Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company’s public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
At-admission hyperglycemia is consistently associated with poor prognosis and early intervention can improve outcomes in patients with COVID-19

Awadhesh Kumar Singh*, Ritu Singh

Department of Diabetes & Endocrinology, G.D Hospital & Diabetes Institute, Kolkata, India

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.

© 2020 Diabetes India. Published by Elsevier Ltd. All rights reserved.

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 worsen 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
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 |
|--------------|----|-------------------|---------------------------------------------|-----------------------------------------|--------------------|---------|---------|
| Fadini et al. | 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% CI, 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. | 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. | 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. | 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. | 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. | 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. | 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. | 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. At-admission hyperglycemia patients receiving insulin infusion had significantly less events in composite endpoints (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 intervention improves the outcome. |

Sardu et al. | 59 | 26 | 7* | NA | 26 | 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 ≥ 6.5% or a random glucose level ≥11.1 mmol/L (≥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 ≥7.78 mmol/L (≥140 mg/dL) at admission; * Group 1: HbA1C < 5.7% and FBG ≥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).

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 > 6.5% or a random glucose level ≥11.1 mmol/L ≥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 ≥7.78 mmol/L ≥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, unacclimated 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 (≥6.1 vs. <6.1 mmol/L or ≥110 mg/dL vs. <110 mg/dL)) had a significant increase in inhospital 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, Jacobells 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.

References

[1] Hyperglycemia and adverse outcomes in acute coronary syndromes: is serum glucose the provocateur or innocent bystander? Diabetes 2014;63:2209–12.
[2] Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metab 2002;87:978–82.
[3] Whitcomb BW, Pradhan EK, Pittas AG, Roghmann MC, Perencevich EN. Impact of admission hyperglycemia on hospital mortality in various intensive care unit populations. Crit Care Med 2005;33: 2772–77.
[4] Falciglia M, Freyberg RW, Almenoff PL, D’Alessio DA, Render ML. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. Crit Care Med 2009;37:3001–9.
[5] Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet 2000;355:773–8.
[6] Angeli F, Verdecchia P, Karthikeyan G, et al. New-onset hyperglycemia and inpatient mortality and major adverse cardiac events after primary percutaneous coronary intervention in patients without diabetes mellitus. Angiology 2014;65:154–9.
[7] Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. Lancet 2009;373:1798–807.
[8] Yang JK, Feng Y, Yuan MY, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med 2006;23:623–8.
[9] Singh AK, Singh R. Hyperglycemia without diabetes and new-onset diabetes are both associated with poorer outcomes in COVID-19. Diabetes Res Clin Pract 2020. https://doi.org/10.1016/j.diabetres.2020.108382. Epub ahead of print.
[10] Fadini GP, Morieri ML, Boscari F, Fioretto P, Maran A, Busetto L, et al. Newly-diagnosed diabetes and admission hyperglycemia predict COVID-19 severity by aggravating respiratory deterioration. Diabetes Res Clin Pract 2020. https://doi.org/10.1016/j.diabetres.2020.108374.
[11] Coppelli A, Giannarelli R, Aragona M, et al. Hyperglycemia at hospital admission is associated with severity of the prognosis in patients hospitalized for COVID-19: the Pisa COVID-19 Study. Diabetes Care 2020. https://doi.org/10.2337/dc20-1380.
[12] Liu Q, Chen H, Li J, et al. Fasting blood glucose predicts the occurrence of critical illness in COVID-19 patients: a multicenter retrospective cohort study. Infect 2020;8:120–3.
[13] Wu J, Huang J, Zhu G, et al. Elevation of blood glucose level predicts worse outcomes in hospitalized patients with COVID-19: a retrospective cohort study. BMJ Open Diab Res Care 2020;8:e001476. https://doi.org/10.1136/bmjdrc-2020-001476.
[14] Smith SM, Boppana A, Trauman JA, et al. Impaired glucose metabolism in patients with diabetes, prediabetes and obesity is associated with severe Covid-19. medRxiv 2020. https://doi.org/10.1101/2020.06.04.20125677. preprint doi.
[15] Iacobellis G, Penaherrera CA, Bermudez LE, et al. Admission hyperglycemia and radiological findings of SARS-CoV2 in patients with and without diabetes. Diabetes Res Clin Pract 2020;164:108185.
[16] Cariou B, Hadjadj S, Wargny M, Pichelin M, Al-Salameh A, Allix I, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. Diabetologia 2020. https://doi.org/10.1007/s00125-020-05180-x.
[17] Sardu C, D’Onofrio N, Balestrieri ML, et al. Hyperglycemia on admission to hospital and COVID-19. Diabetologia 2020. https://doi.org/10.1007/s00125-020-05216-2.
[18] Sardu C, D’Onofrio N, Balestrieri ML, et al. Outcomes in patients with hyperglycemia affected by Covid-19: can we do more on glycemic control? Diabetes Care 2020. https://doi.org/10.2337/dc20-0723.
[19] Emoto M, Iwakiri R, Ono H, et al. Prognostic factors of critically ill COVID-19 patients with diabetes, prediabetes and obesity is associated with severe Covid-19. Diabetes Metab J 2020. https://doi.org/10.4093/dmj.2020.44.5.384. Epub ahead of print.