https://www.scientificarchives.com/journal/journal-of-diabetes-and-clinical-research

Journal of Diabetes and Clinical Research Mini Review

Hyperglycemia and Diabetes in Hospitalized Patients with COVID-19

Nasser Mikhail*, Soma Wali

Department of Medicine, OliveView-UCLA Medical Center, Sylmar, CA 91342, United States

*Correspondence should be addressed to Nasser Mikhail; nmikhail@dhs.lacounty.gov

Received date: June 24, 2020, **Accepted date:** July 01, 2020

Abstract

Background: Patients with diabetes or hyperglycemia have poor prognosis when infected with coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Objective: To review the impact of hyperglycemia and its treatment on prognosis of hospitalized patients with COVID-19.

Methods: Review of English literature by search of electronic databases: Pub/MEDLINE until June 23, 2020. Search terms included diabetes, hyperglycemia, COVID-19, insulin, metformin, hydroxychloroquine. Retrospective studies, meta-analyses, pertinent reviews, and consensus guidelines are reviewed.

Results: Diabetes is the second co-morbidity after hypertension in patients with COVID-19 disease. Yet, after controlling for age, prevalence of diabetes in COVID-19 patients is similar to the general population. Patients with diabetes and COVID-19 have poor prognosis and higher mortality compared with patients without diabetes. Hyperglycemia irrespective of prior diagnosis of diabetes is associated with adverse outcomes among COVID-19 patients. Blood glucose (BG) levels should be lowered below 180 mg/dl. Insulin is the standard therapy to control hyperglycemia in hospitalized patients. Metformin may be continued in mild cases of COVID-19 in absence of contraindications. The anti-diabetic effect of hydroxychloroquine can be virtually beneficial in COVID-19 patients with type 2 diabetes.

Conclusions: Hyperglycemia is associated with poor outcomes in patients with COVID-19. Control of BG below 180 mg/dl by insulin therapy remains the standard of care. Randomized trials are needed to define the optimum range of BG and determine the safety and efficacy of metformin and hydroxychloroquine in hospitalized patients with COVID-19.

Keywords: COVID-19, Diabetes, Hyperglycemia, Insulin, Metformin, Hydroxychloroquine, Mortality

Introduction

The prevalence of diabetes in COVID-19 patients ranges from 5.3% to 58% representing the second comorbidity after hypertension [1,2]. However, when adjusted for age, diabetes prevalence among COVID-19 patients is similar to its prevalence in the general population. A meta-analysis of 12 studies including 2,108 Chinese patients with COVID-19 reported a diabetes prevalence of 10.3% similar to the National prevalence of 10.9% reported in 2013 [3,4].

Impact of Diabetes on Prognosis of COVID-19 Patients

Available data suggest that diabetes confers a poor prognosis in COVID-19 patients. In a meta-analysis of 30 retrospective studies (n=6,452), Huang et al. [5] showed that diabetes was associated with excess mortality: risk ratio (RR) 2.12 (95% CI 1.44-3.03, P<0.001), severe degree of COVID-19: RR 2.45 (95% CI, 1.79-3.35, P<0.001), acute respiratory distress syndrome (ARDS): RR 4.64 (95% CI, 1.86-11.58, P<0.001), and disease progression: RR 3.31 (95% CI, 1.08-10.14, P=0.04). Interestingly, the

association between these poor outcomes and diabetes was stronger in patients with median age <55 years-old compared with older patients [5].

Impact of Previous Glycemic Control as Reflected by Hemoglobin A1c Levels on Prognosis of COVID-19

In a retrospective Chinese study of 132 COVID-19 patients with and without diabetes, Wang et al. [6] found that hemoglobin A1c (HbA1c) values correlated negatively with blood oxygen saturation (Sa O_2) (correlation coefficient r=-22, P=0.01), and positively with inflammation markers C-reactive protein (r=0.22), ferritin (r=0.24), fibrinogen (r=0.27), and erythrocyte sedimentation rate (0.27), P ≤ 0.01. Furthermore, mortality was much higher in the group with median HbA1c of 7.5% compared with the group with median HbA1c of 5.7%, 27% and 9.8%, respectively (P=0.03) [6]. In another retrospective analysis of 952 Chinese patients with COVID-19 and type 2 diabetes, Zhu et al. [7] reported that patients with fairly controlled diabetes having a median BG of 115 mg/dl and HbA1c values of 7.3% had decreased complications compared with patients with worse diabetes control with median BG of 198 mg/dl, and HbA1c of 8.1% [7]. Thus, relative to the group of patients with poor glycemic control, patients with better control had adjusted hazard ratio (HR) for overall mortality of 0.13 (95% CI, 0.04-0.44, P<0.001), ARDS of 0.41 (95% CI, 0.25-0.66, P<0.001), and acute heart injury of 0.21 (95% CI, 0.07-0.59, P=0.003) [7]. On the other hand, in the French retrospective study CORONADO that exclusively included patients having diabetes (n=1,317) with baseline HbA1c (mean ± SD) 8.1% ± 1.9, the authors failed to find an association between HbA1c levels and the primary outcome that consisted of death within 7 days of admission and/or tracheal intubation [8]. The latter results might be limited by the fact that in 35.7% of patients, HbA1c measurement was not available [8]. Nevertheless, the balance of available evidence suggests that poor glycemic control as reflected by HbA1c levels may be associated with worse prognosis of COVID-19 [6,7].

