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Effect of Blood Glucose Level of Patients with Type 2 Diabetes Mellitus and Coronary Heart Disease on the Hypercoagulability and Thromboembolism

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QC, WJ and HL conducted the experiments in this study. JZ, MR, YX and SH contributed to the design and interpretation of the current study and wrote the article.

Key words
Blood glucose level, Type 2 diabetes mellitus, Coronary heart disease, Blood hypercoagulability, Thromboembolism

ABSTRACT

The objective of this study was to investigate the effect of blood glucose level of patients with type II diabetes mellitus and coronary heart disease (CHD) on the hypercoagulability and thromboembolism. A total of 236 patients with type II diabetes mellitus and CHD who were treated in 904 Hospital of Joint Logistic Support Force of PLA were enrolled between January 2018 and January 2020. These patients, according to their 2 h postprandial glucose (2hPG), were divided into the hyperglycemia group (n = 126) and hypoglycemia group (n = 112). Patients in the hypoglycemia and hyperglycemia groups had higher levels of fasting blood glucose (FBG), 2 hPG and glycosylated hemoglobin (HbA1c) when comparing to their counterparts in the control group, with a lower level of fasting insulin (FINS) in serum (all $P < 0.05$); levels of plasma fibrinogen (Fb) and D-dimers (D-D) in serum of patients in the hyperglycemia group were much higher than those in the hypoglycemia group, while serum plasma prothrombin time (PT) and activated partial thromboplastin time (APTT) were much shorter than those in the hypoglycemia group (all $P < 0.05$). Thrombus precursor protein (TpP), P-selectin (Ps), maximum platelet aggregation rate (MAR) and mean platelet volume (MPV) of patients in the hypoglycemia and hyperglycemia group were all higher than their counterparts in the control group, while those in the hyperglycemia group were also higher than the hypoglycemia group (all $P < 0.05$). Besides, incidence rate of thromboembolism in the hypoglycemia group was much lower than that in the hyperglycemia group ($P < 0.05$). During the 2-year follow-up, survival rate of patients in the hypoglycemia group was much higher than that in the hyperglycemia group ($P < 0.05$). It was concluded that for CHD patients with type II diabetes mellitus, poor management of blood glucose may result in the elevation in platelet activation, further inducing the hypercoagulability of blood and increases in the incidence rate of thromboembolism and death rate, suggesting that CHD patients with type II diabetes mellitus should pay more attention to the management of blood glucose and monitor the platelet function and activation of thrombin, thereby minimizing the incidence of acute thromboembolism.

INTRODUCTION

Diabetes mellitus represents a common metabolic disease in clinical practice, and coronary heart disease (CHD) is a major complication of diabetes mellitus, where disorder in glucose metabolism is involved in the development and progression of CHD through a variety of mechanisms. Long-term hyperglycemia status could trigger the damage to the vascular endothelium and activation of coagulation

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system, thereby increasing the risk of cardiovascular diseases, stroke and thromboembolism (Mishiro *et al*., 2014). It has been reported that almost 80% of diabetes mellitus patients have died of thromboembolism, among which 75% of patients are caused by cardiovascular complications, while the remaining patients are suffering from the cerebrovascular and perivascular complications (Carr, 2001).

Tests of prothrombin time (PT) and activated partial thromboplastin time (APTT) are major screening methods to evaluate the endogenous coagulation pathway and the anomaly in the coagulation factor II, V and X or fibrinogen (Devreese, 2021). Plasma fibrinogen, also known as the coagulation factor I, is a protein that is mainly distributed in plasma that is involved in the process of blood coagulation, and is a soluble precursor of fibrin that could be transformed into the fibrin at the last stage of coagulation (May *et al*., 2021; Syyam *et al*., 2022). Any increase in the level of fibrinogen could further elevate the risk of thromboembolism, which is frequently seen in the patients with diabetes mellitus or acute myocardial infarction. D-dimer (D-D), as a kind of plasma fibrin originated from the degraded product of cross-linked fibrin by plasmin. D-D is also a molecular marker for activation of hemostasis that can reflect the cycling status of fibrin, including the formation of intravascular fibrin and subsequent degradation of fibrin clot. In clinical practice, the critical level of D-D is set below 0.5 μg/mL that could be used as an indicator for eliminating the probability of deep vein thrombosis (Von Känel and Dimsdale, 2003). It has been reported that diabetes mellitus patients present increases of prothrombin activators and thrombin-antithrombin complex and a decrease in anti-thrombin, resulting in the clotting balance inclining to the side of thrombogenesis (Abuelgasim *et al*., 2021).

