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COVID-19

Admission Hyperglycemia in Non-diabetics Predicts Mortality and Disease Severity in COVID-19: a Pooled Analysis and Meta-summary of Literature

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Abstract

In the latter part of 2019, a cluster of unexplained pneumonia cases were reported in Wuhan, China. In less than a year, SARS-CoV-2 has infected over 27 million people and claimed more than 800,000 deaths worldwide. Diabetes is a highly prevalent chronic metabolic disease, and recent reports have suggested a possible existence of COVID-19 related new-onset diabetes. Hyperglycemia induces an inflammatory state in the body, which coupled with coronavirus associated immune response is a possible explanation for clinical worsening of patients. We present a summary and pooled analysis of available evidence to ascertain the relationship between hyperglycemia in undiagnosed diabetics and outcomes of COVID-19 disease. Our results showed that hyperglycemia in non-diabetics was associated with higher risk of severe/critical illness (OR 1.837 (95% CI 1.368–2.465, $P < 0.001$) and mortality (2.822, 95% CI 1.587–5.019, $P < 0.001$) compared with those with normal values of blood glucose. The management of hyperglycemia in COVID-19 poses significant challenges in clinical practice, and the need to develop strategies for optimal glucose control in these patients cannot be overlooked.

Keywords COVID-19 · SARS-CoV-2 · Hyperglycemia · Diabetes · Infectious disease

Introduction

The first case of novel coronavirus pneumonia, also known as SARS-CoV-2 (severe acute respiratory distress syndrome coronavirus-2), emerged in December 2019 in Wuhan, China. Designated as coronavirus disease 2019 (COVID-19), it affects the lungs primarily and has a high transmission rate [1].

Diabetes as a risk factor for severe COVID-19 disease has already been studied and reported in detail [2]. SARS-CoV-2 interacts with the body's glucose metabolism via a variety of pathways, the commonest being ACE-2 expression in the pancreas [3]. It is well established that hyperglycemia increases the risk of lower respiratory tract infections and is linked to poor outcomes [4]. Since an acute rise in blood glucose is associated with increased inflammatory mediators [5], it is conceivable that hyperglycemia can potentiate the harmful effects of cytokine storm in patients with COVID-19 pneumonia. Hence, there is growing concern that hyperglycemia independent of diabetes could be a factor contributing to poor prognosis in COVID-19 illness. This study aims to shed light on the correlation between hyperglycemia in those without an established diagnosis of diabetes mellitus and COVID-19-related clinical outcomes.

Methods

A literature search was performed in August and September 2020 using databases PubMed, Google scholar, and Scopus to identify studies reporting an association between blood

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glucose levels and COVID-19 disease outcomes in patients without a history of diabetes. The search strategy consisted of different combinations of the following keywords: "COVID-19," "SARS-CoV-2," "hyperglycemia," "impaired glucose tolerance," "prediabetes," and "impaired fasting glucose." Those with raised blood glucose, no prior history of diabetes, and those with prediabetes and impaired fasting glucose were placed Group 1 designated as "hyperglycemia without diabetes." On the other hand, patients found to have normal blood glucose values on admission were part of the normoglycemia group (Group 2); refer to Table 1. The presence of diabetes was negated by one of the following: a negative history of diabetes as per the patient or his/her medical records, lack of ongoing treatment with glucose-lowering medications, or HBAIc < 6.5. The criteria for inclusion into these two groups for each study have been mentioned in Table 1. Whenever available, data on the following was included: clinical features, in-hospital complications, patient outcomes such as mechanical ventilation and ICU admission, disease severity and mortality among laboratory-confirmed, and SARS-CoV-2 patients in the hyperglycemia and normoglycemia groups. We excluded duplicate studies, letters, case reports, abstracts, reviews, and articles not translated in English.

Statistical analysis was performed using OpenMeta[Analyst] software. Odds ratio (OR) with 95% confidence interval (CI) was determined and pooled analysis performed to determine the pooled odds ratio. Heterogeneity was assessed using the I^2 test, and $I^2 > 50\%$ was considered as a moderate inter-study variation. A $P < 0.05$ was considered statistically significant.

Results

Initial search yielded 423 studies. After excluding irrelevant articles, reviews, and duplicate items, a total of 13 studies were included. Ten studies were included in quantitative analysis (pooled OR for severe/critical COVID-19 and death). These ten studies have been summarized in Table 1.

