Determinants of Increased Fibrinogen in COVID-19 Patients With and Without Diabetes and Impaired Fasting Glucose

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Abstract

Background: To investigate the factors associated with elevated fibrinogen (Fbg) levels in COVID-19 patients with and without diabetes (DM) and impaired fasting glucose (IFG). **Methods:** According to whether or not their glucose metabolism was impaired, COVID-19 patients were subdivided into 2 groups: 1) with DM and IFG, 2) control group. Their demographic data, medical history, signs and symptoms, laboratory results, and final clinical results were analyzed retrospectively. **Results:** 28 patients (16.3%) died during hospitalization, including 21 (29.2%) in group 1 and 7 (7.0%) in group 2 (P < 0.001). Fbg levels in groups 1 and 2 were higher than the normal range, at 5.6 g/L (IQR 4.5–7.2 g/L) and 5.0 g/L (IQR 4.0–6.1 g/L), respectively (P = 0.009). Serum ferritin levels, C-reactive protein (CRP), interleukin-6 (IL-6), IL-8, tumor necrosis factor-α (TNF-α), triglycerides (TG) were significantly increased in group 1 compared to those in the control. TG levels were 1.3 mmol/L in the control, while that in group 1 was 1.8 mmol/L. Multiple linear regression showed that the predicting factors of Fbg in the control group were serum ferritin and CRP, $R^2 = 0.295$; in group 1, serum ferritin, CRP, and TG, $R^2 = 0.473$. **Conclusions:** Fbg in all COVID-19 patients is related to serum ferritin and CRP involved in inflammation. Furthermore, in COVID-19 patients with insulin resistance, Fbg is linearly positively correlated with TG. This suggests that regulation of TG, insulin resistance, and inflammation may reduce hypercoagulability in COVID-19 patients, especially those with insulin resistance.

Introduction

Patients with severe coronavirus disease (COVID-19) without other thrombotic risk factors still exhibit various thrombotic events, including microvascular thrombosis, venous thrombosis and pulmonary thromboembolism, and acute arterial thrombosis.[1] COVID-19-associated coagulopathy (CAC) is an acute thrombosis and is an important cause of organ failure and death in patients.[1,2] The pathogenesis of CAC is still unclear, and many factors, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, inflammation, vascular endothelial injury, coagulation, and fibrinolysis imbalance may be involved.[2-4] Among these, an increased fibrinogen (Fbg) level has been proven as an important part of CAC.[1-3] Currently, anticoagulant and fibrinolytic drugs are used in the treatment of CAC.[5,6]

People with diabetes mellitus (DM) are more likely to experience complications and death due to COVID-19.[7,8]

Laboratory tests show that COVID-19 patients with elevated glycosylated hemoglobin (HbA1c) have higher cytokines and Fbg.[9] The aims of this study is to answer these questions: What factors are related to the increase of Fbg in COVID-19 patients? Is there a difference between patients with and without DM? To investigate these questions, we conducted a small

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Table 1. Demographics and Baseline Characteristics of COVID-19 Patients.

