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.

Contents available at ScienceDirect

Diabetes Research and Clinical Practice

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

Commentary

Hyperglycemia without diabetes and new-onset diabetes are both associated with poorer outcomes in COVID-19

Awadhesh Kumar Singh *, *Ritu Singh*

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

ARTICLE INFO

Article history:
Received 17 August 2020
Accepted 18 August 2020
Available online 25 August 2020

Keywords:
New-onset hyperglycemia
New-onset diabetes
COVID-19
SARS-CoV-2
Outcomes

ABSTRACT

Hyperglycemia with or without blood glucose in diabetes range is an emerging finding not uncommonly encountered in patients with COVID-19. Increasingly, all evidence currently available hints that both new-onset hyperglycemia without diabetes and new-onset diabetes in COVID-19 is associated with a poorer outcome compared with normoglycemic individuals and people with pre-existing diabetes.

1. Introduction

Presence of diabetes was an independent factor associated with poor outcomes during the past coronavirus infections such as Severe Acute Respiratory Syndrome Coronavirus-1 (SARS-COV-1) in 2003 [1] and Middle-East Respiratory Syndrome Coronavirus (MERS-CoV) in 2012 [2]. Interestingly, acute diabetes was commonly observed finding during SARS-COV-1 in patients without prior history of diabetes and without using glucocorticoids, and was an independent predictor for mortality [1]. This acute hyperglycemia was linked to binding of SARS-COV-1 to the angiotensin-converting enzyme 2 (ACE2) receptor present in pancreatic islets with resulting islet damage [3]. It should be noted that knockout of ACE2 gene lead to an acute diabetes in experimental animal studies [4].

While presence of diabetes has been frequently associated with severe Coronavirus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), "new-onset" hyperglycemia with or without diabetes and acute metabolic decompensation of pre-existing diabetes associated with COVID-19 is also not an uncommonly recognized phenomenon. These findings hint to a bidirectional relationship between diabetes and COVID-19. An international group of leading diabetes researchers participating in the CoviDIAB Project, have established a global registry of patients with COVID-19-related diabetes [5]. Nevertheless, emerging data increasingly suggests that "new-onset"

* Corresponding author.
E-mail address: drawadheshkumarsingh@gmail.com (A.K. Singh).
https://doi.org/10.1016/j.diabres.2020.108382
0168-8227/

hyperglycemia is a frequently observed finding especially in admitted patients with COVID-19, who had no history of dysglycemia or diabetes in the past and were currently not on corticosteroids. This entity of "new-onset" hyperglycemia could be classified as - a. "stress-induced" hyperglycemia, b. "new-onset diabetes" in previously unrecognized pre-diabetes, c. hyperglycemia possibly related to SARS-CoV-2 direct effect on pancreas and, d. drug-induced hyperglycemia or "secondary diabetes" during the course of treatment for COVID-19, especially with frequent use of corticosteroids.

American Diabetes Association (ADA) defines new-onset hyperglycemia without diabetes when fasting plasma glucose (FPG) is between 5.6 and 6.9 mmol/L (100–125 mg/dL) and/or HbA1c is between 5.7 and 6.4%, in absence of dysglycemia in past. Similarly, new-onset diabetes would be defined in presence of two abnormal samples either FPG is ≥ 7.0 mmol/L (≥126 mg/dL) or HbA1c ≥ 6.5% or a random glucose level ≥ 11.1 mmol/L (≥200 mg/dL) with symptoms of hyperglycemia, in absence of any history of diabetes in past [6]. Since a stress response to an acute viral infection such as COVID-19 can unlikely impact the HbA1c but may increase the plasma glucose, thus a single FPG value of ≥ 7.0 mmol/L (≥126 mg/dL) in absence of HbA1c ≥ 6.5% has been labelled by researchers as new-onset hyperglycemia without diabetes. Intriguingly, while some studies have used the ADA criteria to define new-onset hyperglycemia with or without diabetes, few had overlapped value of FPG and HbA1c and others have used a completely different cut-off value to evaluate the outcomes in individuals with COVID-19.

