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Admission hyperglycemia as an independent predictor of clopidogrel high on-treatment platelet reactivity in ischemic stroke patients

[2]Haoxuan Chen, [2]Zhenzhen Lou, [2]Yibo Zhan, [2]Huiying Ouyang, [2]Guixian Chen, [2]Changlin Zhang, [2]Hui Mao, [2]Xiaojun Li, [3]Zhiping Huang, [3]Longlong Wen, [3]Haoyou Xu, [3]Zequan Zheng, [1,3]Yuanqi Zhao, [1,3]Min Zhao

[1]State Key Laboratory of Dampness Syndrome of Chinese Medicine, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine [2]The Second School of Clinical Medical Sciences, Guangzhou University of Chinese Medicine, Guangzhou; [3]The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, China

Abstract

Background: Admission hyperglycemia is a predictor of poor prognosis after ischemic stroke (IS). Previous studies have found that admission hyperglycemia was related to clopidogrel high on-treatment platelet reactivity (HTPR) in diabetic patients with myocardial infarction. However, reports on associations between admission hyperglycemia and clopidogrel HTPR remain scarce in IS patients. In this study, we assessed the correlation between admission hyperglycemia and clopidogrel HTPR in patients with IS. *Methods:* In this retrospective study, we included IS patients who were treated with clopidogrel for at least 5 days. Thromboelastography (TEG) was used to evaluate the platelet function. Clopidogrel HTPR was defined if adenosine diphosphate (ADP)-induced platelet fibrin clot strength (MA_{ADP})>47 mm. Otherwise, it would be defined as clopidogrel normal on-treatment platelet reactivity (NTPR). Two groups were divided according to admission glucose of 7.8 mmol/L, consistent with previous studies on admission hyperglycemia. The independent risk factors of clopidogrel HTPR were assessed by multivariate logistic regression analysis. *Results:* A total of 147 patients were evaluated, and 42(28.57%) of patients were identified as clopidogrel HTPR. In the hyperglycemia group (admission glucose level ≥7.8mmol/L), 40.38% patients were defined as clopidogrel HTPR, which was significantly higher than in the normoglycemia group (22.11%, admission glucose level<7.8mmol/L) (P=0.019). According to multivariate analysis, hyperglycemia was independently associated with clopidogrel HTPR (OR=8.36, 1.47-47.55, P=0.017). Admission glucose level was linearly correlated with MA_{ADP} (r=0.29, P=0.005). Furthermore, with the increase of admission glucose level tertiles, the incidence of clopidogrel HTPR increased gradually (P for trend=0.008).
Conclusions: Admission hyperglycemia is an independent predictor of clopidogrel HTPR and the glucose level is linearly correlated with MA_{ADP} in IS patients. Besides, with the increase of glucose level tertiles, the incidence of clopidogrel HTPR increases gradually.

Keywords: Admission hyperglycemia, high on-treatment platelet reactivity, clopidogrel, ischemic stroke.

INTRODUCTION

China bears the biggest stroke burden in the world and about 70% were ischemic stroke (IS).[1] Clopidogrel is the most commonly prescribed antiplatelet drug in secondary prevention of IS. However, high individual variability in clopidogrel response has been reported.[2,3] In recent years, poorly responsive to clopidogrel has been found in IS patients[4,5], which means patients have a higher risk of thrombotic events than normal responders.[6,7] This relatively low response to clopidogrel was referred to as "clopidogrel high on-treatment platelet reactivity (HTPR)".[6] Clopidogrel HTPR was found to be an extremely important independent risk factor for recurrent ischemic events and other vascular events.[6,8,9] However, the mechanism of clopidogrel HTPR has not been fully elucidated.

Admission hyperglycemia is associated with poor clinical outcomes in patients with IS.[10,11]

Address correspondence to: Professor Yuanqi Zhao and Dr. Min Zhao, Department of Neurology, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangdong Provincial Hospital of Chinese Medicine, 111 Dade Road, Guangzhou, 510405, China. E-mail: tcm2008@126.com, 376479808@qq.com

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Previous studies have found that hyperglycemia is linked to high platelet reactivity, but the exact mechanisms involved have not been fully elucidated.[12,13] One potential mechanism for high platelet reactivity in patients with hyperglycemia may be the upregulation of pro-aggregation factors expressions, such as P-selectin, and thromboxane A2, which enhances platelet aggregation.[14] Another possible mechanism is that hyperglycemia induces the activation of protein kinase C, which in turn triggers the transduction pathway of platelet activation.[15] Nevertheless, the relationship between hyperglycemia and response to clopidogrel remains elusive in IS patients.

It has been found that admission hyperglycemia was related to clopidogrel HTPR in diabetic patients with myocardial infarction.[16] Given the equal status of myocardial infarction and stroke, admission glucose level might be helpful to predict IS patients' response to clopidogrel.