Variable	No. (%) Total (n = 172)	Control (n = 100)	DM and IFG (n = 72)	P-value
Age in years, median (IQR)	66.0 (55.3–72.0)	64.0 (48.5–69.0)	68.0 (60.3–76.3)	0.000
Sex				
Male	86 (50.0)	42 (42.0)	44 (61.1)	0.013
Female	86 (50.0)	58 (58.0)	28 (38.9)	
Comorbidities				
Hypertension	80 (46.5)	41 (41.0)	39 (54.2)	0.088
Cardiovascular disease	30 (17.4)	16 (16.0)	14 (19.4)	0.684
Pulmonary disease	14 (8.1)	6 (6.0)	8 (11.1)	0.265
Cerebrovascular disease	9 (5.2)	5 (5.0)	4 (5.6)	1.000
Chronic kidney disease	13 (7.6)	8 (8.0)	5 (6.9)	1.000
Maintenance hemodialysis	11 (6.4)	7 (7.0)	4 (5.6)	0.763
Thyroid disease	3 (1.7)	2 (2.0)	1 (1.4)	1.000
Signs and symptoms				
Fever	114 (66.3)	62 (62.0)	52 (70.7)	0.192
Cough	113 (65.7)	71 (71.0)	42 (58.3)	0.104
Fatigue	73 (42.4)	44 (44.0)	29 (40.3)	0.643
Shortness of breath	109 (63.4)	62 (62.0)	47 (65.3)	0.749
Myalgia	30 (17.4)	16 (16.0)	14 (19.4)	0.684
Diarrhea	21 (12.2)	13 (13.0)	8 (11.1)	0.815
Mortality	28 (16.3)	7 (7.0)	21 (29.2)	0.000
%SaO$_2$ on admission, median (IQR)	95.0 (90.0–97.0)	95.5 (92.0–97.0)	93.0 (85.3–96.8)	<0.001

IQR, interquartile range; DM, diabetes mellitus; IFG, impaired fasting glucose.

retrospective study to provide preliminary insight into the pathogenesis and treatment of CAC.

Materials and Methods

Study Participants and Their Evaluation

Overall, 176 patients were diagnosed with COVID-19 in the Wuhan Tongji Hospital wards between February 9 and 28, 2020. Four patients were excluded (2 patients treated with glucocorticoids and immunosuppressants for renal transplantation and chronic systemic lupus erythematosus, one hemolytic anemia patient, and one patient with myelosuppression after leukemia chemotherapy); thus, 172 were included in the study. The enrolled patients were divided into 2 groups: (1) 72 patients in the DM and impaired fasting glucose (IFG) group, (2) 100 patients in the control group. Patients in the control group had normal fasting glycemia without DM history. In the group with DM and IFG, 32 patients (44.4%) had type 2 DM history, 19 (26.4%) were newly diagnosed with DM, and 21 (29.2%) had high fasting glycemia. Patients with DM history received one or more oral hypoglycemic drugs (metformin was most used, followed by acarbose) before admission, and 12 (16.7%) received insulin therapy before admission. DM and IFG diagnosis were based on 2019 WHO diagnostic criteria for DM.[10] HbA1c was not used as a diagnostic criterion because of acute viral infections in the patients. COVID-19 was diagnosed according to the Diagnosis and Treatment Plan for Chinese New Coronavirus Pneumonia (7th Edition)[11] issued by the National Health Commission of the People's Republic of China. The basic demographic characteristics of the patients are provided in Table 1.

This was a retrospective cohort study. Therefore, data on the patient's characteristics, medical history, symptoms and signs, laboratory test results, and final clinical outcomes were retrieved from the electronic medical record system. Laboratory test results reported white blood cell and lymphocyte count values as minimum values during the entire hospitalization. Conversely, serum ferritin, interleukin (IL), tumor necrosis factor-α (TNF-α), c-reactive protein (CRP), triglyceride (TG), lactate dehydrogenase (LDH), and Fbg levels were reported as maximum values. All laboratory parameters were measured after 8 hours of fasting. All patients were treated according to the "Chinese New Coronavirus Pneumonia Diagnosis and Treatment Plan (7th Edition)"[11] and were followed up until April 6, 2020. The study was approved by the Ethics Committee of Peking University People's Hospital.

Statistical Analyses

Categorical variables were presented as frequencies and percentages, and continuous variables were presented as median and interquartile range (IQR). One-way analysis of variance (ANOVA) was used to calculate the difference between groups for continuous variables that fit the normal distribution, and non-parametric tests were used for non-normally distributed continuous variables. The chi-square test was applied to categorical variables. Multiple linear regression was used to analyze the related factors of Fbg. P < 0.05 was considered

Table 2. Comparison of Laboratory Parameters of COVID-19 Patients With and Without DM and IFG.

