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Diabetes & Metabolic Syndrome: Clinical Research & Reviews 14 (2020) 1641–1644

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

At-admission hyperglycemia is consistently associated with poor prognosis and early intervention can improve outcomes in patients with COVID-19

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ARTICLE INFO

Article history:
Received 22 August 2020
Received in revised form
27 August 2020
Accepted 28 August 2020

Keywords:
At-admission hyperglycemia
COVID-19
SARS-CoV-2
Outcomes
Early interventions

ABSTRACT

Background & Aims: At-admission hyperglycemia have been associated with poorer outcome during critical illnesses. At-admission hyperglycemia in previously unknown diabetes is not uncommonly encountered entity in patients with COVID-19. We sought to find out the outcomes of at-admission hyperglycemia and effect of early intervention to achieve optimal glycemic control in relation to COVID-19 patients.

Methods: We searched the PubMed and Google Scholar database up till August 20, 2020 using specific keywords related to our aims and objectives.

Results: All currently available evidences clearly hint that at-admission hyperglycemia in patients with COVID-19 is associated with a poorer outcome, compared with normoglycemic individuals. Fortunately, early intervention by achieving an optimal glycemic control has also been associated with a significant improvement in the outcomes in patients with COVID-19.

Conclusion: At-admission hyperglycemia should be taken seriously by all clinicians treating patients with COVID-19. All efforts should be made towards an optimal glycemic control in patients with COVID-19, even in absence of pre-existing diabetes.

1. Introduction

At-admission hyperglycemia observed during acute medical or surgical illnesses has been a medical conundrum for a long time. While some find at-admission hyperglycemia as a provocateur, others believe this entity as an innocent bystander [1]. Whatever may be the argument, at-admission hyperglycemia is attributed to – a. Physiological response to the stress hormones (epinephrine or cortisol) released during acute illness that could be directly proportional to the severity of illness, b. Impaired insulin signaling due to metabolic dysregulations associated with the severity of illness. Irrespective of the patho-physiological mechanism, exaggerated inflammatory response induced by stress-hyperglycemia has been linked to endothelial dysfunction, increased oxidative stress as a result of free radial formation, consequently inducing a prothrombotic state leading to cellular and tissue injury in critically-ill patients [2]. Notably, at-admission hyperglycemia has often been linked to a poorer clinical outcome during the critical illnesses [3,4], acute coronary syndrome [5,6] and revascularization procedures [7,8]. Intriguingly, stress-induced hyperglycemia encountered at hospital admission in people who had no history of diabetes has been shown to carry a worser prognosis, compared to individuals with diabetes [9].

Similarly, at-admission hyperglycemia was an independent predictor of poor outcome during the past Severe Acute Respiratory Syndrome Coronavirus infection-1 (SARS-CoV-1) that used angiotensin converting enzymes 2 (ACE2) as a principal entry receptor. It was believed that hyperglycemia induced glycosylation of ACE2 may be associated with an increase in clinical severity with SARS-CoV-1 infection [10]. Since ACE2 is also a principal entry receptor for SARS-CoV-2 infection, it is conceivable that at-admission hyperglycemia may also be associated with a poor outcome in patients with Coronavirus disease-2019 (COVID-19). Recently, we reviewed the literature on outcomes associated with new-onset hyperglycemia with or without blood glucose in diabetes range in patients with COVID-19 [11]. In this short communication, we

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https://doi.org/10.1016/j.dsx.2020.08.034
1871-4021/

Table 1
At-admission hyperglycemia and its outcome in patients with COVID-19.