Ceriello *et al.* [7] and Apicella *et al.* [8] have evaluated a possible pathogenic mechanism of new-onset hyperglycemia in patients with COVID-19. Authors have proposed insulin resistance and possibly insulin secretory defects, both might be at interplay in precipitating acute glycemia in patients with COVID-19, even in the absence of pre-existing diabetes. In this commentary, we sought to review and descriptively analyze the studies that evaluated the outcomes in patients with COVID-19 with "new-onset" hyperglycemia with or without diabetes.

1.1. *Outcomes in patients with new-onset hyperglycemia without diabetes versus normoglycemic COVID-19*

One of the first study by Bode *et al.* [9] found that hyperglycemia in people with diabetes (HbA1c ≥ 6.5%) or, without diabetes (defined as two or more blood glucoses > 180 mg/dL occurred within any 24-hour period with an HbA1C < 6.5% or no HbA1C testing done during hospitalization) was significantly associated with an increase in mortality with COVID-19, compared to people with normoglycemia (28.8% vs. 6.2% respectively; p < 0.001). Zhang *et al.* [10] reported a significant increase (Odds ratio [OR] 5.47; 95% confidence interval [CI], 1.51–19.82; p = 0.010) in composite outcomes risk (mechanical ventilation [MV], admission in intensive care unit [ICU] and death) in people with secondary hyperglycemia and COVID-19 (defined as FPG ≥ 7.0 mmol/L [≥126 mg/dL] but HbA1c < 6.5%), compared to the patients with normoglycemia. Sardu *et al.* [11] showed a 71% relative increase in mortality (Hazard ratio [HR] 0.29; 95% CI, 0.08–0.96; p = 0.04) from severe COVID-19 in individuals with at-admission hyperglycemia (new-onset hyperglycemia without diabetes or pre-existing diabetes, with a plasma glucose > 7.77 mmol/l [>140 mg/dL]), compared to normoglycemic individuals with or without diabetes, through 18 days. The Kaplan-Meier (KM) survival analysis also found significantly less (p < 0.02) numbers of patients with hyperglycemia (with or without diabetes) were free from severe COVID-19, compared to individuals with normoglycemia.

Similarly, Wang *et al.* [12] found a significantly increased 28-day in-hospital complications (OR 2.61; 95% CI, 1.64–4.41) in patients with COVID-19 with hyperglycemia without diabetes (FBG 6.1–6.9 mmol/L), compared with normoglycemic individuals. While Li *et al.* [13] demonstrated an increase trend in all-cause mortality (HR 3.29; 95% CI, 0.65–16.6) in patients with hyperglycemia without diabetes (FPG 5.6–6.9 mmol/L and/or HbA1c 5.7–6.4%), compared to normoglycemic patients (FPG < 5.6 mmol/L and HbA1c < 5.7%) with COVID-19, at a mean follow-up of 30 days. The most recent study by Coppelli and colleagues reported that mortality was significantly higher in hyperglycemia without diabetes (defined as no diabetes and glucose ≥ 7.78 mmol/L at admission) compared with normoglycemic patients (at-admission blood glucose < 7.78 mmol/L) with COVID-19 (39.4% vs. 16.8% respectively; unadjusted HR 2.20; 95% CI, 1.27–3.81; p = 0.005) at a mean observation of 17 days period [14].

1.2. *Outcomes in patients with new-onset hyperglycemia without diabetes versus diabetes (new-onset and or pre-existing diabetes) and COVID-19*

Only few studies reported this outcome. Bode *et al.* [9] showed a significant increase in death in patients with new-onset hyperglycemia without diabetes, compared to patients with pre-existing diabetes (41.7% vs. 14.8% respectively; p < 0.001). In contrast, Zhang *et al.* [10] demonstrated increased trend but no significant differences in composite outcomes (MV, ICU admission and death) between patients with new-onset hyperglycemia without diabetes (OR 2.10; 95% CI, 0.65–6.83; p = 0.22) and with diabetes (new-onset or pre-existing).