Therefore, the aim of this study was to investigate the association between admission hyperglycemia and clopidogrel HTPR as assessed by thromboelastography (TEG) in IS patients. TEG, as one of several efficient platelet function test methods with high specificity, is effective to monitor IS patient's clopidogrel efficacy and response.[5,17]

METHODS

Study design and patients

We retrospectively included IS patients treated with clopidogrel (75 mg per day) in the Department of Neurology, Guangdong Provincial Hospital of Traditional Chinese Medicine, from January 2017 and March 2021. Diagnosis of IS was based on clinical symptoms and imaging (magnetic resonance/computer tomography). Clopidogrel was taken at least 5 days before TEG testing.[18,19]

The main exclusion criteria included: without TEG testing; cardiogenic stroke; missing platelet data; no admission to our neurology department; abnormal baseline platelet counts i.e. <100 ×10^9/L or >450 × 10^9/L; myelodysplastic syndrome; any medication taken within the past week that might affect coagulation function (e.g. ticagrelor, cilostazol, heparin, warfarin and rivaroxaban); recent cerebral or gastrointestinal hemorrhage or bleeding diathesis; major surgery in the past month, loss of admission glucose data.

Medical data collection

All data were obtained through an electronic medical record system. Demographic and laboratory data of each patient were collected, including gender, age, body mass index (BMI). Clinical and laboratory data included: (1) History of smoking or drinking, medical history of diabetes mellitus, stroke, coronary artery disease, hypertension, and hyperlipidemia. (2) Clopidogrel CYP2C19 metabolic genotype (3) Major medication administered in hospital: hypoglycemic agent, statins and proton pump inhibitors (PPIs); (4) Baseline platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT); admission glucose, hemoglobin A1c (HbA1c), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), total cholesterol (TC) and creatinine (Cr); MA_{ADP}:ADP-induced clot strength.

Admission glucose was defined as the first venous blood glucose measured, and hyperglycemia was defined as admission glucose level ≥ 7.8 mmol/L.[11,20]

CYP2C19 genotyping

DNA samples of peripheral blood were collected, and the CYP2C19 genotypes were classified into 3 phenotypic groups: extensive metabolizers (EMs) (*1/*1), poor metabolizers (PMs; *2/*2, *3/*3, or *2/*3), and intermediate metabolizers IMs (*1/*2 or *1/*3).

Platelet reactivity assessment: Thromboelastography

Platelet reactivity was assessed by thromboelastography (TEG) 5000 Hemostasis system (Haemoscope Corporation). Platelet function was performed within 2 hours of blood sample collection in patients who received clopidogrel (75 mg, per day) for at least 5 days. The platelet reactivity was induced by adenosine diphosphate (ADP) activators. MA_{ADP} was the ADP-induced clot strength (inhibition of platelet activation by the ADP pathway). On the basis of prior studies, we defined clopidogrel HTPR as MA_{ADP}>47mm.[5,19]

Statistical analyses

All statistical analyses were completed with SPSS Statistics 18.0, and $P<0.05$ was set as statistically significant difference. Continuous variables were presented as mean ±SD and were

compared by Student's t test or Kruskal–Wallis test. Additionally, counts and percentages were the expressions of categorical variables, which were analyzed using the chi-square test or Fisher's exact test. Pearson's correlation coefficient was used to explore the association between admission glucose level and MA_{ADP}. Logistic regression analysis operated to find out the relationship between hyperglycemia and clopidogrel HTPR. The results were displayed as adjusted odds ratios (OR), along with 95% confidence intervals (CI).

This study has been approved by the Guangdong Provincial Hospital of Traditional Chinese Medicine (No.YE2021-311-01).

RESULTS

A total of 4,785 IS patients were screened. After excluding 4,389 patients without TEG detection, 9 patients with missing platelet data, and 38 non-resident neurology patients, 349 patients were initially enrolled. Then we further removed patients according to the following criteria: abnormal platelet counts (15), using any other drugs that affect platelet function (88), major surgery in the past month (2), use of clopidogrel for less than 5 days before TEG testing (96) and loss of blood glucose data (1). The final 147 patients were included into our study (Figure 1).

The demographic and clinical data of all patients were presented in Table 1. The mean age of all patients was 64.77±9.95 years, and 51(34.70%) of them were females. 42(28.57%) of patients exhibited clopidogrel HTPR. The patients with clopidogrel HTPR had a remarkably higher levels of admission glucose (10.37±6.83 vs. 6.96±3.08, P=0.001) than clopidogrel NTPR. There were 20(47.60%) females in the clopidogrel HTPR group and 31(29.50%) females in the clopidogrel NTPR group (P=0.037). In addition, clopidogrel HTPR patients had higher level of TC, PCT and lower level of BMI compared with clopidogrel NTPR patients. No statistical differences were found in other baseline characteristics between the two groups.