First Author	N	Normo-glycemia (n)	New-onset hyper-glycemia without diabetes (n)	New-onset/ Newly detected diabetes (n)	Known diabetes (n)	Results	Remarks
		Group 1	Group 2	Group 3A	Group 3B		
Fadini et al.[12]	413	306	NA	21*	86	At-admission blood glucose level was closely correlated with severity and adverse outcome, and a significantly stronger association (interaction $p < 0.001$) was observed in patients with new-onset diabetes, compared with those having pre-existing diabetes. At each 2 mmol/L (36 mg/dL) increase in FPG at admission had a significantly (21% relative) increase in severity (RR 1.21; 95% CI, 1.11−1.32; $p < 0.001$). In unadjusted analysis, Group 3A showed a stronger association in increase ($p = 0.004$) in ICU admission or death (RR 3.06; 95% CI, 2.04−4.57) than Group 3B (RR 1.55, 95% C.I. 1.06−2.27) when compared with Group 1. Even after the adjustment for age and sex, Group 3A had strong association and a significant increase in ICU admission and death compared with Group 3B and Group 1.	At-admission hyperglycemia had adverse outcomes in patients with COVID-19.
Coppelli et al.[13]	271	149^	66^	NA	56	Only hyperglycemia at admission (Group 2) remained an independent predictor of mortality (HR 1.80; 95% CI 1.03−3.15; $p = 0.04$) after the multiple adjustments. Mortality was significantly higher in Group 2 compared with Group 1 (39.4% vs. 16.8%; unadjusted HR 2.20; 95% CI, 1.27−3.81; $p = 0.005$) and only marginally higher in Group 3B compared to Group 1 (28.6% vs. 16.8%; unadjusted HR 1.73; 95% CI, 0.92−3.25; $p = 0.09$).	At-admission hyperglycemia is an independent predictor of adverse outcomes in patients with COVID-19.
Liu et al.[14]	123	33	69[$]	NA	21	Multivariate logistic regression analysis found FBG on admission was an independent risk factor for critical illness (OR 1.25; 95% CI, 1.03−1.51). Even after adjustment of previous diabetes, FBG was risk factor for predicting critical illness (OR 1.25; 95% CI, 1.06−1.47).	At-admission hyperglycemia had adverse outcomes in patients with COVID-19.
Wu et al.[15]	2041	1078	963[$] [including known DM]	NA	274	Multivariable Cox model analysis found, admission blood glucose level as an independent risk factor for progression to critical cases/death (HR 1.30; 95% CI, 1.03−1.63; $p = 0.026$). Similarly, higher admission blood glucose level had a significantly increase in in-hospital mortality (HR 1.84; 95% CI, 1.14−2.98; $p = 0.013$) at 30-days.	At-admission hyperglycemia is an independent predictor of adverse outcomes in patients with COVID-19.
Smith et al.[16]	184	26[#]	54[#]	29[#] [6 from Group 1 and 23 from Group 2]	104	Mean FBG at admission was also significantly higher with intubated vs. non-intubated patients (238.0 vs. 163.7 mg/dL; $p = 0.013$).	At-admission hyperglycemia had adverse outcomes in patients with COVID-19.
Iacobellis et al.[17]	85	NA	NA	NA	27	Day-1 average blood glucose was the strongest independent variable predicting radiographic abnormalities.	At-admission hyperglycemia had adverse outcomes in patients with COVID-19.
Cariou et al.[18]	1317	NA	NA	NA	1317	At admission plasma glucose level was significantly associated with an increase in composite of intubation or death ($p = 0.0001$) and death ($p = 0.006$) on day 7, in age and sex-adjusted nonlinear models.	At-admission hyperglycemia had adverse outcomes in patients with COVID-19.
At-admission hyperglycemia and effect of early intervention							
Sardu et al.[19]	132	NR	102[@]	NA	30	A decrease in glucose levels within 24 h of admission was associated with a lower rate of progression to severe disease and death at 20 days in both Group 2 and Group 3B.	Early intervention improves the outcome.
Sardu et al.[20]	59	26	7[@]	NA	26	At-admission hyperglycemic patients receiving insulin infusion had significantly less events in composite end-points (admission to an intensive care unit, use of invasive ventilation, or death), compared to those not receiving insulin infusion (33.3 vs. 80.0%, $p = 0.03$).	Early and intensive intervention improves the outcome.