Clinical Features and Demographics

Studies have shown that COVID-19 patients with hyperglycemia are older compared with those with normal blood glucose levels. A retrospective study by Zhang et al. included data of 312 COVID-19 patients and stratified them according to diabetic status into the following three groups—diabetes, impaired fasting glucose (IFG), and normal fasting glucose (NFG). Those who were diagnosed as having an impaired fasting glucose were older than those with normal fasting glucose (mean age 62 years vs 46 years, $P < 0.001$) and had a higher burden of comorbidities (45% vs 25%, $P < 0.001$). Men comprised a larger proportion of COVID-19 patients presenting with impaired fasting glucose, compared with those without hyperglycemia (55% vs 34%). Further, they also reported data on common coronavirus disease symptoms. Dyspnea (55% vs 33%) and hypoxemia (48% vs 24%) were more commonly seen in the IFG cohort compared with the normal fasting glucose group ($P < 0.001$). Fever (92% vs 82%), chest pain (42% vs 40%), diarrhea (27% vs 20%), nausea and vomiting (15% vs 11%), and polypnea (13% vs 5%) were also seen with a greater frequency in among those with IFG, compared with those with NFG, although the difference was not statistically significant ($P > 0.05$) [6].

Lab Markers and Imaging

Compared with patients with normal glucose levels, those with hyperglycemia had more abnormalities in lab markers. Zhang et al. reported various irregularities in laboratory values of COVID-19 patients who were also concurrently diagnosed as having raised blood glucose. Increased neutrophils and leukocytes, decreased eosinophils, were more commonly seen in those with hyperglycemia compared with known diabetics and those with normal blood glucose levels. Abnormalities in liver function test components such as hypoalbuminemia and raised ALT levels were also more commonly recognized in patients belonging to the hyperglycemia group vs the normoglycemia and diabetic group. Similar trend was observed in case of inflammatory markers such as lactate dehydrogenase (LDH), ferritin, and C-reactive protein (CRP). Interestingly, IL-8, an important component of inflammatory response, was also significantly higher in this group compared with the other two (23.8% vs 4.8%, $P < 0.05$) [7].

Disturbed coagulation profile is an important prognostic finding in COVID-19 patients. Significantly raised D-Dimer (27% vs 17%) and fibrinogen levels (68% vs 37%) were observed in those with impaired fasting glucose compared with ones with a normal fasting glucose in the retrospective observational study by Zhang et al. [6]. They also reported higher Troponin 1, AST, ALT, cystatin C, neutrophil/lymphocyte (N/L) ratios, and decreased lymphocytes and platelets in the same subset of patients, compared with those with normal glucose tolerance ($P < 0.05$).

Aggravated findings on CT scan imaging of the chest were more frequently observed in those with impaired fasting glucose compared with COVID-19 patients with normal fasting glucose [6]. Lacobellis et al. reported that admission hyperglycemia (day-1 average blood glucose levels) was the strongest predictor of radiographic findings of SARS-CoV2 pneumonia in patients without a known history of diabetes, even after accounting for body temperature [16]. It would not be wrong to believe that heightened inflammation and exacerbated immune response, as a result of acute hyperglycemia, could be responsible for radiographic progression of ARDS in these patients.

Table 1 Summary of studies included in quantitative analysis (pooled OR for severe/critical COVID-19 illness and mortality)

