Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 4477 - 4481
Received 16 February 2021; Accepted 08 March 2021.

Association of COVID-19 and Hba1c Levels and Other Clinical Characteristics in Patients with Critical Case Illnesses.

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Abstract
Hyperglycemia in critically ill patients is a serious indicator of disease intensity and is associated with higher death rate. The aim of the study is to to detect prevalence of hyperglycemia in COVID-19 patients' previous diabetes history and its relation to poor prognosis related to organ dysfunction. To achieve that goal Fifty Covid-19 PCR verified patients were enrolled in this study. HbA1c among many other parameters related to liver and renal function was performed beside two important inflammatory markers (IL-6, CRP).Results revealed that there is a strong correlation between hyperglycemia of the COVID 19 patients and many defects in vital organs function parameters beside the profound elevation in inflammatory parameters.

Keywords: COVID 19, Hyperglycemia, Inflammatory cytokines.

INTRODUCTION

Several studies indicated that dysglycemia whether it is hyperglycemia or hypoglycemia or even glycemic variability within time, have a significant association with death rate and before that considered as a vital bio-meter for the severity of a disease, although this role seems to be not significant in patients with previous diabetes mellitus (1,2). In the absence of diabetes, if blood glucose values exceeding 7.78 mmol/L it is called Stress hyperglycemia which is seen in severe acute illness (3). Since the declaration of Covid-19 as a disease in October 2019, diabetes was associated with a higher mortality rate and the need for intensive care. In critically ill patients with Covid-19, stress hyperglycemia is associated with dwindle clinical results through the hospitalization period (4), which may lead to extend of the duration hospital stay (5,6), a bio-meter that is closely related to poor outcomes in COVID-19 patients (7). Here we detected the evidence mounting hyperglycemia in the absence of previous diabetes in critically ill COVID-19 patients as an indicator of poor clinical outcomes represented by renal and liver functions, and as a consequences high mortality.

MATERIALS AND METHODS

Patients: Fifty Covid-19 PCR verified patients were enrolled in this study. They were admitted to in the wards or the intensive care units (ICU) of Baghdad teaching hospitals in Baghdad for the period from April 2020 to October 2020. COVID-19 was confirmed by

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reverse-transcriptase polymerase-chain-reaction assays of nasopharyngeal swab specimens.

Methods:

Biochemical analysis:

- HbA1c was measured upon admission (HBA1C assay are counted by Alere Afnion AS 100 analyzer , which is an in vitro diagnosis test for quantitative determination of glycated hemoglobin in human whole blood).
- Liver function and renal function levels were measured by an accredited clinical laboratory according to standard laboratory procedures.
- Serum Vitamin D: Serum level of vitamin D (25- hydroxyvitamin D [25(OH)D]) was measured using a radio-immunoassay RIA from the following source :(Vitamin D total, Roche Diagnostics, Mannheim, German) depending on the manufacturer's directory. The electro-chemiluminescence binding assay was performed by using Elecsys and Cobas immunoassay analyzers, with a measurement ranges of 3.00 to 70.0 ng/mL and 7.50 to 175 nmol/L. Vitamin D situation was defined depending on the classical classification as ''deficient'' (<20 ng/mL, level 1), ''insufficient'' (20–30 ng/mL, level 2), and ''sufficient'' (>30 ng/mL, level 3).
- Serum isolated from five milliliters vinous blood for each participant. The sera were assessed for IL-6 and CRP by an ELISA kit (CUSABIO, USA). The instructions of manufacturer were followed to assess the two variables.

Statistical analysis: A package for the social science system version SPSS 20 was used for data analyzing. ANOVA-test has been done to calculate previous studies. P value equal or less than 0.05 was considered as the level of statistically significance.

RESULTS

Table (1) shows that patients included in the study were classified according to HbA1c value into three categories. Twenty-seven (54%) were considered to have diabetes mellitus (HbA1c ≥ 6.5%), 14(28%) were considered prediabetic (HbA1c ≥ 5.7% < 6.5%), and 9 (18%) were consider asnon-Diabetic (HbA1c < 5.7%). None of all patients had ever required insulin before hospitalization indicating no previous history of diabetes. A higher maximum CRP and IL-6 levels were elevated in patients with increased HbA1c levels. There were no significant differences between BMI values among the three categories.

Table (1): Characteristics of involved patients, grouped by HbA1c value.

Characteristic Total 50 patient (%)	HbA1c < 5.7% *N* = 9(18%)	HbA1c ≥ 5.7 < 6.5% *N* = 14(28%)	HbA1c ≥ 6.5% *N* = 27 (54%)	P value
Age—median (years)	51.5 (42.3–58.2)	54.7(48.4–60.2)	55.2 (45.5–61.4)	NS
BMI—median (kg/m^2)	27.9 (25.9–30.1)	26.7 (26.5–33.2)	28.3 (25.7–31.3)	NS

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SARS-CoV-2-PCR positive—no. (%)	9(100%)	14(100%)	27 (100%)	
HbA1c—median (%)	5.3 (5.1–5.6)	6.1 (5.8–6.4)	6.6 (6.5–7.4)	0.01
Diabetes mellitus type I	1 (11.1)	3(21.4)	5 (18.5)	0.05
Diabetes mellitus type II	2 (22.2)	5(35.7)	11(40.7)	0.01

In the context of the wider coronavirus pandemic, an early evidence have raised that IL-6 can be used as an inflammatory indicator of severe COVID-19 infection with poor prognosis (8), and thus we chose IL-6 and CRP as two important indicative inflammatory markers, and their results in table (2) showed a significant elevation of both markers among group 3 markers.