1.3. *Outcomes in patients with new-onset diabetes versus normoglycemic COVID-19*

New-onset diabetes has been increasingly being reported as a case series during the pandemic of COVID-19, sometime presenting with acute diabetic ketoacidosis [15,16]. Several studies have recently reported the outcomes with new-onset diabetes compared with normoglycemic individuals with COVID-19. In a retrospective analysis of 166 patients Zhang *et al.* [10] found new-onset diabetes (FBG ≥ 7.0 mmol/L twice or HbA1c ≥ 6.5%) in 16% of cases (26/166) of COVID-19 but did not report the outcomes separately of this group. Interestingly, no significant increase (OR 2.61; 95% CI, 0.86–7.88; p = 0.09) in composite outcomes risk (MV, ICU admission and death) was noted in group having diabetes (both new-onset and pre-existing) compared to the normoglycemic people with COVID-19. In contrast, Li *et al.* [13] found 21% (94/453) patients had new-onset diabetes (FPG ≥ 7 mmol/L and/or HbA1c ≥ 6.5%) and reported a significant increase in

Table 1 – Types of hyperglycemia and outcomes in patients with COVID-19.

First author	N	Normo-glycemia (n) Group 1	New-onset hyper-glycemia without diabetes (n) Group 2	New-onset/Newly detected diabetes (n) Group 3A	Known diabetes (n) Group 3B	Results	Remarks
Bode et al. [9]	1122	671	257[!]	NA	194	A significant increase in mortality was observed in Group 2 and Group 3B compared with Group 1 (28.8% vs. 6.2% respectively; p < 0.001). In addition, a significant increase in death was reported in Group 2 compared with Group 3B (41.7% vs. 14.8% respectively; p < 0.001).	Increased mortality in patients with hyperglycemia due to any cause, compared with normoglycemia. New-onset hyperglycemia without diabetes had even poorer outcome compared with pre-existing diabetes.
Zhang et al. [10]	166	84[#]	21[#]	26[#]	35[#]	Significant increase in composite outcomes risk (MV, admission in ICU and death) in Group 2 (OR 5.47; 95% CI, 1.51–19.82; p = 0.010) compared with group 1. No significant differences in composite outcomes (OR 2.61; 95% CI, 0.86–7.88; p = 0.09) in groups 3 (A + B) compared with group 1, and between group 2 (OR 2.10; 95% CI, 0.65–6.83, p = 0.22) and group 3 (A + B).	Poorer outcomes in patients with hyperglycemia without diabetes compared with normoglycemic COVID-19.
Sardu et al. [11]	59	26	7[^]	NA	26	Risk-adjusted Cox regression analysis found a 71% relative increase in mortality (HR 0.29; 95% CI, 0.08–0.96; p = 0.04) from severe disease through 18 days in Group 2 and 3B, compared with Group 1.	Both new-onset hyperglycemia without diabetes and pre-existing diabetes had poorer outcomes compared with normoglycemic patients with COVID-19
Wang et al. [12]	605	329	100[$]	176[$]	NA	28-day in-hospital complications were significantly higher in Group 3A (OR 3.99; 95% CI, 2.71–5.88) and Group 2 (OR 2.61; 95% CI, 1.64–4.41) compared with Group 1. All cause-death at 28-day after a multi-variable analysis in Group 3A was significantly higher (HR 2.30; 95% CI, 1.49–3.55; p = 0.002), compared to Group 1.	Both new-onset diabetes and hyperglycemia without diabetes had poorer outcomes compared with.2 normoglycemic COVID-19. New-onset diabetes had worst prognosis.
Li et al. [13]	453	132	129[*]	94[*]	98[*]	At a mean follow up of 30 days, all-cause death was significantly higher in Group 3A (HR 9.42; 95% CI, 2.18–40.7), and Group 3B (HR 4.63; 95% CI 1.02–21.0) but only a trend in increase was observed in Group 2 (HR 3.29; 95% CI, 0.65–16.6), compared to Group 1 after the adjustment of age, sex, smoking, SBP and TC.	Patients with new-onset diabetes had worst outcome compared with pre-existing diabetes and normoglycemic COVID-19.
Coppelli et al. [14]	271	149	66[@]	NA	56[@]	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). 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.	New-onset hyperglycemia without diabetes had poorer outcomes compared with normoglycemic COVID-19.
Yang et al. [17]	69	NA	NA	69[**]	NA	Multivariable analysis found Group 3A was an independent predictor for death (HR 3.75; 95% CI 1.26–11.15; p = 0.017). KM survival analysis found a significantly higher mortality rate in Group 3A (p = 0.002).	New-onset diabetes has worst prognosis.
Fadini et al. [18]	413	306	NA	21[##]	86	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 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).	Both new-onset diabetes and pre-existing diabetes has poorer outcomes compared with normoglycemic COVID-19. New-onset diabetes has even worser prognosis compared with pre-existing diabetes and normoglycemic COVID-19.