Author	Type of study	Region	Patients included	Criteria for classification into Group 1 and Group 2
Zhang et al. [6]	Multicenter retrospective cohort study	China	312 hospitalized patients with COVID-19; status of diabetes and hyperglycemia ascertained at admission	Based on Group1—Normal fasting glucose (NFG)—< 5.6 mmol/L and Group 2—impaired fasting glucose (IFG)—5.6–6.9 mmol/L
Zhang et al. [7]	Single-center retrospective cohort study	China	166 hospitalized COVID-19 patients with blood glucose measurement at admission	Group 1—Fasting plasma glucose (FPG) < 7.0 mmol/L and no history of diabetes, Group 2—FPG ≥ 7.0 mmol/L once and HBA1c < 6.5
Fadini et al. [8]	Retrospective observational study	Italy	413 COVID-19 patients; fasting plasma glucose measured at admission	Diabetes was defined as HBA1c < 6.5 or random blood glucose > 200 mg/dL or based on patient's electronic medical records, medication history, and self- reporting; reported odds ratio in non-diabetics.
Liu et al. [9]	Multicenter retrospective cohort study	China	123 COVID-19 patients; glucose measurement at hospital admission	Ruled out diabetes with negative history and adjusted for diabetes in the calculation of odds ratio.
Coppelli et al. [10]	Retrospective observational study	Italy	271 hospitalized COVID-19 patients; at admission glycemia status	Group 1: Normoglycemia—glucose level < 7.78 mmol/L; Group 2: glucose level < 7.78 mmol/L and no previous history of diabetes mellitus.
Wang et al. [11]	Multicenter retrospective cohort study	China	605 COVID-19 hospitalized patients without a previous diagnosis of diabetes; fasting plasma glucose (FPG) was measured at admission	Group 1: FPG < 6.1 mmol/L; Group 2: FPG 6.1–6.9 mmol/L
Li et al. [12]	Single-center retrospective cohort study	China	453 hospitalized COVID-19 patients; blood glucose measured at admission	Group 1—normal glucose; Group 2—hyperglycemia - 5.6–6.9 mmol/L
Wu et al. [13]	Multicenter retrospective cohort study	China	2041 hospitalized COVID-19 patients; median blood glucose in hospital	Group 1: median glucose < 6.1 mmol/L, Group 2: blood glucose ≥ 6.1 mmol/L after admission
Bode at al [14]	Retrospective observational study	USA	1122 hospitalized COVID-19 patients included in the GLYTEC database.	Group 1: uncontrolled hyperglycemia—two blood glucose measurements > 180 mg/dL within any 24-h periods and HBA1c < 6.5%; Group 2: patients who did not meet the criteria for inclusion into Group 1
Smith et al. [15]	Retrospective observational study	USA	184 hospitalized COVID-19 patients; diabetic status ascertained at admission	Group 1: Non-DM—fasting blood≤125 mg/dL (6.9 mmol/L) and HBA1c < 5.7; Group 2: Pre DM-HBA1c 5.7–6.4

Disease Severity and Complications

Sardu et al. in a study assessing the role of insulin in controlling blood sugar levels among COVID-19 patients also compared the risk of severe disease in patients with diabetes, hyperglycemia without diabetes, and normoglycemia. After risk-adjusted Cox regression analysis, they found that patients with hyperglycemia had an increased risk of severe COVID-19 disease [17].

Six studies reported quantitative data on severe/critical COVID-19 illness. Critical illness/severe disease was defined by the occurrence of adverse clinical outcomes such as respiratory failure requiring mechanical ventilation, ICU admission for organ failure, in-hospital complications, shock, or death. Some Chinese studies defined disease severity as per Chinese COVID-19 management guidelines or COVID-19 guidelines issued by Chinese National Health Committee. One study defined severe COVID-19 using the Infectious Disease Society of America/American thoracic society CAP severity criteria. Pooled odds ratio was calculated using a random effects model. Pooled OR for severe/critical COVID-19 illness among patients with hyperglycemia was 1.837 (95% CI 1.368–2.465, $P < 0.001$) (Fig. 1a). Other studies reported separately the clinical outcomes that comprise critical/severe COVID-19 illness, as shown in Table 2.

Recent evidence suggests that every 2 mmol/L (36 mg/dL) increase in fasting plasma glucose levels correlates with increasing COVID-19 severity in both diabetics and non-diabetics, but the association was stronger among the latter [8]. Furthermore, the optimal fasting blood glucose levels for predicting critical COVID-19 illness were reported to be ≥ 6.50 mmol/L [9]. PaO_2:FiO_2 ratio is the worst among those with hyperglycemia compared with diabetic individuals and those with normal blood glucose values [10].

Mortality

Eight studies reported a higher mortality in patients with hyperglycemia compared with those with normal blood glucose levels. Random effects model was used to compute pooled odds ratio for the same. SARS-CoV-2 infected patients who presented with raised blood glucose levels had an approximately threefold increased risk of dying when compared with those with normal glucose levels at presentation (pooled OR 2.822, 95% CI 1.587–5.019, $P < 0.001$) (Fig. 1b).

