose level exceeds 110 mg/d. The development of stress-induced hyperglycemia in critically sick individuals without preexisting type 2 diabetes is affected by the complicated metabolic environment and is a result of the activation of the response to stress [Gao, D. *et al*., 2009 – Duncan, A. E. *et al*., 2012]. The presence of excessive counterregulatory hormones that include glucagon, GH, catecholamines, glucocorticoids, and cytokines like to be IL-1, IL-6, and TNF-α, along with the administration of catecholamines, dextrose, alongside nutritional support, and relative insulin deficiency all contribute significantly [Sachwani, G. R. *et al*., 2016 – Perlman, S, 2020], the primary contributors to elevated blood sugar levels are heightened gluconeogenesis and impaired insulin sensitivity in the liver. Insulin resistance in sepsis patients plays a role in the development of stress-related hyperglycemia. In sepsis, the process of insulin-induced tyrosine phosphorylation for insulin receptor substrate-1 is disrupted, leading to the

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impairment of phosphatidylinositol 3-kinase activation [Zhou, P. *et al*., 2020; Hoffmann, M. *et al*., 2020]. As a consequence, there is a defect in the translocation of the glucose transporter (GLUT)-4 receptor, resulting in reduced glucose uptake in skeletal muscle and liver and ultimately causing insulin resistance [Stringhini, S. *et al*., 2020]. Glucose enhances the upregulation and plasma levels of matrix metalloproteinase-2 as well as matrix metalloproteinase-9, which facilitates the dissemination of inflammation. Patients with hyperglycemia are more likely to develop infections [Meyerowitz, E. A. *et al*., 2021]. There is an inverse correlation between glucose levels and the reactivity of leukocytes activated by inflammatory mediators in vitro [Li, F]. Acute high blood sugar levels decrease the amounts of nitric oxide in the endothelium, leading to aberrant responsiveness of blood vessels and impaired blood flow to organs. Glucose seems to have a toxic effect on critically unwell and wounded people, comparable to its toxicity in diabetes patients. Coronaviruses are significant infections that affect both humans and animals. [Cheng, H. Y. *et al*., 2020; Scott, R. A. *et al*., 2013]

2. METHODS

2.1. Study design

A prospective cohort study that involved a recently newly diagnosed COVID-19- infected patient (reverse transcriptase polymerase chain reaction, RT-PCR confirmed), the diagnosis according to the recent Iraqi guideline in 2021 [June] authorized by the Iraqi Ministry of Health **(Table 2.1)**. Severity of COVID-19 infections range from (mild, moderate, and severe, while critically ill patients were excluded). Each patient was followed up prospectively for the duration of admission, and random plasma glucose was recorded for each patient at diagnosis, during the active infection, and 14 days after remission. Patients with elevated blood glucose are treated with insulin therapy. After admission, COVID-19 patients were classified according to clinical evaluation to mild cases (no pneumonia on a CT scan), moderate cases (pneumonia on a CT scan), severe cases (respiratory rate ≥ 30 breaths /min, oxygen saturation ≤ 93% or patients with pneumonia on a CT scan) and critical cases (respiratory failure/need mechanical ventilation). All patients were treated according to the MOH treatment protocol which relies on patient severity status.

Table 2.1: WHO classification of COVID

Types	Findings
- Mild	Mild clinical symptoms [fever <38°C (quelled without treatment), with or without cough, no dyspnea, no gasping, no chronic disease] No imaging findings of pneumonia.
- Moderate	Fever, respiratory symptoms, imaging findings of pneumonia.
- Severe	Meet any of the following: a. Respiratory distress, RR ≥30 times/min b. SpO2 <93% at rest c. PaO2/FiO2 ≤ 300 mmHg C *Patients showing a rapid progression (>50%) on CT imaging within 24- 48 hours should be managed as severe (added in the trial sixth edition).
- Critical	Meet any of the following: a. Respiratory failure needs mechanical assistance b. Shock c. Extrapulmonary" organ failure, an intensive care unit is needed.

2.2. Study setting

The study was carried out in the Baghdad Teaching Medical City complex outpatient clinic. The study started in January 2021 and was completed in March 2021 (about three months).