P-selectin (Ps) can mediate the initial adhesion between the white blood cell and endothelial cell, and Ps expressed by activated platelet could promote the aggregation of white blood cell and platelet towards to the thrombus (O'Sullivan *et al*., 2005). Thrombus precursor protein (TpP), a direct precursor of insoluble fibrin in thrombus, can reflect the activity of thrombin in circulation by its concentration in plasma. Any increase in the level of TpP indicates the risk of acute thromboembolism, showing a potent specificity in diagnosis (Mega *et al*., 2008). Detection of maximum platelet aggregation rate (MAR) and mean platelet volume (MPV) could reflect the platelet function objectively. It has been reported that platelet agonist elevates as the platelet contraction force (PCF) increases, together with the increases in the platelet-released products, including thromboglobulin (Hughes *et al*., 1983) platelet factor 4 (Borsey *et al*., 1984) and thrombocytin B2 (Frade *et al*., 1987). As such, it has been inferred that an acute increase in the activity of platelet in diabetes mellitus patients may correlate to the progression of hypoglycemia and outcome of adverse cardiovascular events.

Currently, there remain fewer mass studies involving the control of blood glucose level and indicators above in type II diabetes mellitus patients with CHD. Therefore, the present study aims to investigate the coagulation function and the effect of platelet function on hypercoagulability and thromboembolism event in these patients.

MATERIALS AND METHODS

Clinical data

Between January 2018 and January 2020, we enrolled a total of 236 type II diabetes mellitus patients with CHD who were admitted to 904 Hospital of Joint Logistic Support Force of PLA and were diagnosed according to the diagnostic criteria of type II diabetes mellitus and CHD. According to the level of 2 hPG, these patients were divided into the hyperglycemia group (2 hPG ≥ 7.80 mmol/L) and hypoglycemia group (2hPG < 7.80 mmol/L). In the hyperglycemia group, there were 126 patients consisting of 72 males and 54 females, aged between 45 and 64 years old, with an average age of (52.46 ±5.26) years. In the hypoglycemia group, there were 112 patients consisting of 65 males and 47 females, aged between 43 and 61 years old, with an average age of (51.38 ± 5.35) years. During the same period, we enrolled 115 healthy subjects who attended the physical examination as the control group, consisting of 63 males and 52 females, aged between 43 and 58 years old, with an average age of (51.87 ± 5.14) years. Comparison of the general data among three groups showed no significant differences ($P > 0.05$).

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients with stenosis in cardiovascular radiology at least one major coronary artery (left anterior descending branch, left circumflex artery and right coronary artery) > 50%. (2) Patients with the type II diabetes mellitus conforming to the diagnostic criteria stipulated in 1999 by the World Health Organization. (3) Patients meeting the corresponding requirement of the Medical Ethical Board of 904 Hospital and signing the written informed consents.

Exclusion criteria: (1) Patients who received the percutaneous coronary intervention, coronary artery bypass grafting or thrombolytic therapy. (2) Patients complicated with severe cardio- or cerebrovascular diseases. (3) Patients with liver or kidney disorders. (4) Patients with the clarified mental disorders or drug abuse history. (5)

Patients who failed to cooperate with the treatment or did not fulfill the follow-up.

Indicators and methods

Sample collection and treatment: For all subjects, 2.7 mL elbow venous blood was collected into the vacuum tubes supplemented with citrate sodium buffer and mixed sufficiently. Then, samples were centrifuged at 3000 rpm for 10 min at room temperature to isolate the plasma. Detection would be fulfilled within 2 h.