FPG-fasting plasma glucose; FBG-fasting blood glucose; OR-odds ratio; HR-hazard ratio; RR-risk ratio; ICU- intensive care unit; NA-not available/applicable; DM-diabetes mellitus; * Group 3A: defined by a HbA1c $\geq$ 6.5% or a random glucose level $\geq$11.1 mmol/L ($\geq$200 mg/dL) with signs and symptoms of hyperglycemia; ^ Group 1: at-admission blood glucose <7.78 mmol/L (<140 mg/dL), Group 2: no diabetes and glucose $\geq$7.78 mmol/L ($\geq$140 mg/dL) at admission; [$] FBG $\geq$6.1 mmol/L ($\geq$110 mg/dL); [#] Group 1: HbA1C < 5.7% and FBG $\leq$ 125 mg/dL, Group 2: Prediabetes/HbA1C of 5.7−6.4%, Group 3A: persistently elevated FBG >125 mg/dL and requiring insulin therapy; [@] at-admission hyperglycemia was defined, if plasma glucose >7.77 mmol/l (>140 mg/dL).

sought to review and descriptively analyze the studies that evaluated the outcomes of at-admission hyperglycemia in patients with COVID-19. Additionally, we also evaluated the outcomes associated with early intervention in patients with COVID-19, who presented with at-admission hyperglycemia.

2. Methods

We searched the PubMed and Google Scholar database up till August 20, 2020 using specific keywords that includes “COVID-19”, OR “SARS-CoV-2” AND “At-admission hyperglycemia”, OR “Clinical severity”, OR “Outcomes”, OR “Glycemic control”. We retrieved full

text of all the articles including the cross references related to our topics published in English language.

3. Results

Nine studies so far have studied the outcomes of at-admission hyperglycemia in patients with or without diabetes and COVID-19. While 2 studies additionally evaluated the outcomes with new-onset hyperglycemia, 2 studies also evaluated the outcomes of early intervention to achieve optimal glycemic control in patients with COVID-19 and higher at-admission hyperglycemia.

3.1. Studies that evaluated the outcomes of at-admission hyperglycemia in patients with COVID-19

Several studies have recently evaluated the outcomes of at-admission hyperglycemia in patients with COVID-19. While in some studies at-admission hyperglycemia was defined when blood glucose measured at the time of hospital admission was higher, other studies defined it when fasting plasma glucose (FPG) measured on the immediate next day of admission were higher. In a retrospective analysis of 413 patients with COVID-19, Fadini et al. [12] showed at-admission blood glucose level was closely correlated with increased clinical severity and adverse outcomes, and a significantly stronger association (interaction $p < 0.001$) was observed in patients with new-onset diabetes (defined by a HbA1c $\geq$ 6.5% or a random glucose level $\geq$11.1 mmol/L [$\geq$200 mg/dL] with signs and symptoms of hyperglycemia), compared with those having pre-existing diabetes. Moreover, with each 2 mmol/L (36 mg/dL) increase in fasting plasma glucose (FPG) at admission, there was a significant (21% relative) increase in severe COVID-19 (Risk Ratio [RR] 1.21; 95% Confidence Interval [CI], 1.11–1.32; $p < 0.001$). Similarly, another very recent retrospective study of 271 patients of COVID-19, Coppelli and Colleagues [13] have concluded that only hyperglycemia at admission remained as an independent predictor of mortality (Hazard Ratio [HR] 1.80; 95% CI 1.03–3.15; $p = 0.04$), after the multiple adjustments of other confounders. In addition, mortality was significantly higher in cohorts with "new-onset" hyperglycemia without diabetes (no history of diabetes in past and glucose $\geq$7.78 mmol/L [$\geq$140 mg/dL] at admission), compared with normoglycemic (<7.78 mmol/L) patients (39.4% vs. 16.8% respectively; unadjusted HR 2.20; 95% CI, 1.27–3.81; $p = 0.005$) with COVID-19. Interestingly, mortality was not significantly higher in patients with pre-existing diabetes, compared with normoglycemic COVID-19 (28.6% vs. 16.8% respectively; unadjusted HR 1.73; 95% CI, 0.92–3.25; $p = 0.09$). This suggest, unaccustomed acute hyperglycemia, irrespective of underlying mechanism in previously unknown diabetes, carries a poorer prognosis compared with accustomed pre-existing diabetes.