Impact of New Onset Hyperglycemia on Prognosis of COVID-19

In a retrospective study of 2,041 COVID-19 patients, most of whom (87%) did not have diabetes, Wu et al. [9] have shown that hyperglycemia on hospital admission defined as BG levels >110 mg/dl, was independent risk factor for progression to the critical form of COVID-19 (defined as intensive care admission, mechanical ventilation, hemodynamic compromise or death), HR being 1.30 (95% CI 1.03-1.63, P=0.026) [9]. In patients who were already critical on admission, BG >110 mg/dl was independent risk factor for mortality with HR of 1.84, (95% CI, 1.14-2.98, p=0.013) [9]. These results were similar in patients with diabetes (13% of patients) and the remaining majority without diabetes [9]. In another retrospective study from the USA, the authors compared mortality between 88 patients with type 2 diabetes and 96 patients with stress hyperglycemia (defined as 2 BG values >180 mg/dl within 24 h) [10]. Interestingly, despite similar BG levels between the 2 groups during hospitalization, death rates were significantly higher in subjects with stress hyperglycemia compared with those with diabetes, 41.7% versus 14.8%, respectively (P<0.001) [10]. This unfavorable outcome in patients with new onset or stress hyperglycemia may reflect possible multi-organ involvement by the COVID-19 and subsequent damage of pancreatic beta cells by SARS-CoV-2 virus. Indeed, SARS-CoV-2 virus may bind to angiotensin-converting enzyme 2 (ACE 2) receptors in pancreatic beta cells [11].

Glycemic Targets in Patients with COVID-19

Optimum glycemic targets among patients with hyperglycemia and COVID-19 are not well studied. Zhu et al. [7] defined "well-controlled BG" as BG levels between 72-180 mg/dl. Sardu et al. [12] found that for every 10 mg/dl reduction in BG concentrations there was an 11% relative reduction in risk of developing severe form of COVID-19. Meanwhile, the latter relation was not shown in patients with BG values <139 mg/dl on admission [12]. Taken together, available data suggests that optimum BG levels in COVID-19 may lie between 139 and 180 mg/dl. The latter BG range is in line with the glycemic target of 140-180 mg/dl recommended by the American Diabetes Association (ADA) in most hospitalized patients [13].

Management of Hyperglycemia in Patients with COVID-19

Insulin

Insulin remains the drug of choice to control hyperglycemia in critically-ill patients with COVID-19 for several reasons. First, the extensive experience with its intravenous or subcutaneous administration. Second, its flexibility of dosing, and unlimited efficacy except if hypoglycemia occurs. Third, insulin exerts anti-inflammatory actions in hospitalized patients with critical illness [14]. Finally, the ADA recommends protocol-based intravenous insulin infusion as the most effective method for achieving glycemic targets in the critical care setting [13]. The route of insulin administration may also make a difference. In one small observational Italian study, intravenous insulin infusion was associated with better control of BG and prognosis compared with subcutaneous insulin administration. The mean ± SD of BG concentrations during hospitalization were 138 ± 33 mg/dl and 191 ± 15 mg/dl in the intravenous insulin and subcutaneous insulin groups, respectively [12]. The composite endpoint

(severe disease, admission to an intensive care unit, use of mechanical ventilation, or death) occurred in 33% (5 of 15 patients) in the insulin infusion group, and 80% (8 of 10 patients) in the subcutaneous insulin group (p<0.01) [12]. Meanwhile, in one retrospective study, Chen et al. [15] found that insulin use was associated with poor prognosis (adjusted odds ratio 3.58, 95% CI 1.37-9.35, P=0.009). However, the latter finding may be attributed to the fact that patients with severe hyperglycemia and/or severe COVID-19 are those who are more likely to receive insulin. Nonetheless, randomized studies are needed to determine the role of insulin in control of hyperglycemia in COVID-19 patients.