Variable	Normal range	Total (n = 172)	Median (IQR) Control (n = 100)	DM and IFG (n = 72)	P-value
Fasting blood glucose (mmol/L)	4.11–6.05	5.7 (5.1–7.1)	5.2 (4.9–5.6)	7.9 (6.5–11.6)	0.000
Fbg (g/L)	2.0–4.0	5.2 (4.1–6.6)	5.0 (4.0–6.1)	5.6 (4.5–7.2)	0.009
Leukocytes ($\times 10^9$/L)	3.5–9.5	5.0 (4.1–6.2)	4.8 (4.0–5.7)	5.3 (4.1–6.9)	0.031
Lymphocytes ($\times 10^9$/L)	1.1–3.2	0.8 (0.5–1.4)	0.9 (0.7–1.5)	0.7 (0.4–1.1)	0.006
Serum ferritin (µg/L)	30.0–400.0	666.4 (349.4–1519.9)	527.0 (310.2–1153.9)	990.7 (433.7–2299.5)	0.000
LDH (U/L)	135.0–225.0	286.0 (234.0–431.3)	286.0 (225.5–369.3)	292.0 (242.3–514.8)	0.067
CRP (mg/L)	<1.0	36.1 (5.3–105.2)	27.0 (4.1–66.0)	59.0 (11.1–185.4)	0.000
IL-1β (pg/mL)	<5.0	5.0 (5.0–5.0)	5.0 (5.0–5.0)	5.0 (5.0–5.6)	0.327
IL-2 (U/mL)	223.0–710.0	714.0 (440.0–1193.0)	655.0 (403.0–1023.0)	802.0 (509.0–1477.0)	0.054
IL-6 (pg/mL)	<7.0	15.3 (4.0–57.4)	10.2 (3.0–40.3)	36.7 (8.7–116.9)	0.014
IL-8 (pg/mL)	<62.0	13.1 (6.8–30.9)	10.8 (6.4–22.5)	25.6 (7.4–43.4)	0.018
IL-10 (pg/mL)	<9.1	5.0 (5.0–7.6)	5.0 (5.0–6.4)	5.0 (5.0–12.6)	0.209
TNF-α (pg/mL)	<8.1	9.2 (6.1–13.7)	8.3 (5.7–13.3)	10.6 (7.3–15.8)	0.011
TG (mmol/L)	<1.7	1.6 (1.1–2.2)	1.3 (0.9–2.0)	1.8 (1.3–2.4)	0.046

CRP, C-reactive protein; DM, diabetes mellitus; IFG, impaired fasting glucose; IQR, interquartile range; IL, interleukin; TG, triglycerides; LDH, lactate dehydrogenase; TNF- α, tumor necrosis factor-α; Fbg, fibrinogen.

statistically significant. All statistical analyses were performed using SPSS 24.0 (IBM, Armonk, NY, United States).

Results

A total of 86 male and 86 female patients were included. All patients' median age was 66 years (IQR 55.3–72.0 years), ranging from 24 to 95 years. For the DM and IFG as well as control groups, the median age was 68.0 years (IQR 60.3–76.3 years) and 64.0 years (IQR 48.5–69.0 years), respectively (P < 0.001). Among all enrolled patients, 105 (61.0%) had comorbidities, of which hypertension was the most common (46.5%), followed by cardiovascular and cerebrovascular diseases (22.8%), and chronic respiratory diseases (8.1%). Moreover, 11 (6.4%) had been treated for long-term maintenance hemodialysis due to chronic kidney disease. After SARS-CoV-2 infection, they underwent intermittent renal replacement therapy at the bedside. SaO_2 without oxygen inhalation on admission was 95% (IQR 90-97%) for all patients and 93.0% (IQR 85.3–96.8%) and 95.5% (IQR 92.0–97.0%) for groups 1 and 2, respectively (P < 0.001). Overall, 28 patients (16.3%) died during hospitalization, including 21 (29.2%) in the group with DM and IFG and 7 (7.0%) in the control group. There was a statistically significant difference in mortality between the 2 groups (P < 0.001). All the deceased patients were previously treated with mechanical ventilation (Table 1).