Admission glucose level and clopidogrel HTPR

Admission glucose level was significantly higher in clopidogrel HTPR group than in clopidogrel NTPR group (OR=1.17, 1.070-1.288, P=0.001). The incidence of clopidogrel HTPR occurred more frequently in females (OR=2.17, 1.039-4.533, P=0.039). The level of TC (OR=1.43, 1.040-1.978, P=0.028) and PCT (OR=1.008, 1.001-1.014, P=0.023) in clopidogrel HTPR group were higher than in clopidogrel NTPR group, as listed in Table 2.

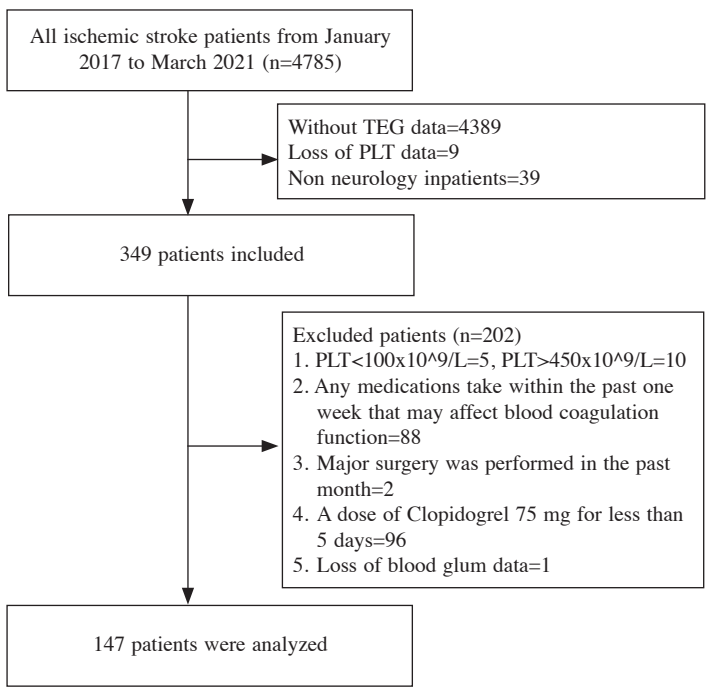

Figure 1. Flow chart
TEG: Thromboelastography; PLT: platelet count.

Table 1: Demographic and clinical characteristics of clopidogrel on-treatment platelet reactivity

	ALL(n=147)	NTPR(n=105)	HTPR(n=42)	P
Age, y, mean ± SD	64.77±9.95	64.04±10.23	66.6±9.09	0.160
Female, n, (%)	51(34.70%)	31(29.50%)	20(47.60%)	0.037
BMI, kg/m^2, mean ± SD	24.16±3.24	24.56±2.82	23.22±3.97	0.119
EMs, n (%)	49(44.10%)	35(45.50%)	14(41.20%)	0.676
Hyperglycemia, n (%)	52(35.37%)	31 (29.52%)	21 (50.00%)	0.019
Medical history, n, (%)				
Smoking	57(38.80%)	42(40.00%)	15(35.70%)	0.630
Drinking	36(24.50%)	26(24.80%)	10(23.80%)	0.903
Diabetes mellitus	55(37.40%)	36(34.30%)	19(45.20%)	0.215
Hypertension	101(68.70%)	74(70.50%)	27(64.30%)	0.465
Stroke	28(19.00%)	21(20.00%)	7(16.70%)	0.642
Coronary heart disease	20(13.60%)	14(13.30%)	6(14.30%)	0.879
Hyperlipemia	16(10.90%)	11(10.50%)	5(11.90%)	1.000
Medication history, n, (%)				
Statins	142(96.60%)	102(97.10%)	40(95.20%)	0.624
Hypoglycemic agent	53(36.10%)	34(32.40%)	19(45.20%)	0.142
PPIs	106(72.10%)	76(72.40%)	30(71.40%)	0.907
Baseline laboratory evaluation				
PLT, × 10^9/L, mean ± SD	246.99±63.72	240.95±63.36	262.1±62.83	0.069
PCT, 0/000, mean ± SD	230.10±55.36	223.41±53.82	246.82±56.27	0.020
MPV, fl, mean ± SD	9.37±0.98	9.36±0.97	9.39±1.00	0.884
PDW, %, mean ± SD	15.77±1.19	15.81±1.11	15.65±1.36	0.453
HDL-C, mmol/L, mean ± SD	1.09±0.27	1.06±0.26	1.15±0.30	0.120
LDL-C, mmol/L, mean ± SD	2.78±1.14	2.67±1.04	3.08±1.35	0.075
TG, mmol/L, mean ± SD	1.68±1.11	1.60±1.13	1.92±1.03	0.146
TC, mmol/L, mean ± SD	4.27±1.25	4.12±1.15	4.70±1.42	0.021
Cr, μmol/L, mean ± SD	81.35±35.84	82.06±39.16	79.58±26.22	0.706
AG, mmol/L, mean ± SD	7.93±4.72	6.96±3.08	10.37±6.83	0.001
HbA1c, %, mean ± SD	7.00±1.93	6.85±1.65	7.40±2.54	0.702
MA_{ADP}, mm, mean ± SD	35.43±17.44	27.06±12.76	56.36±6.47	<0.001

