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Glycosylated hemoglobin is associated with systemic inflammation, hypercoagulability, and prognosis of COVID-19 patients

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ARTICLE INFO

Article history:
Received 3 May 2020
Accepted 7 May 2020
Available online 18 May 2020

Keywords:
COVID-19
HbA1c
Diabetes
Inflammation
Prognosis

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 SaO_2, 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 SaO_2 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 SaO_2 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 assessing inflammation, hypercoagulability, and prognosis of COVID-19 patients.

1. Introduction

Coronavirus disease (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This virus mainly causes lung and immune system damage. COVID-19 is currently a global pandemic and has caused a large number of deaths in many countries. Several studies have shown that the severity and mortality with COVID-19 are related to age and comorbidities including diabetes, hypertension, cardiovascular, and cerebrovascular diseases [1,2].

HbA1c is considered the gold standard for evaluating blood glucose level and provides an average value of the past

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https://doi.org/10.1016/j.diabres.2020.108214
0168-8227/

3 months, and high HbA1c level is related to the risk of complications in diabetic patients [3]. However, whether the increase in HbA1c level is related to high inflammation, hypercoagulability, and mortality in COVID-19 patients has not been reported. We performed a retrospective study to evaluate the effect of high HbA1c level on mortality and inflammation in COVID-19 patients with abnormal glucose metabolism.

2. Materials and methods

2.1. Study participants and their evaluation

During the admission period from February 9–28, 2020, the HbA1c levels of 136 patients tested positive for COVID-19 in 3 wards of Wuhan Tongji Hospital were determined. Four patients were excluded from the study because the following factors affected the HbA1c level: 2 patients were receiving glucocorticoids for kidney transplantation and chronic systemic lupus erythematosus; 1 was a hemolytic anemia patient; and 1 patient had myelosuppression after leukemia chemotherapy. After excluding these patients, 132 patients were finally included. The patients' baseline demographic characteristics are given in Table 1. COVID-19 was diagnosed based on the "The Chinese novel coronavirus pneumonia diagnosis and treatment plan (trial version seven)" issued by the National Health Commission of the People's Republic of China [4]. Diabetes was diagnosed based on the 2019 WHO diagnostic criteria for diabetes [5]. The COVID-19 patients were divided into three groups: A, B, and C. Patients in group A had no diabetes and their HbA1c level was $\leq$6.0; patients in group B had no diabetes and their HbA1c level was >6.0; patients in group C were diabetic. There were 41 patients in group A, 44 patients in group B, and 47 patients in group C. Thirty-one patients (66.0%) in Group C had a history of type 2 diabetes and 16 patients (34.0%) were newly diagnosed with diabetes; patients with history of diabetes received more than one oral hypoglycemic drug before hospital admission (the most common drug received was metformin followed by acarbose), of which 12 patients (25.5%) were receiving insulin therapy before admission.

Since this was a retrospective cohort study, the data pertaining to patient characteristics, medical history, symptoms and signs, laboratory examination results, blood oxygen saturation (SaO_2) at admission, and final clinical outcomes were collected from an electronic medical record system for analysis. Of all the laboratory examination results, the minimum blood leukocyte and lymphocyte count values, and the maximum values of ferritin, CRP, interleukin, tumor necrosis factor-α (TNF-α), and lactate dehydrogenase (LDH) levels, fibrinogen (Fbg), and erythrocyte sedimentation rate (ESR) were considered in this study. The date of onset of COVID-19 was considered based on the date of onset of symptoms. All patients were treated in accordance with the "The Chinese novel coronavirus pneumonia diagnosis and treatment plan (trial version seven)" and were followed up until April 6, 2020. The study was approved by the Ethics Committee of Peking University People's Hospital.

3. Statistical analyses

Categorical variables are expressed in terms of frequency and percentage, and were compared using the Chi-square test. Continuous variables are expressed as mean ± standard deviation for normal distribution and were compared by performing analysis of variance. Median and interquartile range (IQR) were used for skewed distribution. A P-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS Statistics for Windows, version 24.0 (IBM, USA).

Table 1 – Demographics and baseline characteristics of COVID-19 patients.