Status of oral anti-diabetic agents in hospitalized COVID-19 patients

It is advisable to stop oral anti-diabetic agents in hospitalized COVID-19 patients due to lack of data, presence of adverse effects, and limited efficacy. This recommendation is in agreement with ADA guidelines in patients with diabetes in general who are admitted to the hospital [13]. One possible exception is metformin (see below).

Role of metformin in hospitalized COVID-19 patients with type 2 diabetes

Metformin has been shown to improve the immune response and reduce inflammation [16]. It could therefore serve as potential agent in host-directed therapy for COVID-19. Chen et al. [15] found that levels of IL-6 were lower in metformin users than non-users. In a retrospective study, Luo et al. [17] evaluated the outcomes of 2 groups of hospitalized COVID-19 patients with diabetes based on metformin therapy. No significant differences between the 2 groups of patients were present with respect to disease severity, glycemic control, and duration of hospital stay [17]. However, in-hospital mortality was 2.9%, (3 of 104) among patients who received metformin compared with 12.3% (22 of179) in the non-metformin group [17]. These authors proposed to use metformin as host-directed therapy irrespective of presence of diabetes [17]. It should be emphasized that metformin should not be used in presence of hypoxia, decreased tissue perfusion, sepsis, acute or chronic kidney disease, and acute heart and liver failure to avoid the risk of lactic acidosis [18].

Hydroxychloroquine

Hydroxychloroquine is being investigated in many clinical trials for prophylaxis and treatment of COVID-19 thanks to its anti-inflammatory effects [19]. This drug is currently used in many countries of the world for treatment of COVID-19 patients despite lack of convincing efficacy. In the meantime, this drug has multiple glucose-lowering actions, and has been used as anti-diabetic agent [19]. Indeed, hydroxychloroquine is approved in India as add-on therapy to patients with type 2 diabetes [19]. This additional anti-diabetic effect is potentially beneficial in patients with COVID-19 and type 2 diabetes. Close observation of BG levels is recommended in patients taking hydroxychloroquine to avoid hypoglycemia whether or not they have diabetes [19].

Relation of renin-angiotensin-aldosterone system inhibitors to COVID-19

The receptor of SARS-CoV-2 is the angiotensin-converting enzyme 2 (ACE2) [20]. ACE2 is part of the renin-angiotensin-aldosterone system (RAAS). Treatment with RAAS inhibitors can increase tissue expression of ACE2 and its presentation at the cell surface [21]. Therefore, there was a concern that treatment with RAAS inhibitors such as ACE inhibitors and angiotensin-receptor blockers (ARB) might increase risk and severity of COVID-19. However, all available retrospective studies did not show any association between RAAS inhibitors and increased prevalence or severity of COVID-19 [22-24]. On the contrary, in one study from the UK, the use of ACE inhibitors or ARB was associated with decreased risk of death or transfer to a critical care unit, adjusted odds ratio 0.63, 95% CI, 0.47-0.84 (P<0.001) [22]. Moreover, in another Spanish study, use of RAAS inhibitors among patients with diabetes was associated with decreased risk of having COVID-19 requiting hospital admission, adjusted odds ratio 0.53%, 95% CI, 0.34-0.80, (P=0.008) [23]. Based on these findings, ACE inhibitors or ARB should not be discontinued due to presence of COVID-19.

Conclusions and Future needs

While patients with diabetes may not be particularly susceptible to COVID-19, they have poor outcomes once they are infected with this disease. The severity of outcomes generally correlates with the degree of hyperglycemia. Insulin should be the standard therapy for rapid control of hyperglycemia in COVID-19 patients. Metformin may be continued in mild cases if there are no contraindications based on weak evidence that it might decrease mortality. All current data related to COVID-19 and diabetes is based on retrospective studies prone for multiple bias and confounding factors. Randomized trials are urgently needed to determine the optimum glycemic range and management of hyperglycemia in hospitalized COVID-19 patients. In addition, metformin and hydroxychloroquine should be studied with respect to their safety, efficacy and impact on prognosis of COVID-19.

Disclosure

The authors do not have any conflict of interest to disclose.

References

1. Singh AK, Gupta R, Ghosh A, Misra A. Diabetes in COVID-19: Prevalence, pathophysiology, prognosis and practical considerations. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020 Apr 9.

2. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et.al. China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease. The New England Journal of Medicine 2020; 382: 1708-1720.