Table (2): Inflammatory markers among study groups

Characteristic Total 50 patient (%)	HbA1c < 5.7% *N* = 9(18%)	HbA1c ≥ 5.7 < 6.5% *N* = 14(28%)	HbA1c ≥ 6.5% *N* = 27 (54%)	P value
Maximum CRP*—Median (mg/dl)	18.3 (16.9–20.9)	29.8 (19.7–35.9)	33.0 (22.4–35.8)	0.01
Maximum IL-6**—median (0– 16.4 (pg/Ml))	234.9 (189.7–277.3)	876.9 (345.8–1986.8)	965.8(386.9–2341.8)	0.001

*CRP C-reactive protein NV below 3.0 mg/L ; **IL-6 interleukin-6 NV(0– 16.4 pg/ml)

Table (3) shows a significant differences in liver function indicating parameters (TSB, S.AST, S.ALT, S.ALK.PHO.) except for S.ALT among the three categories with a clear increase in these parametes levels in group 3 (HbA1c ≥ 6.5%)

Table (3): levels of Liver function parameters

Liver function parameter	HbA1c < 5.7% *N* = 9(18%)	HbA1c ≥ 5.7 < 6.5% *N* = 14(28%)	HbA1c ≥ 6.5% *N* = 27 (54%)	P value
TSB Median (0.1-1mg/dl)	0.2 (0.1-0.5)	0.3 (0.1-0.7)	0.5 (0.3-0.9)	0.05
S.AST Median 8-55 (U/L)	35 (28-45)	54 (44-67)	61 (55-81)	0.05
S.ALT Median (7-45 U/L)	21(14-38)	33 (28-43)	37 (31-44)	NS
S.ALK.PHO. Median 20 to 140 (IU/L)	80 (67-120)	97 (88-128)	135 (128-148)	0.01
VD3 30-80 (ng /mL.)	22 (19-33)	25 (18-31)	23 (16-28)	NS

Regarding renal function parameters, it is very clear through table (4) that there is a significant differences in values of these parameters with a very clear and significant elevation in these parameters among members of group 3.

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Table (4): levels of Renal function parameters

Renal Function parameters	HbA1c < 5.7% *N* = 9(18%)	HbA1c ≥ 5.7 < 6.5% *N* = 14(28%)	HbA1c ≥ 6.5% *N* = 27 (54%)	P value
Urea Median (15-45mg/dl)	34 (22-43)	45 (38-59)	65 (55-78)	0.01
Creatinine Median (0.2-1.2mg/dl)	0.4 (0.3-0.9)	1.1 (0.9-1.2)	1.6 (1.3-2.8)	0.01

DISCUSSION:

Stress hyperglycemia is a frequent disorder in hospitalized patients in the absence of previous diabetes mellitus (DM) (9). There are many scenarios that can be accredited to interpret hyperglycemia in critically ill patients of COVID-19 as well as other serious infectious diseases. This type of hyperglycemia may be a result of many immune-inflammatory and hormonal alterations that characterize critical illness and systemic inflammation, represented by the presence of pro-inflammatory cytokines and increased levels of hormones that are counter regulatory to insulin (glucagon, cortisol, catecholamines and growth hormone), which may lead to increase in hepatic glucose generation (neoglucogenesis and glycogenolysis) combined by the peripheral resistance to insulin (10,11)

In 2016, Jafar *et.al.* revealed that hyperglycemia could change the response of the innate immune system through inducing Toll-like receptor expression or inhibiting neutrophil function, increasing permeability and decreasing vascular dilation (12). Also it can cause direct glycosylation of proteins, modifying the structure of complement proteins, ending with a case of hyper-cytokinemia (12,13) Varga *et.al.* demonstrates that the presence of coronavirus particles in endothelial cells of several organs may lead to "endotheliitis" as a possible mechanism of organ failure represented by abnormal organs function parameters, as our results pointed, leading to critical illness in COVID-19 patients which may be associated with endothelial dysfunction associated in both pre-diabetes and diabetes (14).

The clear inflammatory activation among our patients represented by IL-6 and CRP concentrations was in agreed with many studies that have the same results which proposed to be associated with decreased insulin secretion and increased insulin resistance as in many other infectious diseases (15,16). Sardu et al also (17) showed that hyperglycemia during hospitalization correlated with interleukin-6 and D-dimer concentrations in COVID-19 patients. Regarding the liver and renal abnormal concentrations of their markers, it is unknown whether it is due to the stress hyperglycemia or due to the direct consequences of coronavirus pathogenicity mechanisms, for that we recommend further studies with bigger sampling to reveal the reasons causes these abnormalities. We also recommend that HbA1c to be included with the routine laboratory investigation that COVID-19 patients should undergo the moment they admit the hospitals.

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