Unsurprisingly, these findings are aligned and consistent with other studies that looked for outcomes with at-admission hyperglycemia in patients with COVID-19. In a multivariate logistic regression analysis, Liu et al. [14] found fasting blood glucose (FBG) on admission was an independent risk factor for critical illness (Odds Ratio [OR] 1.25; 95% CI, 1.03–1.51), and even after the adjustment of previous diabetes, FBG was an independent risk factor for predicting critical illness (OR 1.25; 95% CI, 1.06–1.47). In a larger retrospective study ($n = 2041$), Wu et al. [15] showed at-admission blood glucose level was an independent risk factor for progression to critical illness and or death (HR 1.30; 95% CI, 1.03–1.63; $p = 0.026$) in a multivariable Cox model analysis, and a higher at-admission blood glucose level ($\geq$6.1 vs. <6.1 mmol/L or $\geq$110 mg/dL vs. <110 mg/dL)) had a significant increase in in-hospital death (HR 1.84; 95% CI, 1.14–2.98; $p = 0.013$) at 30-days. Smith et al. [16] found mean FBG at admission to be significantly higher in intubated vs. non-intubated patients (238.0 vs. 163.7 mg/dL; $p = 0.013$). Indeed, in a small retrospective analysis, Iacobellis et al. [17] showed at-admission hyperglycemia to be the strongest independent variable predicting radiographic abnormalities in patients with COVID-19. Needless to mention, at-admission plasma glucose level was significantly associated with an increase in composite of intubation or death ($p = 0.0001$) the primary outcome, and the death ($p = 0.006$) a secondary outcome on day 7, in age and sex-adjusted nonlinear models of CORONADO (Coronavirus disease and diabetes outcome) study ($n = 1317$), conducted in patients with pre-existing diabetes [18].

3.2. Outcomes with early intervention in patients with COVID-19 with at-admission hyperglycemia

Only a limited number of studies have reported the outcomes whether early and intensive treatment with insulin can improve the outcome in COVID-19 patients with at-admission hyperglycemia. To this end, Sardu et al. [19] demonstrated that in patients with hyperglycemia without diabetes and pre-existing diabetes ($n = 132$), a decrease in glucose levels within 24-h of admission was associated with a lower rate of progression to severe disease and death at 20-days. Similarly, in another study ($n = 59$) Sardu et al. [20] demonstrated that at-admission hyperglycemic patients receiving insulin infusion had significantly less events in composite end-points (admission to an intensive care unit, use of invasive ventilation, or death), compared to those not receiving insulin infusion (33.3 vs. 80.0% respectively, $p = 0.03$). Table 1 summarizes the finding from studies done to evaluate the outcomes associated with at-admission hyperglycemia in patients with COVID-19. Additionally, some studies also evaluated the outcomes in patients with new-onset hyperglycemia with or without diabetes, compared with normoglycemic individuals and pre-existing diabetes with COVID-19.

Collectively, this suggest that at-admission hyperglycemia is associated with poor outcomes. Moreover, these findings have immense importance in the context of countries like India given that prevalence of undiagnosed diabetes is very high and being detected for the first time during this pandemic of COVID-19. Furthermore, this underlines the importance of recent *call for action* for strict glycemic control in patients with COVID-19 by the group of Indian clinicians [21].

4. Conclusions

In summary, these evidences suggest – a. At-admission hyperglycemia is strongly correlated with poorer outcomes in patients with COVID-19, b. An early intervention to optimally lower the blood glucose might help in improving the outcomes, although we still lack large intervention studies in such patients with COVID-19. Nevertheless, all attempts must be made to achieve an optimal glycemic control in those having at-admission hyperglycemia, even in the absence of pre-existing diabetes. This is in concordance to a recent *call for action* for strict glycemic control in patients with COVID-19 by the group of Indian clinicians.

Funding

None.

Authors contribution

AKS conceptualized and RS retrieved all the related articles. AKS wrote the first draft. AKS and RS revised the manuscript and both authors agreed to submit the manuscript.

Declarations of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no financial support for this work.

Authorship

All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship and take responsibility for the integrity of the work. They confirm that this paper will not be published elsewhere in the same form, in English or in any other language, including electronically.

Declaration of competing interest

We hereby declare that we have no conflict of interest, related to this article.

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