Discussion

Our pooled analysis showed an increased risk of critical illness or severe COVID-19, as well as mortality in patients who presented with raised glucose levels and no prior history of diabetes compared with those with normal glucose levels. Diabetes is a comorbidity that negatively affects prognosis of COVID-19 disease, but the impact of hyperglycemia in those without an established diagnosis of diabetes is a more concerning matter for clinicians. Research has shown that acute hyperglycemia can cause impairment in innate immunity, leading to a heightened risk of infections [19]. There is substantial evidence to suggest that hyperglycemia at admission is associated with worse outcomes in community-acquired pneumonia [20]. Few studies have also reported similar results with SARS and MERS viruses [21, 22]. Glucose is pro-inflammatory and causes generation of reactive oxygen species (ROS), leading to acute oxidative and inflammatory stress [23]. This milieu of heightened inflammation can possibly be a contributing factor to the cytokine storm witnessed in COVID patients, resulting in more severe illness. It is well-known that glycosylation (a consequence of sustained hyperglycemia) of the ACE2 receptor increases the propensity of virus linkage to this cellular receptor [24]. Conceivably, this aberrantly glycosylated ACE2 in the tissue in uncontrolled hyperglycemia not only favors the cellular intrusion of SARS-CoV2 but subsequently leads to a wide-spread organ involvement and a greater disease severity, thus translating

Table 2 Studies reporting adverse clinical outcomes in COVID-19 patients with hyperglycemia

Author, year	Findings
Liu et al. [18]	Fasting blood glucose at admission (irrespective of diabetic status) was an independent predictor of ICU admission (OR 1.587, 95% CI1.299–1.939, $P < 0.001$)
Zhang et al. [7]	Patients with hyperglycemia were more likely to need mechanical ventilation (38.1% vs 9.5%), stay in the hospital for a longer duration (26.2 ± 14.8 vs 20.5 ± 11.3 days)
Smith et al. [15]	Disease severity was defined in terms of the requirement for intubation. The intubation rate in non-diabetic patients was 4%, while that of pre-diabetics was 18.5%
Wang et al. [11]	Among patients without a previous diagnosis of diabetes, admission fasting plasma glucose (FBG) ≥ 7.0 mmol/L and 6.1–6.9 mmol/L were at a higher risk of in-hospital complications compared with those with FPB < 6.0 mmol/L (OR 3.99,95% CI 2.71–5.88; OR 2.61, 95% CI 1.64–4.41, respectively)
Li et al. [12]	Compared with hyperglycemia, normoglycemia in COVID-19 was associated with a higher chance of developing acute respiratory distress syndrome (0.8% vs 3.1%), acute kidney injury (1.5% vs 3.1%), shock (2.3% vs 4.7%), non-invasive ventilation (2.3% vs 5.4%), invasive ventilation (2.3% vs 4.7%), and admission to ICU(1.5% vs 6.2%) ($P < 0.05$)
Zhang et al. [6]	Risk of acute respiratory distress syndrome (3% vs 2%), acute kidney injury (2% vs 0%), and septic shock (8% vs 2%) was higher in the impaired fasting glucose group vs normal fasting glucose ($P < 0.05$).