2.3. Inclusion criteria

- Newly diagnosed COVID
- HbA1c [< 5.7%] (ADA criteria 2021 (30))
- Age above 18 years according to WHO criteria for adults

2.4. Exclusion criteria

- Diabetic patients.
- Patients with a history of malignancy.
- Pregnant women. (More than 24 weeks of gestation)
- Use of Diabetogenic drugs (Steroid, Phenytoin, Thiazide diuretics, cyclosporine)

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2.5. Measured variables

Patient's age, gender, family history of DM, past medical history, steroid use during admission, and random plasma glucose were taken from each patient.

2.6. Definition

New-onset hyperglycemia without diabetes:

American Diabetes Association (ADA) defines new-onset hyperglycemia without diabetes when a random glucose level ≥ 11.1 mmol/L (≥200 mg/dL) with symptoms of hyperglycemia in the absence of any history of diabetes in the past (Table 2.2).

Table 2.2- Criteria for the diagnosis of diabetes

FPG 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least eight hours.*
OR
2-h PG200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g of anhydrous glucose dissolved in water. *
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay. *
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, random plasma glucose is 200 mg/dL (11.1 mmol/L).

2.7. Statistical analysis

Anderson Darling test was done to asses if continuous variables follow a normal distribution; if they follow a normal distribution, then mean and standard deviation were used; if they did not follow a normal distribution, then median and interquartile range (25% to 75% percentile range) will be used to present the data and used to assess test-paired t. The change in blood glucose during the study. While logistic regression analysis is used to examine the risk factors for hyperglycemia SPSS 22.0.0 (Chicago, IL), GraphPad Prism version 8.0.0 for Windows, GraphPad Software, San Diego, California USA, software package used to make the statistical analysis, P-value considered when appropriate to be significant if less than 0.05.

RESULTS

The study of 96 patients, with a mean age of 47.7 ± 15.1 years with a similar male-to-female ratio, 27.1% of the patients had hypertension, followed by asthma and ischemic heart disease (IHD). 41.7% of the patients had a positive family history of DM, and 68.8% used steroids during admission, as illustrated in Table 3.1.

Table 3.1: Assessment of demographical and clinical data

Variables	Value
Number	96
Age (years), mean ± SD	47.7 ± 15.1
Gender, n (%)	
Female	46 (47.9%)
Male	50 (52.1%)
Past medical history, n (%)	
Asthma	8 (8.3%)
Hypertension	26 (27.1%)
IHD	6 (6.3%)
Family Hx of DM, n (%)	40 (41.7%)
Steroid use, n (%)	60 (68.8%)

There was a significant change in blood glucose during infection from its baseline value. Also, there is a significant change in post-remission glucose levels from the infection period (33.3% had levels above 200 mg/dl during infection and reduced to 2.1% post-remission), whoever its value was not significantly elevated during remission (similar to baseline value), as illustrated in **Table 3.2 and Figure 3.1.**

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Table 3.2: Assessment of new-onset diabetics

	Baseline at admission	During infection	Post remission
Total number	96	96	96
>200 mg/dl Diabetic	10 (10.4%)	32 (33.3%)	2 (2.1%)