Fbg levels in the DM and IFG group and control group were higher than the normal range, at 5.6 g/L (IQR 4.5–7.2 g/L) and 5.0 g/L (IQR 4.0–6.1 g/L), respectively (P = 0.009). TG levels were 1.6 mmol/L (IQR 1.1–2.2 mmol/L) in all patients and 1.3 mmol/L (IQR 0.9–2.0 mmol/L) in the control group. Their median did not exceed the normal range. However, the TG level in the DM and IFG group was 1.8 mmol/L (IQR 1.3–2.4 mmol/L), which not only exceeded the normal range but also increased significantly compared to that in the control

Table 3. Correlation Analysis of Fbg in COVID-19 Patients With and Without DM and IFG.

Variable	Control group Pearson's r	P-value	DM and IFG group Pearson's r	P-value
Lymphocytes	-0.368	0.000	-0.35	0.003
Serum ferritin	0.367	0.000	0.282	0.017
CRP	0.516	0.000	0.637	0.000
IL-2	0.278	0.005		
TNF-α	0.239	0.017		
TG			0.305	0.010

CRP, C-reactive protein; DM, diabetes mellitus; IFG, impaired fasting glucose; IL, interleukin; TNF- α, tumor necrosis factor-α; TG, triglycerides.

group (P = 0.046). Table 2 shows that leukocytes, serum ferritin, CRP, IL-6, IL-8, and TNF-α levels also significantly increased in the DM and IFG group compared to the control, while lymphocytes decreased significantly (P < 0.05).

The correlation analysis between the 2 groups of measurement data and Fbg showed that the related factors of Fbg in the control group were lymphocytes, serum ferritin, CRP, IL-2, and TNF-α, while in the group with DM and IFG were lymphocytes, serum ferritin, CRP, and TG (Table 3). To solve the problem of multicollinearity among related factors, we included them in multiple linear regression equations. The results showed that the factors influencing Fbg in the control group were serum ferritin and CRP, $R^2 = 0.295$, while in the DM and IFG group, serum ferritin, CRP, and TG, $R^2 = 0.473$ (Table 4).

Discussion

Fbg, as an acute phase reactive protein, is involved in coagulation and inflammation.[12,13] On the other hand, inflammation can lead to a significant increase in the expression of Fbg in the

Table 4. Multiple Regression Analysis of Fbg in COVID-19 Patients With and Without DM and IFG.

Variable	Control group		DM and IFG group	
	Standardized coefficient	P-value	Standardized coefficient	P-value
Serum ferritin	0.206	0.049	0.348	0.006
CRP	0.4	0.000	0.246	0.014
TG			0.748	0.000

CRP, C-reactive protein; DM, diabetes mellitus; IFG, impaired fasting glucose; TG, triglycerides.

liver.[14,15] That is, inflammation and Fbg drive each other. Improperly elevated Fbg can lead to hypercoagulability and excessive inflammation.[13] Fbg can act as a ligand for the surface receptors (such as VE-cadherin, ICAM-1, $\alpha_{IIb}\beta_3$, $\alpha_5\beta_1$, $\alpha_V\beta_3$, $\alpha_M\beta_2$, and $\alpha_X\beta_2$) of leukocytes, vascular endothelial cells, platelets, fibroblasts, and smooth muscle cells.[16] Among them, G protein-coupled protease activated receptors can control the expression of cytokines and chemokines.[16,17] Our research shows that inflammation-related cytokines and Fbg are elevated in COVID-19 patients, especially in patients with DM and IFG. Multiple regression analysis showed that serum ferritin and CRP related to inflammation affect Fbg levels, and are positively correlated with Fbg. This indicates that in COVID-19 patients, there may also be a mutual driving effect between inflammation and Fbg.