Detection of biochemical indicators: HITACHI Automatic Biochemical Analyzer was used to measure the levels of fasting insulin, fasting blood glucose (FBG) and 2 hPG, while SIEMENS Automatic Monitor for glycosylated hemoglobin (HbA1c). SYSMEX-CA500 Automatic Coagulation Analyzer was used to measure the activated partial thromboplastin time (APTT) and plasma prothrombin time (PT). Immunoturbidity method was adopted to evaluate the content of plasma fibrinogen (FB; Shanghai Runyu Biotechnology Co., Ltd). Enzyme-linked immunosorbent assay (ELISA) was conducted to determine the content of D-dimer (D-D; Nanjing Jiancheng Biotech Institute). Levels of thrombus precursor protein (TpP), P-selectin (Ps) were determined by using the ELISA with the kits provided by BPB Biomedicals, Inc and Shanghai Westang BIO-TECH Co., Ltd. Maximum platelet aggregation rate (MAR) was determined by using the spcm method on a PL-12 Multifunctional Platelet Analyzer, while MPV by the records by blood routine tests. All procedures were conducted in strict accordance with the instructions of instruments and kits.

Observation in follow-up

A two-year follow-up was carried out for all patients, during which telephone follow-up was performed every 2 months, or clinic follow-up was performed once. During the whole follow-up, thromboembolism events, including cardiovascular diseases (acute myocardial infarction), cerebrovascular diseases (acute cerebral infarction, or transient ischemic attack), acute pulmonary embolism or thrombus of lower extremity veins, were recorded. Besides, survival rates of patients were compared between the hyperglycemia group and the hypoglycemia group.

Data analysis

SPSS 17.0 software was utilized to perform the data analysis. Measurement data in normal distribution were expressed in form of mean ± standard deviation (SD). Comparison among several groups was conducted by using the analysis of variance, while pairwise comparison by least significant difference test (LSD-t). Count data were compared by using the chi-square test. Survival of patients was described by using the Kaplan-Meier survival curve. $P < 0.05$ suggested that the difference had statistical significance.

RESULTS

Indicators of blood glucose

FBG, 2 hPG and HbA1c levels in serum of patients in hypoglycemia and hyperglycemia groups were all higher than those in the control group, while FINS was lower (all $P < 0.05$); FINS in serum of patients of hyperglycemia group was much lower than that in the hypoglycemia group, while FBG, 2 hPG and HbA1c in serum were higher (all $P < 0.05$; Fig. 1).

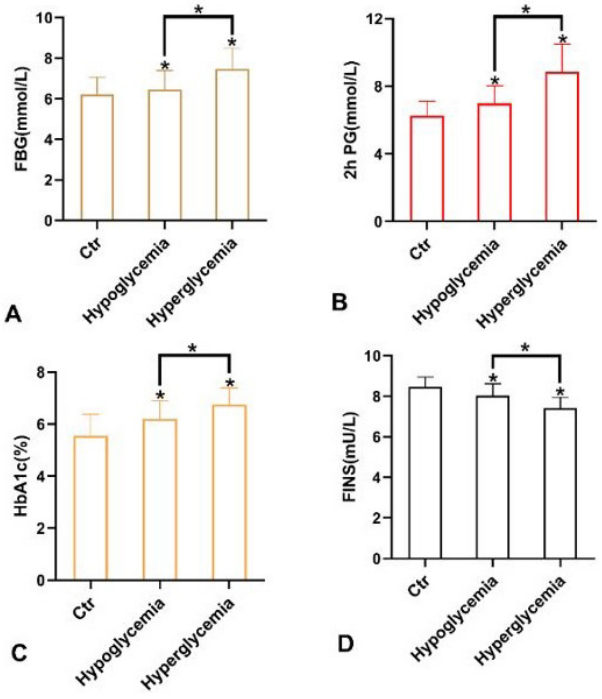

Fig. 1. Effect of blood glucose level of patients on hypercoagulability. A, fasting blood glucose (FBG); B, 2 h postprandial glucose (2hPG); C, glycosylated hemoglobin (HbA1c); D, fasting insulin (FINS).

Hypercoagulative indicators

PT and APTT of patients in hypoglycemia and hyperglycemia groups were all shorter than tht in the control group, while FIB and D-D levels were higher (all $P < 0.05$); PT and APTT of patients of hyperglycemia group were shorter than those in the hypoglycemia group, while FIB and D-D in serum were lower (all $P < 0.05$; Fig. 2).