	No. (%) Total (n = 132)	A (n = 41)	B (n = 44)	C (n = 47)
Age, median (IQR), y	66.0 (56.0–72.0)	64.0 (44.0–73.0)	66.0 (58.0–71.0)	68.0 (61.0–72.0)
Gender				
Male	68 (51.5)	18 (43.9)	21 (47.7)	29 (61.7)
Female	64 (48.5)	23 (56.1)	23 (52.3)	18 (38.3)
Comorbidities				
Hypertension	66 (50.0)	18 (44.4)	21 (47.7)	27 (57.4)
Cardiovascular disease	22 (16.7)	7 (17.0)	5 (11.4)	10 (21.3)
Pulmonary disease	9 (6.8)	3 (7.3)	4 (9.1)	2 (4.3)
Cerebrovascular disease	10 (7.6)	2 (4.9)	5 (11.4)	3 (6.4)
Chronic kidney disease	10 (7.6)	7 (17.1)	0	3 (6.4)
Maintenance hemodialysis	7 (5.3)	4 (9.8)	0	3 (6.4)
Thyroid disease	2 (1.5)	1 (2.4)	1 (2.3)	0
Signs and symptoms				
Fever	94 (71.2)	26 (63.4)	34 (77.3)	34 (72.3)
Cough	96 (72.7)	31 (75.6)	27 (61.4)	38 (80.9)
Fatigue	39 (29.5)	11 (26.8)	14 (31.8)	14 (29.8)
Shortness of breath	105 (79.5)	32 (78.0)	34 (77.3)	39 (83.0)
Myalgia	28 (21.2)	6 (14.6)	15 (34.1)	7 (14.9)
Diarrhea	11 (8.3)	3 (7.3)	3 (6.8)	5 (10.6)
SaO_2 on admission, median (IQR), %	95 (90–97)	96 (93–97.5)	95 (86.25–97)	93 (85–96)
Time from onset to admission, median (IQR), d	14 (10.0–17.8)	13.0 (8.5–18.5)	15.0 (11–18.75)	13.0 (9–17)

4. Results

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%), cardiovascular 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. SaO_2 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 SaO_2, 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 SaO_2 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).

5. Discussion

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 inflammations markers such as serum ferritin level, CRP level, and ESR in COVID-19 cases and the coagulation factor Fbg were positively correlated with HbA1c level, while SaO_2 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

Table 2 – Comparison of laboratory parameters among the three groups of COVID-19 patients.

	Normal range	Total (n = 132)	Median (IQR) Group A (n = 41)	Group B (n = 44)	Group C (n = 47)	P-value
HbA1c (%)	4.0–6.0	6.4 (5.8–7.2)	5.7 (5.4–5.8)	6.4 (6.2–6.5)	7.5 (7.1–8.7)	<0.01
Fbg (g/L)	2.0–4.0	5.3 (4.3–6.8)	4.6 (3.8–5.7)	5.4 (4.4–7.0)	5.8(4.7–7.3)	<0.01
Leukocytes ($\times 10^9$/L)	3.5–9.5	4.9 (4.1–6.0)	4.6 (3.9–5.3)	5.0 (4.2–6.4)	5.3 (4.1–6.8)	0.12
Lymphocytes ($\times 10^9$/L)	1.1–3.2	0.8 (0.5–1.3)	0.8 (0.6–1.5)	0.8 (0.5–1.4)	0.8 (0.5–1.2)	0.68
Serum ferritin (μg/L)	30.0–400.0	668.3 (349.7–1488.3)	372.8 (226–1064.9)	734.3 (354.8–1502.9)	1255.0 (564.3–2110.1)	<0.01
LDH (U/L)	135.0–225.0	289.0 (241.0–431.3)	276.0 (226.0–319.0)	325.0 (263.5–451.0)	276.0 (239.0–473.0)	0.64
CRP (mg/L)	<1.0	38.3 (5.3–107.8)	17.3 (2.9–61.7)	41.6 (5.2–109.7)	57.9 (11.0–185.6)	<0.01
IL-1β (pg/mL)	<5.0	5.0 (5.0–5.0)	5.0 (5.0–5.0)	5.0 (5.0–5.0)	5.0 (5.0–5.8)	0.09
IL-2 (U/mL)	223.0–710.0	657 (416.1–1146)	565.0 (378.5–974.0)	739.5 (407.1–1164.8)	808.0 (501.0–1336.0)	0.09
IL-6 (pg/mL)	<7.0	14.9 (4.0–56)	12.7 (3.5–40.5)	9.6 (3.2–64.5)	29.6 (8.5–90.7)	0.04
IL-8 (pg/mL)	<62.0	16.1 (7.8–29.3)	12.1 (7–17.0)	18.5 (9.1–31.9)	21.0 (7.3–43.2)	0.15
IL-10 (pg/mL)	<9.1	5.0 (5.0–7.5)	5.0 (5.0–6.9)	5.0 (5.0–6.9)	21.0 (7.3–43.2)	0.11
TNF-α (pg/mL)	<8.1	9.2 (5.9–14.0)	8.4 (5.3–13.9)	8.7 (5.9–12.8)	11.0 (6.9–15.9)	0.17
ESR (mm/h)	0.0–15.0	37.0 (18–64)	22.0 (9.0–53.0)	39.5 (24.3–63.3)	46.0 (20.0–82.3)	<0.01
TG (mmol/L)	<1.7	1.5 (1.1–2.1)	1.3 (1.0–1.9)	1.2 (1.0–1.9)	1.8 (1.3–2.3)	0.08