Our research shows that in COVID-19 patients with DM and IFG, Fbg is not only related to serum ferritin and CRP involved in inflammation but also positively related to TG. Insulin resistance is one of the important pathophysiological mechanisms of IFG and Type 2 DM, and hypertriglyceridemia is one of the typical features of insulin resistance.[18] Studies on visceral obesity and insulin resistance have shown that TG is degraded by lipoprotein lipase to produce free fatty acids (FFA), which leads to a significant increase of FFA in plasma. FFA can activate the NF-κB pathway and increase the liver expression of various pro-inflammatory cytokines, including TNF-α, IL1-β, IL6, and monocyte chemoattractant protein 1 (MCP-1).[19] In addition, elevated plasma FFA can also promote Fbg production and reduce fibrinolytic capacity.[20] Studies have shown that Fbg levels are related to insulin resistance.[19-21] The use of rosiglitazone in patients with type 2 DM to improve insulin resistance can significantly reduce the level of Fbg.[22] In patients with metabolic syndrome, the application of the lipid-lowering drug fenofibrate not only improves blood lipids but also improves insulin resistance and reduces Fbg.[23] Recently, research by Ehrlich et al suggests that elevated lipid metabolism may underlie aspects of COVID-19 pathogenesis, and fenofibrate can treat COVID-19 by disrupting lipid metabolism.[24]

According to sequential organ failure assessment (SOFA) score, the severity of coagulation disorders in patients with COVID-19 seems to be related to the degree of organ dysfunction.[25] We compared the parameters in non-survivors to those in survivors, with significant increases in Fbg, TG, and cytokines in non-survivors (Supplemental Table 1). An increased level of Fbg is one of the characteristics of CVC. Friedrich et al showed that even with conventional antithrombotic therapy, Fbg levels peaked at the third week of the disease and remained significantly elevated at the eighth week.[26] The persistently high Fbg level may affect the occurrence of thromboembolic events, especially in diabetic patients with higher Fbg levels. Ranucci et al described the correlation between IL-6 and Fbg levels.[27] Similarly, our study also showed that Fbg in all COVID-19 patients is related to serum ferritin and CRP involved in inflammation. Moreover, to the best of our knowledge, our study is the first to associate hyperfibrinogenemia with elevated TG levels in insulin-resistant COVID-19 patients. Our preliminary research suggests it may be possible to reduce the level of TG to reduce Fbg in such patients while undergoing conventional thrombotic treatment, thereby reducing the risk of thrombosis.

Of course, as a retrospective study with a small sample size, our research has limitations. In particular, we lack indicators to quantitatively assess insulin resistance. Using the triglyceride and glucose (TyG) index as indicators of insulin resistance, the study by Ren et al showed that the TyG index was significantly associated with an increased risk of severe case and mortality of COVID-19, after controlling for potential confounders (OR for severe case, 2.9, P = 0.007; OR for mortality, 2.9, P = 0.016).[28] Unfortunately, their study did not provide data on Fbg and other coagulation related factors. Therefore, we still need to do more research.

Conclusions

Fbg in all COVID-19 patients is related to serum ferritin and CRP involved in inflammation. Furthermore, in COVID-19 patients with insulin resistance, Fbg is linearly positively correlated with TG. This suggests that regulation of TG, insulin resistance, and inflammation may reduce hypercoagulability in COVID-19 patients, especially those with insulin resistance.

Author contributions

Zhenzhou Wang, Zhe Du, These authors contributed equally. ZD and ZZW designed the study, wrote and revised the manuscript. TBW and FXZ analyzed the data. XJZ and FZG reviewed the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

The study was approved from by the Ethics Committee of Peking University People's Hospital, and written informed consent was obtained from all participants before enrolment in the study. All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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