Platelet functions

TpP, Ps, MAR and MPV of patients in hypoglycemia

Table I. Incidence rates of thromboembolism between the hypoglycemia group and hyperglycemia group.

	Hypoglycemia (n=112)	Hyperglycemia (n=126)	Chi-squared	P-Value
Acute myocardial infarction (n)	4	8	4.435	0.042
Acute cerebral infarction (n)	5	5		
Transient ischemic attack (n)	6	9		
Acute pulmonary embolism (n)	3	5		
Lower extremity vein thrombosis (n)	4	6		
Total thrombotic events (n)	19	33		
1-year follow-up (n)	112 (100%)	126 (100%)	4.073	0.044
2-year follow-up (n)	105 (93.75%)	108 (85.71%)		

and hyperglycemia groups were all higher than those in the control group, while those in the hyperglycemia group were also higher than those in the hypoglycemia group (all $P < 0.05$); the incidence rate of thromboembolism in patients of hyperglycemia group was much lower than that in the hypoglycemia group ($P < 0.05$; Table I and Fig. 3).

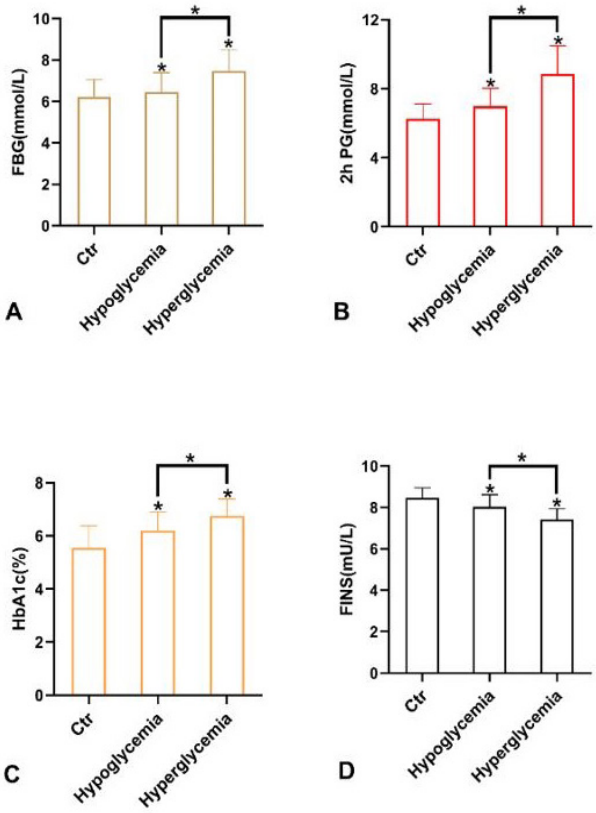

Fig. 2. Effect of blood glucose level of patients on hypercoagulability. A, prothrombin time (PT); B, activated partial thromboplastin time (APTT); C, D-dimers (D-D); D, fibrinogen (Fb).

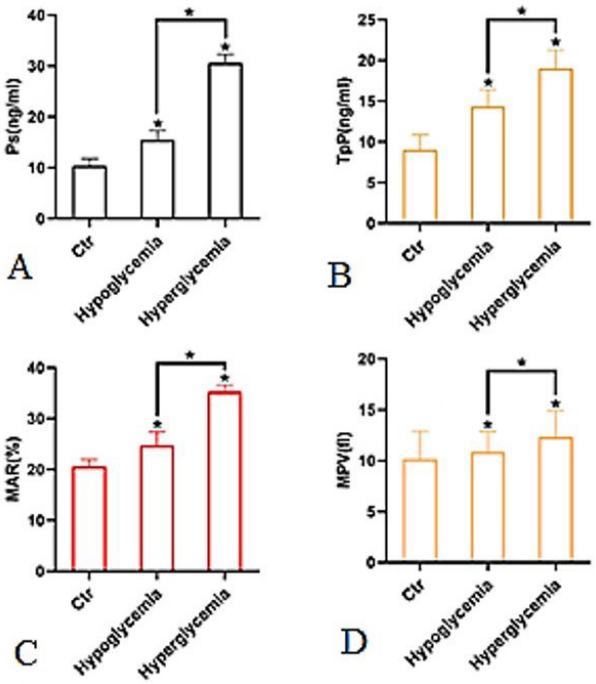

Fig. 3. Effect of blood glucose level of patients on platelet functions. A, P-selectin (Ps); B, thrombus precursor protein (TpP); C, maximum platelet aggregation rate (MAR); D, mean platelet volume (MPV).