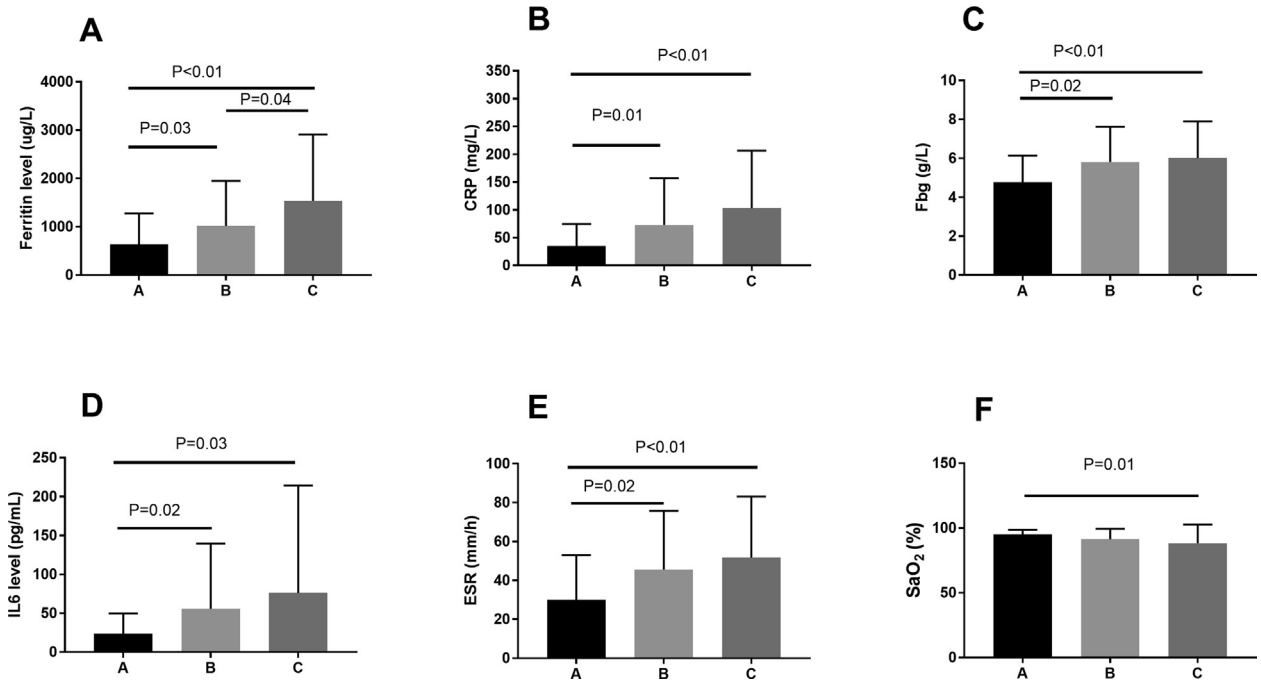

Fig. 1 – Inflammatory factors in blood and oxygen saturation among the three groups.