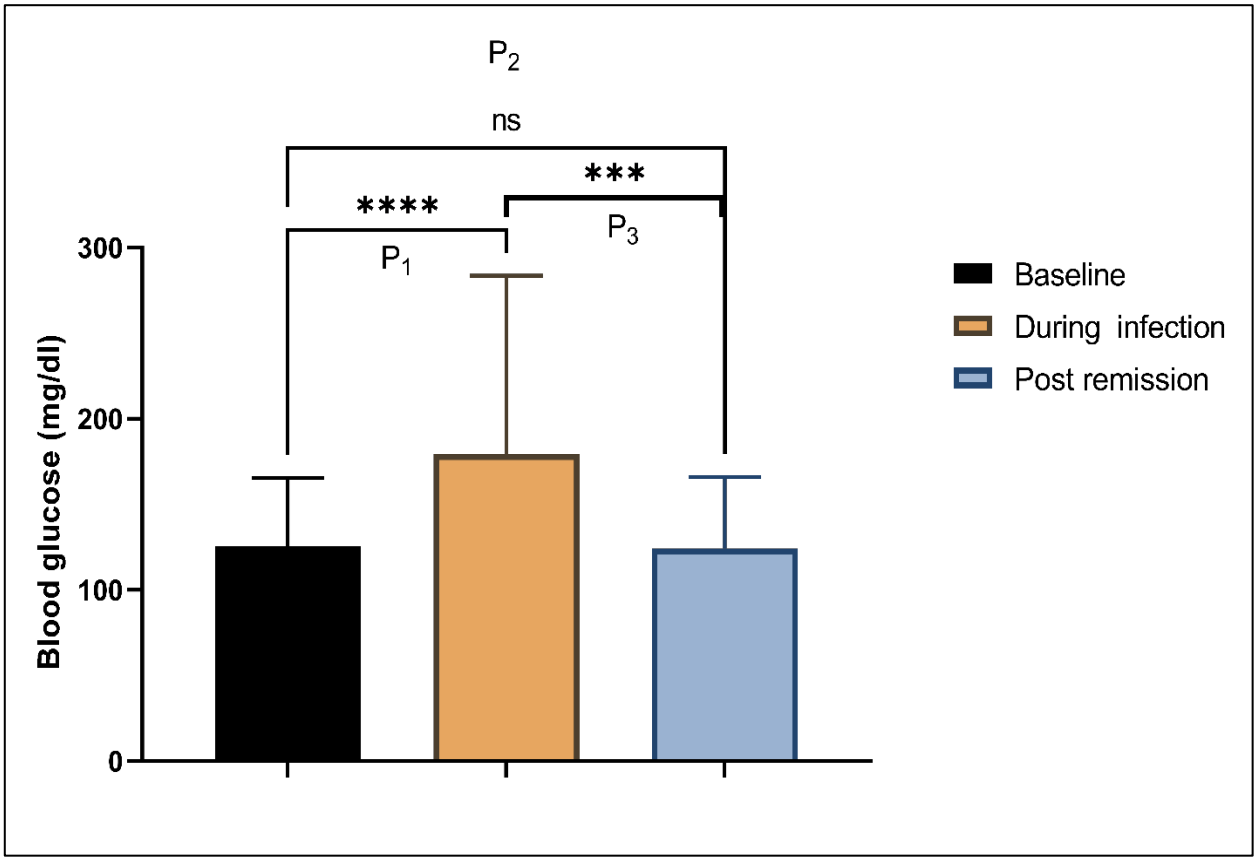

Figure 3.1: Assessment of blood glucose during the study

In univariate analysis, the following factors were associate with the increased risk of hyperglycemia: increased age, male gender, hypertension, IHD, family history of diabetics, and use of steroid therapy. While in multivariate analysis, only age and steroid remain significant, which indicates both are independent predictors of hyperglycemia, as illustrated in **Table 3.3.**

Table 3.3: Assessment of risk factors of hyperglycemia during admission

	OR (95%CI)	P-value	OR (95%CI)	P-value
	Univariate		Multivariate	
Age	1.118 (1.071-1.167)	<0.001	1.118 (1.058-1.180)	<0.001 [S]
Gender (male)	4.385 (1.708-11.257)	0.002	2.179 (0.602-7.887)	0.235
Hypertension	5.4 (2.053-14.205)	0.001	1.320 (0.380-4.586)	0.662
IHD	4.429 (0.766-25.6154)	0.097	1.313 (0.150-11.499)	0.806
FHx	3.667 (1.506-8.926)	0.004	2.024 (0.607-6.745)	0.251
Steroid	4.789 (1.501-15.283)	0.008	7.967 (1.415-44.863)	0.019 [S]