Incidence of thromboembolism

During the whole follow-up, no patient was found to be lost to the follow-up in the hypoglycemia group and hyperglycemia group. The incidence rate of thromboembolism in the hypoglycemia group was 16.96% (19/112), significantly lower than 26.19% (33/126) in the hyperglycemia group ($P < 0.05$; Table I, Fig. 4).

Survival rates

During the 2-year follow-up, we found that patients

in the hypoglycemia group had a survival rate of 93.75%, significantly higher 85.71% in the hyperglycemia group ($P < 0.05$; Table I and Fig. 5).

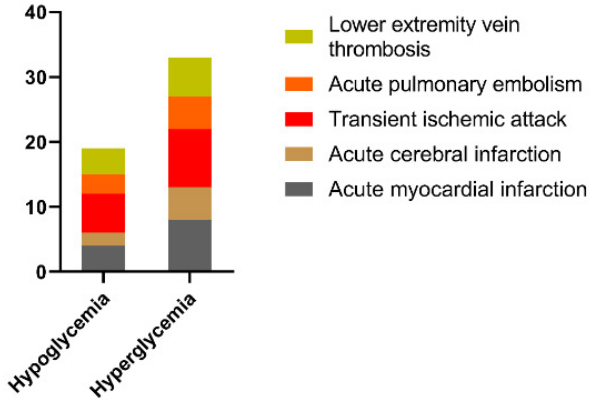

Fig. 4. Effect of blood glucose level of patients on thromboembolism.

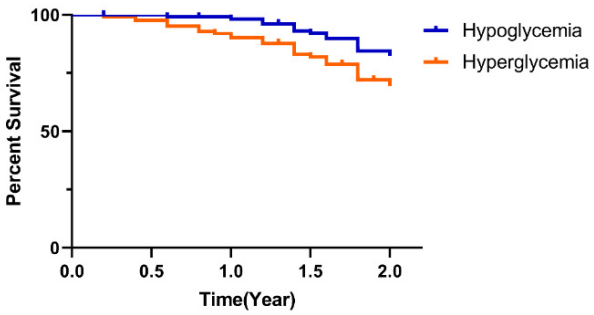

Fig. 5. Effect of blood glucose level of patients on Survival of patients in 2-year follow-up.

DISCUSSION

Currently, China is witnessing the significant progression in aging process and life quality and tremendous changes in the lifestyle and diet structure, together with an acute increase in the proportion of type II diabetes mellitus patients with CHD (Xiong *et al*., 2015). Type II diabetes mellitus and CHD are the most common chronic, incurable physical disorders, concomitant with a high morbidity rate and mortality rate (Gungoren *et al*., 2016). Type II diabetes mellitus can trigger the disorder in carbohydrate and fat metabolism, thereby accelerating the development and progression of atherosclerosis of coronary artery, bringing about severe adverse prognosis (Koshel'skaia *et al*., 2015). In this study, patients in the hypoglycemia and hyperglycemia groups had higher levels of FBG, 2 hPG and HbA1c when comparing to their counterparts in the control group, with a lower level of FINS in serum (all $P < 0.05$), suggesting the damage to the function of pancreas islet, insufficient secretion of insulin, insulin resistance in type II diabetes mellitus patients with CHD, triggering increases in the blood glycemia and glycosylated hemoglobin, which could further deteriorate the functions of vascular endothelium. Ma and Bi (2019) reported that rosuvastatin raises the level of FINS in type II diabetes mellitus patients with CHD, while application of rosuvastatin shows significance in ameliorating the insulin function and resistance. Chen *et al*. (2018) demonstrated that Telmisartan could better regulate the level of blood glucose and reduce the insulin resistance and inflammation, thus improving the vascular endothelial functions in diabetes mellitus patients with CHD.