FPG- fasting plasma glucose; KM- Kaplan-Meier; OR- odds ratio; HR – hazard ratio; RR- risk ratio; MV- mechanical ventilation; ICU- intensive care unit; SBP- systolic blood pressure; TC- total cholesterol; [!] two or more blood glucoses > 180 mg/dL occurred within any 24-hour period with an HbA1C < 6.5% or no HbA1C testing done during hospitalization; [#] Group 1: patients without a history of diabetes and FPG < 7.0 mmol/L, Group 2: FPG ≥ 7.0 mmol/L (≥126 mg/dL) once and HbA1c < 6.5%, Group 3A: FBG ≥ 7.0 mmol/L twice or HbA1c ≥ 6.5%, Group 3B: history of diabetes; [^] at-admission hyperglycemia was defined if plasma glucose > 7.77 mmol/l (>140 mg/dL); [$] Group 2: FBG 6.1–6.9 mmol/L, Group 3A: FBG ≥ 7.0 mmol/L; [*] Group 1: FPG < 5.6 mmol/L and HbA1c < 5.7%, Group 2: FPG 5.6–6.9 mmol/L and/or HbA1c 5.7–6.4%, Group 3A: FPG ≥ 7 mmol/L and/or HbA1c ≥ 6.5%; [@] Group 1: at-admission blood glucose < 7.78 mmol/L, Group 2: no diabetes and glucose ≥ 7.78 mmol/L at admission; [**] FBG ≥ 7.0 mmol/L for two times during hospitalization and without a history of diabetes and corticosteroid intake; [##] 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.

all-cause death (HR 9.42; 95% CI, 2.18–40.7) in a multi-variable analysis at a mean follow-up of 30 days, compared to individuals with normoglycemia and COVID-19. Similarly, Wang *et al.* [12] reported 29% cases (176/605) of new-onset diabetes (FBG $\geq$ 7.0 mmol/L) had significantly higher 28-day in-hospital complications (OR 3.99; 95% CI, 2.71–5.88) and all-cause death (HR 2.30; 95% CI, 1.49–3.55; p = 0.002), compared to normoglycemic COVID-19. In a retrospective study of all 69 patients with new-onset diabetes, Yang *et al.* [17] found new-onset diabetes (FBG $\geq$ 7.0 mmol/L for two times) as an independent predictor for death (HR 3.75; 95% CI 1.26–11.15; p = 0.017) even after a multivariable analysis. KM survival analysis found a significantly (p = 0.002) higher mortality rate in new-onset diabetes with COVID-19. In a very recent study by Fadini *et al.* [18] that analyzed 413 patients and had 5% cases (21/413) of new-onset diabetes (HbA1c $\geq$ 6.5% or a random glucose level $\geq$ 11.1 mmol/L ($\geq$200 mg/dL) with symptoms of hyperglycemia), there was a significant increase (RR 3.06; 95% CI, 2.04–4.57) in severe COVID-19 (ICU admission and death) in people with new-onset diabetes, compared to normoglycemic individual.

1.4. *Outcomes in patients with new-onset diabetes versus pre-existing diabetes*

Two studies compared the outcomes between new-onset and pre-existing diabetes. Notably, Li *et al.* [13] at a mean follow-up of 30 days reported nearly 2-fold higher risk of all-cause death in individuals with new-onset diabetes (HR 9.42; 95% CI, 2.18–40.7), in comparison to pre-existing diabetes (HR 4.63; 95% CI 1.02–21.0) vs. normoglycemic people with COVID-19. Coincidentally, Fadini *et al.* [18] also found a stronger association in increase (p = 0.004) in ICU admission or death in people with new-onset diabetes (RR 3.06; 95% CI, 2.04–4.57), compared with pre-existing diabetes (RR 1.55, 95% C.I. 1.06–2.27) vs. normoglycemic patients with COVID-19, in unadjusted analysis. Even after the adjustment for age and sex, new-onset diabetes had a stronger association and a significant increase in ICU admission and death, compared to people with pre-existing diabetes.