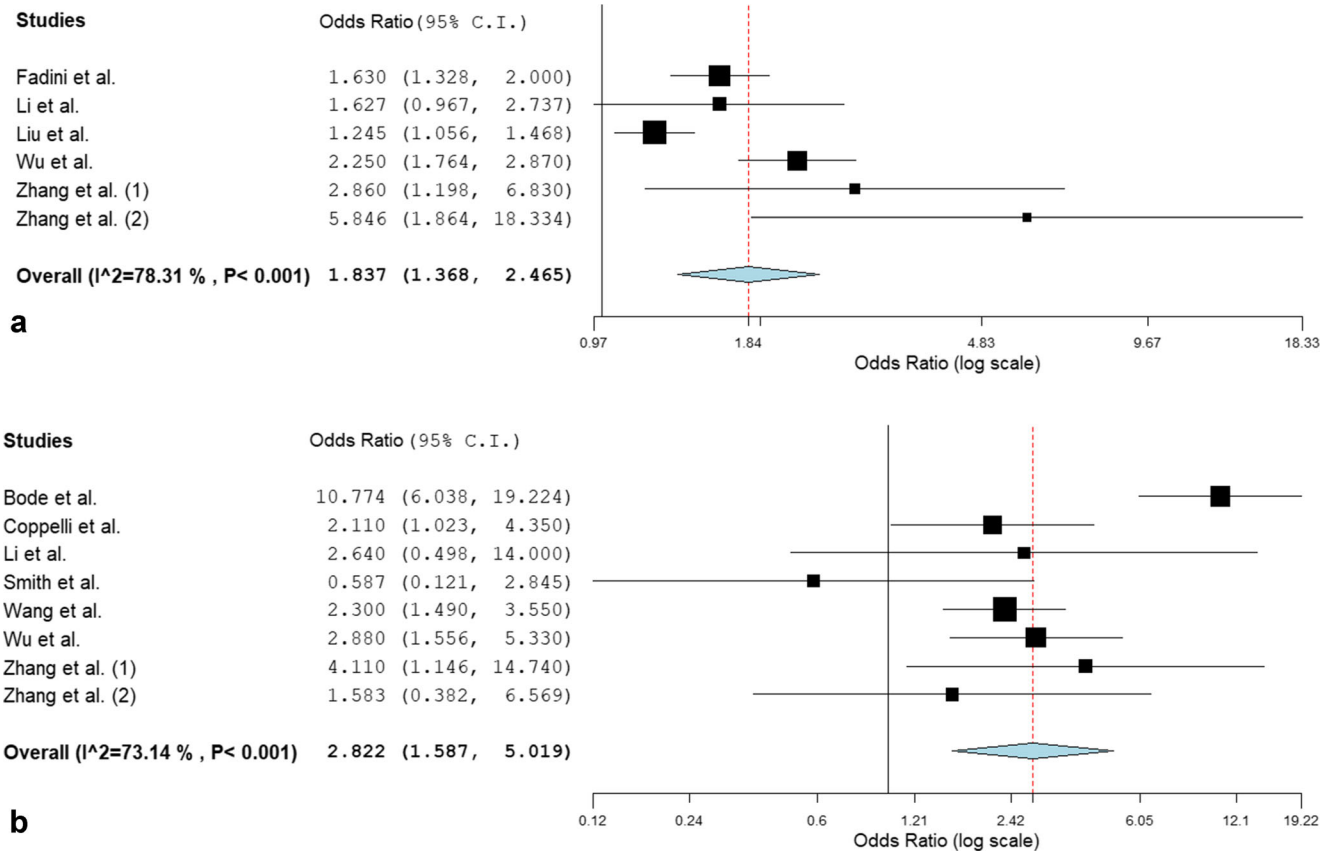

Fig. 1 Pooled OR for **a** severe/critical COVID-19 illness. **b** Mortality in COVID-19

into worse outcomes. Worsening respiratory function is believed to be the major factor responsible for the detrimental effect of hyperglycemia in patients infected by SARS-CoV-2 [8]. It has been observed that there exist varying magnitudes of association between fasting blood glucose levels and severe/critical COVID-19 illness among patients presenting with hyperglycemia without a known diagnosis of diabetes. Additionally, the shape of such an association is J-shaped as shown by Zhu et al. in their study [25].

Further, it has been reported that optimal glycemic control of hyperglycemia in COVID-19 patients leads to a reduction in the risk of severe disease and death [17]. Therefore, it is of utmost importance that plasma sugar values be strictly monitored in all COVID-19 patients, more so in the critically- ill patients.

We do acknowledge some limitations to our study. Patients presenting with raised glucose levels (especially glucose levels > 7.0 mmol/L) may be cases of new-onset diabetes or may have missed being diagnosed in the past. Criteria for placing patients into the normoglycemia and hyperglycemia groups was not consistent throughout all studies (refer Table 1). Also, comorbidities such as hypertension, cardiovascular disease, chronic kidney, and liver disease were not accounted for in all included studies.

Conclusions

Hyperglycemia is a significant blood finding in patients admitted in view of COVID-19 and can be used as a prognostic marker to stratify based on risk of severe disease and death, thus enabling early intervention resulting in improved patient outcomes. Glycemic status rather than a prior diagnosis of diabetes is a predictor of adverse outcomes. The need for timely recognition and management of blood glucose levels should be emphasized in COVID-19 disease. Large-scale patient studies are warranted in order to establish appropriate treatment guidelines for hyperglycemia in COVID-19 patients, so as to minimize worse outcomes for these patients.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent NA

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