Hypercoagulative status of blood has now been regarded as a high-risk factor for a variety of cardio- or cerebrovascular diseases and thrombotic diseases. Any disorders in coagulative system could give rise to increases in the proteins and cytokines, which could contribute to the thrombosis and inhibition of fibrinolysis, thereby damaging the vascular wall to expose the endothelial collagen, endothelial damage and increase in the coagulation rate. Damage to the endothelial functions, as the foundation of vasculopathy, has been frequently seen in patients with vasculopathy, including hypertension or coronary atherosclerotic heart disease (Se Linglin, 2016). Previous results have shown that TT, PT and APTT in type II diabetes mellitus patients are shortened, with a significant increase in the level of FIB in serum (Mishra *et al*., 2020), coinciding with our findings: In the type II diabetes mellitus patients with CHD of hypoglycemia group and hyperglycemia group, PT and APTT were much shorter than those in the control group, while the level of serum FIB and D-D were higher. Such phenomenon indicates abnormal coagulation in type II diabetes mellitus patients with CHD, suggesting the pre-thrombus status, and medical staff should concentrate more on the coagulation of patients and intervene as early as possible.

Ps, as one of the selectins of adhesion molecules, is mainly distributed in the resting platelet α particle and Weibel-Palade body in endothelial cells, and any attack from hypoxemia, free radical and coagulative enzyme could result in the discharge of particle and up-regulation of Ps, thereby mediating the adhesion of leukocyte and endothelial cells, playing a central part in the inflammation and thrombosis (Shebuski and Kilgore, 2002; Carter *et al*., 2003), TpP, a polymer, soluble fibrin, is the desAABB polymer deriving from the Fibrinopeptide B sliced from the β chain by thrombin after the initiation of blood clotting response. TpP can form the insoluble fibrin by continuous polymerization and crosslinking, which can further give

rise to the thrombus. Thus, the level of TpP in plasma can reflect the activity of thrombin in circulation, and the increase of TpP level indicates that fibrin monomers have already polymerized, suggesting the following, possible thrombosis, and as such, TpP has been seen as the indicator for the activity of thrombus (Mega *et al*., 2008; Grundy, 2012). In this study, we found that in the type II diabetes mellitus patients with CHD, TpP and Ps further increased, suggesting that in these patients, intravascular atheromatous plaque may have already existed or even been ruptured, thereby increasing the risk of thrombus and the risk of cardiovascular events, which correlates with the progression of diabetes mellitus and poor management of blood glucose. MAR and MPV are the indicators reflecting the size and activity of platelet and have been frequently applied in clinical practice as a common item in routine blood test. Increase in MPV results from the augmentation in the quantity of huge, highly active platelets generated from the megakaryocytes of bone marrow. In this study, we noted that type II diabetes mellitus patients with CHD presented a higher level of MPV than that in the non-diabetes mellitus patients, coinciding with the previous literatures (Ding *et al*., 2021; Sansanayudh *et al*., 2016), which may be attributed to the stimulation of insulin to the megakaryocytes of bone marrow and hyperglycemia-caused osmotic expansion.

Moreover, we compared the incidence rate of thrombotic events and survival rates in a 2-year follow-up between the hypoglycemia group and hyperglycemia group and found that in the hyperglycemia group, the incidence rate of thrombotic events was much higher than that in the hypoglycemia group, with a lower survival rate in 2-year follow-up, suggesting that the management of blood glucose in type II diabetes mellitus patients may associate with the hypercoagulation and thrombotic events in CHD patients.

This study also has limitations. The sample size included in this study is small and retrospective analysis, and the follow-up time is also short. It is expected to be further improved by expanding the sample size, carrying out prospective and central control studies, and extending the follow-up time.

CONCLUSIONS

For CHD patients with type II diabetes mellitus, poor management of blood glucose may result in the elevation in platelet activation, further inducing the hypercoagulability of blood and increases in the incidence rate of thromboembolism and death rate, suggesting that CHD patients with type II diabetes mellitus should pay more attention to the management of blood glucose and monitor the platelet function and activation of thrombin, thereby minimizing the incidence of acute thromboembolism.

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Statement of conflict of interest

The authors have declared no conflict of interest.

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