3. Fadini GP, Morieri ML, Longato E, Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. Journal of Endocrinological Investigation. 2020 Jun;43(6):867-869.

4. Wang L, Gao P, Zhang M, Huang Z, Zhang D, Deng Q, et.al. Prevalence and ethnic pattern of diabetes and prediabetes in China in 2013. JAMA. 2017 Jun 27;317(24):2515-23.

5. Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia–a systematic review, meta-analysis, and meta-regression. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020 Apr 17;14(4):395-403.

6. Wang Z, Du Z, Zhu F. Glycosylated hemoglobin is associated with systemic inflammation, hypercoagulability, and prognosis of COVID-19 patients. Diabetes Research and Clinical Practice. 2020 Jun 1;164:108214.

7. Zhu L, She ZG, Cheng X, et.al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell metabolism. 2020 May 1.

8. 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 May 29:1-6.

9. Wu J, Huang J, Zhu G, Wang Q, Lv Q, Huang Y, et al. Elevation of blood glucose level predicts worse outcomes in hospitalized patients with COVID-19: a retrospective cohort study. BMJ Open Diabetes Research and Care. 2020 Jun 1;8(1):e001476.

10. 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. Journal of Diabetes Science and Technology. 2020 May 9:1932296820924469.

11. Rubino F, Amiel SA, Zimmet P, Alberti G, Bornstein S, Eckel RH, et al. New-Onset Diabetes in Covid-19. New England Journal of Medicine. 2020 Jun 12.

12. Sardu C, D'Onofrio N, Balestrieri ML, Barbieri M, Rizzo MR, Messina V, et al. Outcomes in Patients With Hyperglycemia Affected by Covid-19: Can We Do More on Glycemic Control?. 2020 Jul;43(7):1408-1415.

13. American Diabetes Association. 15. Diabetes Care in the Hospital: Standards of Medical Care in Diabetes—2020. Diabetes Care. 2020 Jan 1;43(Supplement 1):S193-202.

14. Hansen TK, Thiel S, Wouters PJ, Christiansen JS, Van den Berghe G. Intensive insulin therapy exerts anti-inflammatory effects in critically ill patients and counteracts the adverse effect of low mannose-binding lectin levels. The Journal of Clinical Endocrinology & Metabolism. 2003 Mar 1;88(3):1082-8.

15. Chen Y, Yang D, Cheng B, Chen J, Peng A, Yang C, Liu C, Xiong M, Deng A, Zhang Y, Zheng L. Clinical characteristics and outcomes of patients with diabetes and COVID-19 in association with glucose-lowering medication. Diabetes Care. 2020 May 13.

16. Cameron AR, Morrison VL, Levin D, Mohan M, Forteath C, Beall C, et al. Anti-inflammatory effects of metformin irrespective of diabetes status. Circulation Research. 2016 Aug 19;119(5):652-65.

17. Luo P, Qiu L, Liu Y, Liu XL, Zheng JL, Xue HY, et al. Metformin Treatment Was Associated with Decreased Mortality in COVID-19 Patients with Diabetes in a Retrospective Analysis. The American Journal of Tropical Medicine and Hygiene. 2020 May 21:tpmd200375.

18. DeFronzo R, Fleming GA, Chen K, Bicsak TA. Metformin-associated lactic acidosis: Current perspectives on causes and risk. Metabolism. 2016 Feb 1;65(2):20-9.

19. Infante M, Ricordi C, Fabbri A. Antihyperglycemic properties of hydroxychloroquine in patients with diabetes: risks and benefits at the time of COVID-19 pandemic. Journal of Diabetes. 2020 May 13.

20. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. Journal of Virology. 2020 Mar 17;94(7).

21. Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-enzyme inhibition and angiotensin II blockers on cardiac converting angiotensin-converting enzyme 2. Circulation. 2005 May 24;111(20):2605-10.

22. Bean D, Kraljevic Z, Searle T, Bendayan R, Pickles A, Folarin A, et al. Treatment with ACE-inhibitors is associated with less severe disease with SARS-Covid-19 infection in a multi-site UK acute Hospital Trust. medRxiv. 2020 Jan 1.

23. de Abajo FJ, Rodríguez-Martín S, Lerma V, Mejía-Abril G, Aguilar M, García-Luque A, et al. Use of renin–angiotensin–aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. The Lancet. 2020 May 14.

24. Reynolds HR, Adhikari S, Pulgarin C, Troxel AB, Iturrate E, Johnson SB, et al. Renin–angiotensin–aldosterone system inhibitors and risk of Covid-19. New England Journal of Medicine. 2020 Jun 18;382(25):2441-2448.