In summary, these findings suggest – a. Patients with new-onset hyperglycemia even without a frank diabetes due to any cause (Stress-induced/ COVID-19-induced/ pre-existing dysglycemia), are associated with a poorer outcome compared to the normoglycemic individuals as well as those with pre-existing diabetes and COVID-19. b. New-onset diabetes in patients with COVID-19 is associated with a significantly higher complications and all-cause death, compared to individuals with normoglycemia and pre-existing diabetes. Table 1 summarizes the outcomes from all the studies that studied new-onset hyperglycemia.

Author contributions

AKS conceptualized and searched the medical database; RS wrote the first draft; AKS revised the text; and both approved the final manuscript.

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

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

REFERENCES

[1] Yang JK, Feng Y, Yuan MY, Yuan SY, Fu HJ, Wu BY, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med 2006;23(6):623–8.

[2] Alraddadi BM, Watson JT, Almarashi A, Abedi GR, Turkistani A, Sadran M, et al. Risk factors for primary Middle East respiratory syndrome coronavirus illness in humans. Saudi Arabia 2014. Emerg Infect Dis 2016;22:49–55.

[3] Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol 2010;47:193–9.

[4] Niu MJ, Yang JK, Lin SS, Ji XJ, Guo LM. Loss of angiotensin-converting enzyme 2 leads to impaired glucose homeostasis in mice. Endocrine 2008;34:56–61.

[5] Rubino F, Amiel SA, Zimmet P, Alberti G, Bornstein S, Eckel RH, et al. New-onset diabetes in Covid-19. N Engl J Med 2020. https://doi.org/10.1056/NEJMc2018688.

[6] American Diabetes Association. Classification and diagnosis of diabetes: standards of medical care in diabetes-2020. Diabetes Care 2020 Jan;43(Supplement 1):S14–31.

[7] Ceriello A, Nigris VD, Prattichizzo F. Why is hyperglycemia worsening COVID-19 and its prognosis? Diabetes Obes Metab. 2020 May 28 : 10.1111/dom.14098.

[8] Apicella M, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Del Prato S. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. Lancet Diabetes Endocrinol. https://doi.org/10.1016/S2213-8587(20)30238-2

[9] Bode B, Garrett V, Messler J, McFarland R, Crowe J, Booth R, et al. Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States. J Diabetes Sci Technol 2020;14(4):813–21.

[10] Zhang Y, Li H, Zhang J, Cao Y, Zhao X, Yu N, et al. A single-centre, retrospective, observational study in Wuhan. Diabetes Obes Metab. 2019;2020. https://doi.org/10.1111/dom.14086.

[11] Sardu C, D'Onofrio N, Balestrieri ML, Barbieri M, Rizzo MR, Messina V, et al. Hyperglycaemia on admission to hospital and COVID-19. Diabetologia 2020. https://doi.org/10.1007/s00125-020-05216-2.

[12] Wang S, Ma P, Zhang S, Song S, Wang Z, Ma Y, et al. Fasting blood glucose at admission is an independent predictor for 28-day mortality in patients with COVID-19 without previous diagnosis of diabetes: a multicentre retrospective study. Diabetologia. 10 July 2020 [Epub ahead of print]. DOI: 10.1007/s00125-020-05209-1

[13] Li H, Tian S, Chen T, Cui Z, Shi N, Zhong X, et al. Newly diagnosed diabetes is associated with a higher risk of mortality than known diabetes in hospitalized patients with COVID-19. Diabetes Obes Metab 2020. https://doi.org/10.1111/dom.14099.

[14] Coppelli A, Giannarelli R, Aragona M, Penno G, Falcone M, Tiseo G, 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.

[15] Chee YJ, Ng SJH, Yeoh E. Diabetic ketoacidosis precipitated by Covid-19 in a patient with newly diagnosed diabetes mellitus. Diabetes Res Clin Pract 2020;164:108166.

[16] Potier L, Julla JB, Roussel R, Boudou P, Gauthier DC, Ketfi C, et al. COVID-19 symptoms masking inaugural ketoacidosis of type 1 diabetes. Diabetes Metab 2020. https://doi.org/10.1016/j.diabet.2020.05.004.

[17] Yang JK, Jin JM, Liu S, Bai P, He W, Wu F, et al. New onset COVID-19–related diabetes: an indicator of mortality. medRxiv preprint doi: https://doi.org/10.1101/2020.04.08.20058040

[18] 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;168:108374. https://doi.org/10.1016/j.diabres.2020.108374.