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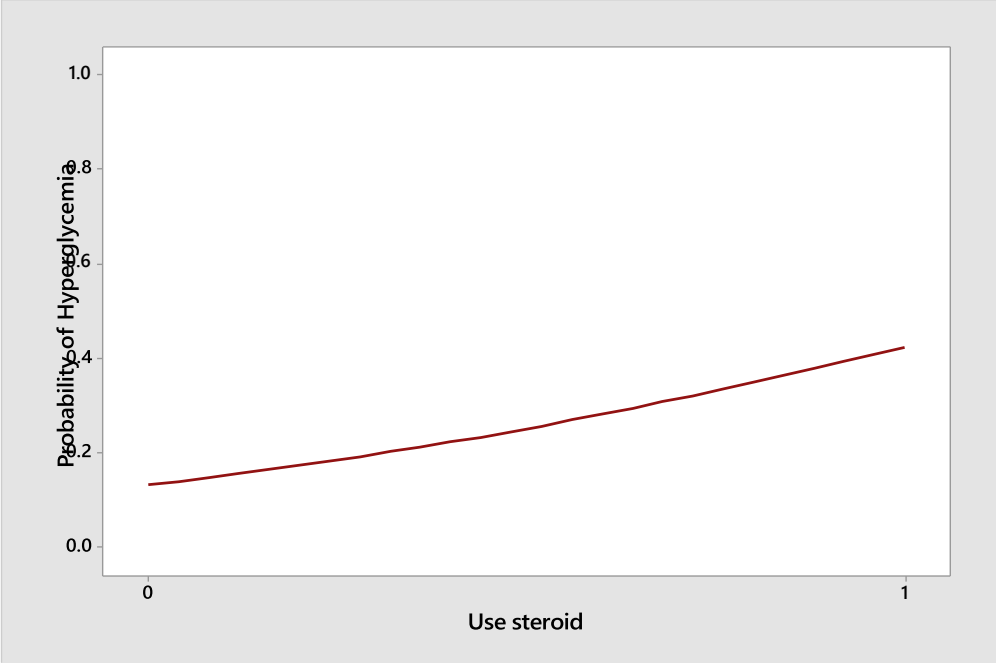

Figure 3.2: Probability plot that assesses the risk of hyperglycemia with steroid use.

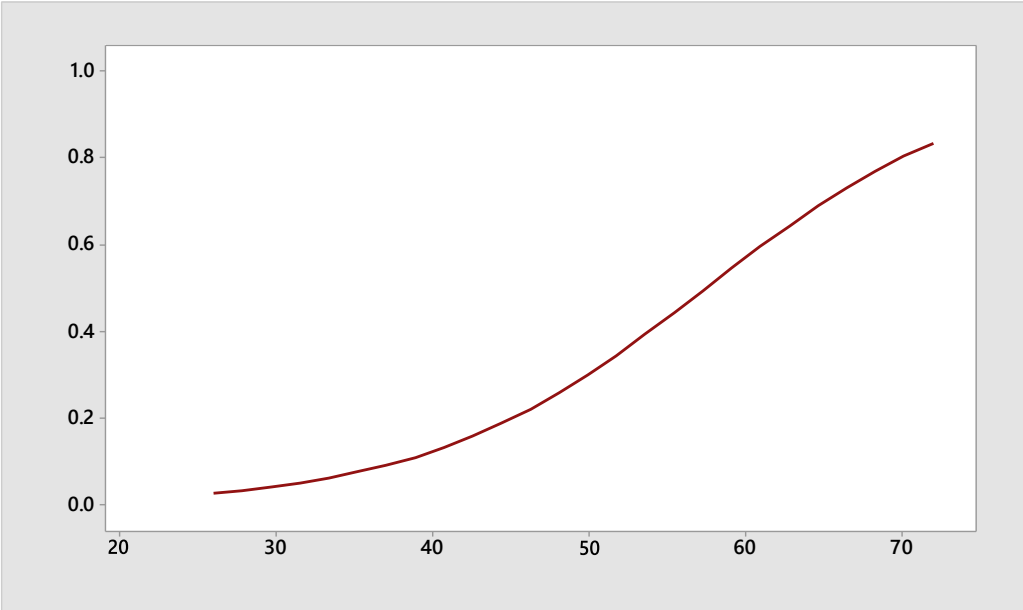

Figure 3.3: Probability plot that assesses the risk of hyperglycemia with age.