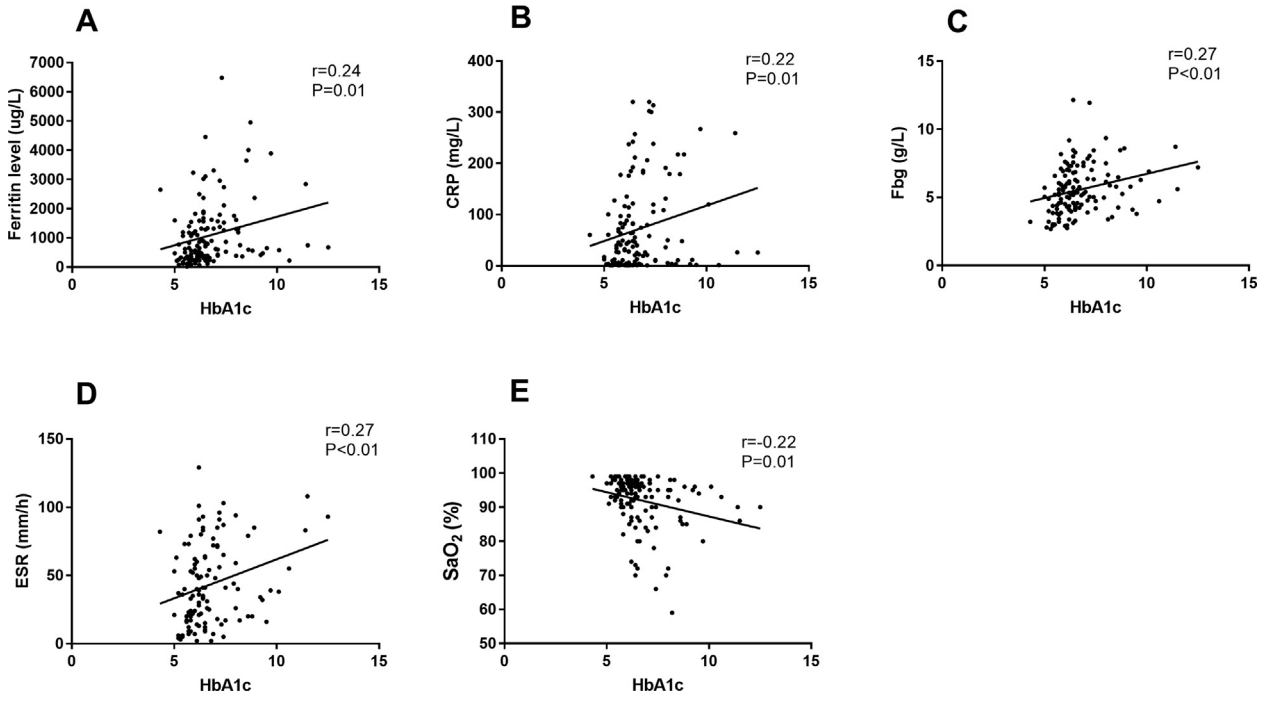

Fig. 2 – Correlation analysis of inflammatory factors, blood oxygen saturation, and HbA1c level.

Table 3 – Mortality rate among the three groups of COVID-19 patients.

	Total (n = 132)	Group A (n = 41)	Group B (n = 44)	Group C (n = 47)	X^2	P
Survivors	110	37	39	34	6.39	0.04
Non-survivors	22	4	5	13		
Mortality rate	16.7%	9.8%	11.40%	27.7%		

Note: Group A vs. B, P = 0.81; Group B vs. C, P = 0.05; Group A vs. C, P = 0.03.

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 β cell damage and insulin resistance. Previous studies have reported that some viruses can directly cause pancreatic β-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-α, IL-1β, and IL-6 have been shown to be increased in obese and type 2 diabetic patients. IL-1β can cause islet β 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 β cell damage and insulin resistance [14]. Inflammatory factors released in response to SARS-CoV-2 may also be involved in islet β-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.

There are some limitations in this study. First, it was a retrospective study, and the bias caused by excluding the 4 patients may have affected the results. Second, due to the limitation caused by the number of deaths, multivariate regression analysis could not be performed to determine whether the increase in HbA1c level was an independent risk factor for the death of COVID-19 patients. Third, after 3 years of follow-up of SARS patients, Yang et al. found that the fasting blood glucose, postprandial blood glucose, and insulin levels of the SARS group and their paired healthy non-SARS siblings were similar, suggesting that SARS-CoV-related islet damage and insulin resistance is for a short duration. Similarly, whether the increase in HBA1c level in COVID-19 patients is transient is also uncertain due to the short observation time; hence, further investigations are required.

In conclusion, HbA1c is associated with inflammation, hypercoagulability, and low SaO_2 in COVID-19 patients, and the mortality rate is higher in diabetic patients. Performing the HbA1c test after admission is helpful for assessing inflammation, hypercoagulability, and prognosis.

Acknowledgements

The authors would like to acknowledge the contribution of the survey team members. This study was supported by Natural Science Foundation of Beijing municipality, China (7204321) and Peking University People's Hospital Scientific Research Development Funds (2019-02), Michigan Medicine–Peking University Health Science Center Joint Institute for Translational and Clinical Research (BMU20160527).

Declaration of Competing Interest

We declare no conflict of interest.

Authors' Contribution

ZD and ZZW designed the study, wrote and revised the manuscript. FXZ reviewed the manuscript. All authors read and approved the final manuscript.

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