Glycosylated hemoglobin is associated with systemic inflammation, hypercoagulability, and prognosis of COVID-19 patients - Fengxue Zhu - Peking University People’s Hospital, Beijing, China

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Abstract

Background: Diabetes is a risk factor for the progression and prognosis of coronavirus disease (COVID-19), but the relationship between glycosylated hemoglobin (HbA1c) level, inflammation, and prognosis of COVID-19 patients has not been explored. Methods: This was a retrospective study of COVID-19 patients who underwent an HbA1c test. Their demographic data, medical history, signs and symptoms of COVID-19, laboratory test results, and final outcomes of COVID-19 treatment were collected and analyzed. Results: A total of 132 patients were included and divided into three groups based on their blood glucose status. There were significant differences in SaO₂, serum ferritin level, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen (Fbg) level, and IL6 level among the three groups. A pairwise comparison of the groups showed that groups B and C were significantly different from group A in terms of CRP, ESR, and Fbg, IL6, and serum ferritin levels (P < 0.05). Correlation analysis showed that there was a linear negative correlation between SaO₂ and HbA1c (r = 0.22, P = 0.01), while there was a linear positive correlation between serum ferritin, CRP, Fbg, and ESR levels and HbA1c (P < 0.05). Conclusions: High HbA1c level is associated with inflammation, hypercoagulability, and low SaO₂ in COVID-19 patients, and the mortality rate (27.7%) is higher in patients with diabetes. Determining HbA1c level after hospital admission is thus helpful in assessing inflammation, hypercoagulability, and prognosis of COVID-19 patients. A total of 132 patients tested positive for COVID-19 by undergoing the SARS-CoV-2 RNA test were included in our study. The median age of the patients was 66 years (IQR 56–72 years), ranging from 24 to 88 years. The number of men was 68, while the number of women was 64. A total of 88 (66.7%) of the patients had comorbidities, of which hypertension was the most common (50.0%), followed by diabetes (35.6%), cardio-vascular or cerebrovascular disease (24.2%), and chronic kidney disease (7.6%). Seven patients had chronic renal failure undergoing long-term maintenance hemodialysis and received intermittent renal replacement therapy (IRRT) at bedside during hospitalization. The median time from onset to admission was 14 (IQR 10.0–17.8) days. SaO₂ was 95% (IQR 90–97%) without oxygen inhalation at the time of admission, ranging from 59% to 99% (Table 1). The median HbA1c level was 6.4 (IQR 5.8–7.2%), and there were significant differences among the groups with regard to various parameters including SaO₂, serum ferritin, CRP, ESR, fibrinogen (Fbg), and IL6 levels (P < 0.01, Table 2). A pairwise comparison within the groups showed that the differences between groups C and A, and groups B and A were statistically significant in terms of ESR, CRP, serum ferritin, Fbg, and IL6 levels (Fig. 1). Correlation analysis revealed that there was a linear negative correlation between SaO₂ and HbA1c, while there was a linear positive correlation between serum ferritin, CRP, Fbg, and ESR levels and HbA1c (Fig. 2). A total of 22 patients died (16.7%) during hospitalization, including 4 deaths in group A (9.8%), 5 deaths in group B (11.40%), and 13 deaths in group C (27.7%); All patients underwent terminal withdrawal of mechanical ventilation. There was a statistically significant difference between groups A and C in terms of mortality rate (P = 0.03, Table 3). In our study, owing to the presence of acute viral infections, we did not consider HbA1c as the diagnostic standard for diabetes, according to the guidelines[5]. This is the first study to report that diabetic patients contracting COVID-19 have more severe inflammation and higher mortality[6], and that inflammation markers such as serum ferritin level, CRP level, and ESR in COVID-19 cases and the coagulation

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factor Fbg were positively correlated with HbA1c level, while SaO2 was negatively correlated with HbA1c level. Even in patients with only elevated HbA1c level and no diabetes, the levels of inflammation markers and Fbg were also significantly increased (Fig. 1, P < 0.05). However, little is known about the mechanism concerning the increase in the levels of inflammation markers and HbA1c level in case of COVID-19 patients. Previous studies have shown that diabetes not only causes epithelial dysfunction of pulmonary cilia, increased vascular system permeability, alveolar epithelial damage, and alveolar collapse but also contributes to abnormal immune system function[7,8]. Similarly, in severely ill COVID-19 patients, the lungs, spleen, and lymph node structures are damaged, and lymphocyte counts are reduced[9]. Both diabetes and COVID-19 may synergistically damage the immune and respiratory systems. Further, diabetic patients have more comorbidities due to which there is more target organ damage; this together with COVID-19 leads to a more severe inflammation, hypercoagulability, an even low oxygenation, and eventually higher mortality. COVID-19 patients with higher HbA1c level may exhibit relatively higher level of severity, and the infection itself may also lead to an increase in HbA1c level. Previous studies have also found that in severe acute respiratory syndrome (SARS) patients, even those with mild symptoms (who do not receive glucocorticoid therapy during the course of the disease), had higher fasting blood glucose levels[10]. In our study, after excluding treatment with exogenous corticosteroids, hemolysis, the HbA1c level of 66.7% (88/132) patients was still higher than normal (4.0–6.0%), of which 12.1% (16/132) patients were newly diagnosed with diabetes. For the new-onset diabetes patients, previously reported studies along with this study suggest that COVID-19 may cause and aggravate abnormal glucose metabolism. The possible mechanisms of COVID-19 causing abnormal glucose metabolism include islet b-cell damage and insulin resistance. Previous studies have reported that some viruses can directly cause pancreatic b-cell damage[11,12], and angiotensin converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor has higher expression in pancreatic endocrine tissues than in exocrine tissues[13]. Autopsy showed that although a small number of islet cells were degenerated in pancreatic tissue, while immunohistochemical analysis and polymerase chain reaction tests did not detect the presence of SARS-CoV-2 in pancreatic islet cells[9], thus indicating that there is insufficient evidence regarding SARS-CoV-2-induced damage of islet cells. Levels of plasminogen activator inhibitor 1, CRP, serum amyloid A, TNF-a, IL-1b, and IL-6 have been shown to be increased in obese and type 2 diabetic patients. IL-1b can cause islet cell dysfunction and apoptosis, and the levels of these factors can be reduced by lifestyle-related changes and weight loss, which suggests that inflammatory markers may be involved in islet cell damage and insulin resistance[14].

Inflammatory factors released in response to SARS-CoV-2 may also be involved in islet b-cell damage and insulin resistance resulting in abnormal glucose metabolism. In our study, patients had 14 (IQR 10.0–17.8) days from the onset of symptoms to admission. Abnormal glucose metabolism for a long period of time may cause an increase in HBV1c level.