DISCUSSION

SARS-CoV-2 is responsible for the COVID-19 pandemic. Hyperglycemia, which is characterized by a blood glucose level over 200 mg/dL, can be observed in both diabetic and non-diabetic patients who are hospitalized for COVID-19. It is prevalent in patients admitted to the hospital for acute care and those who are critically sick, including individuals who have never had hyperglycemia. However, there is a scarcity of accurate data about the frequency and incidence of stress hyperglycemia during infection. [Meigs, J. B. *et al*., 2000; Menke, A. *et al*., 2015]

In this study, the initial blood glucose level at admission was 125.3±40.1 mg/dL. At this point, 10.4% for the patients were having levels above 200 mg/dL. Throughout the active infection period, the blood glucose level increased to 179.4±104.2 mg/dL [Bancks, M. P. *et al*., 2017]. At this stage, 33.3% of the total patients had levels of 200 mg/dL or higher. After remission, the blood glucose level decreased to 124.3±41.8 mg/dL. Only 2.1% of the patients were a blood glucose level above or below 200 mg/dL. A substantial change was seen from admission until the period during active infection (P-value <0.001) [Bancks, M. P. *et al*., 2017], whereas no significant change

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was observed between admission and after remission. The results of this study are consistent with previous research carried out by Sardu *et al*. In their study, 42.4% of patients had glycemic levels above 7.7 mmol/L and were diagnosed with hyperglycemia. Upon admission, the blood glucose levels of patients receiving insulin infusion had been 12.32 ± 1.48 mmol/L, while those not receiving insulin infusion had levels of 11.06 ± 1.98 mmol/L. The average blood sugar level throughout the hospital is 10.65 ± 0.84 mmol/L for the group that did not receive insulin infusion, as well as 7.69 ± 1.85 mmol/L for the group that received insulin infusion ($P < 0.001$). The insulin infusion group saw a larger decrease in plasma glucose levels compared to the group that did not receive insulin infusion (4.57 ± 1.09 vs. 1.96 ± 1.06 mmol/L; $P < 0.001$) after the treatment period. [Biggs, M. L; Del Prato, S]

New-onset hyperglycemia is being increasingly described with COVID-19 in adults without a previous history of diabetes, albeit with significant mortality and morbidity [Friedman, J. E. *et al*., 2010; DeFronzo, R. A. *et al*., 1993]. While infection-induced inflammation and cytokine activation and resultant insulin resistance could lead to stress hyperglycemia, it is uncertain as to what extent the direct viral destruction of islet cells with decreased insulin production and release might be contributing.

A more recent multicenter study from the UK describes an apparent increase in new-onset T1DM in children, with evidence of SARS-CoV-2 infection or exposure in some of these. Seventy percent (21/30) of children presented with DKA, and 52% (11/21) had severe DKA (pH 6.82–7.05). 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 hypokalemia, and one PCR-positive child suffered a hypokalemia-related cardiac arrest but recovered fully [Reis, J. P. *et al*., 2011]. Interestingly, the majority had only a short duration of preceding symptoms of diabetes, refuting the previous notion of delayed presentation as the reason for the increase in the incidence of DKA at disease onset. SARS-CoV-2 reduces ACE2 expression, leading to decreased degradation of angiotensin II, which can cause increased secretion of aldosterone and renal potassium loss. Whether this phenomenon was the basis for severe hypokalemia seen in the PCR-positive child needs further evidence. There are a few case reports of COVID-19 inducing acute onset diabetes and DKA in several individuals, mimicking T1DM. However, on follow-up, there was a reduced need for insulin, and ultimately, insulin could be discontinued in all the three patients. At the last follow-up, these patients had normoglycemia on oral antihyperglycemic medication. [Abbas, H. M. *et al*., 2021]

CONCLUSIONS

a. Development of hyperglycemia is common in non-diabetics newly diagnosed with COVID-19.

b. The majority of patients who develop hyperglycemia return to normal glycemic levels after remission.

c. Age and steroids are the main independent risk factors for the development of hyperglycemia in newly diagnosed COVID-19 patients.

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