BMI: body mass index, EMs: extensive metabolizers, PPIs: proton pump inhibitors, PLT: platelet count, PCT: plateletcrit; MPV (mean platelet volume); PDW, (platelet distribution width); HDL-C: high-density lipoprotein-cholesterol, LDL-C: low-density lipoprotein-cholesterol, TG: triglyceride, TC: total cholesterol; Cr: creatinine; AG: admission glucose; HbA1c: hemoglobin A1c; MA_{ADP}:ADP-induced clot strength

All patients included in this study were divided into hyperglycemia group and normoglycemia group. As shown in Table 3, patients with clopidogrel HTPR were observed 21 (40.38%) in hyperglycemia group and 21 (22.11%) in normoglycemia group (P=0.019). Additionally, the proportion of women and diabetes mellitus as well as the rate of hypoglycemic agent in hyperglycemia group were higher than in normoglycemia group. Meanwhile, the hyperglycemia group had higher levels of TG, TC, HbA1c and MA_{ADP} than normoglycemia group.

A remarkable correlation was observed between admission glucose level and clopidogrel HTPR as measured by TEG. Pearson correlation analysis revealed that the admission glucose level was linearly correlated with the MA_{ADP} (r = 0.290, P = 0.004), Figure 2. In our research, hyperglycemia was significantly associated with clopidogrel HTPR.

Risk factors of clopidogrel HTPR

Several factors could influence patient's clopidogrel on-treatment platelet reactivity, including gender, age, BMI, drinking, smoking, CYP2C19 gene, stroke, coronary artery disease, hypertension, diabetes mellitus, PPIs, statins and the level of PCT, PLT, LDL-C, TG, HLD-C, TC, Cr.[2,3,6,21] Based on multivariate regression analysis, hyperglycemia was independently associated with clopidogrel HTPR (OR=8.36, 1.47-47.55, P=0.017), as detailed in Table 4. Additionally, with

Table 2: Risk factors for clopidogrel HTPR by univariate logistic regression analysis model

	OR (95% CI)	P
Age, y, mean ± SD	1.03(0.989-1.068)	0.161
Female, n, (%)	2.17(1.039-4.533)	0.039
BMI, kg/m^2	0.88(0.766-1.003)	0.055
EMs, n (%)	0.84(0.371-1.902)	0.676
Hyperglycemia, n (%)	2.39(1.143-4.983)	0.021
Smoking	0.83(0.397-1.750)	0.630
Drinking	0.95(0.411-2.193)	0.903
Diabetes mellitus	1.58(0.764-3.283)	0.217
Hypertension	0.75(0.353-1.609)	0.465
Stroke	0.80(0.312-2.052)	0.642
Coronary heart disease	1.08(0.386-3.038)	0.879
Hyperlipemia	1.16(0.375-3.552)	0.802
Statins	0.59(0.095-3.653)	0.569
Hypoglycemic agent	1.73(0.829-3.588)	0.144
PPIs	0.95(0.431-2.111)	0.907
PLT, × 10^9/L	1.005(1.000-1.011)	0.071
PCT, 0/000, mean ± SD	1.008(1.001-1.014)	0.023
MPV, fl, mean ± SD	1.03(0.713-1.483)	0.883
PDW, %, mean ± SD	0.90(0.678-1.190)	0.455
HDL-C, mmol/L	3.04(0.740-12.52)	0.123
LDL-C, mmol/L	1.35(0.959-1.906)	0.085
TG, mmol/L	1.27(0.909-1.779)	0.161
TC, mmol/L	1.43(1.040-1.978)	0.028
Cr, μmol/L	1.00(0.987-1.009)	0.706
AG, mmol/L	1.17(1.070-1.288)	0.001
HbA1c, %	1.15(0.940-1.403)	0.175

BMI: body mass index, EMs: extensive metabolizers, PPIs: proton pump inhibitors, PLT: platelet count, PCT: plateletcrit; MPV (mean platelet volume); PDW, (platelet distribution width); HDL-C: high-density lipoprotein-cholesterol, LDL-C: low-density lipoprotein-cholesterol, TG: triglyceride, TC: total cholesterol; Cr: creatinine; AG: admission glucose; HbA1c: hemoglobin A1c; MA_{ADP}:ADP-induced clot strength.

the increase of admission glucose level tertiles, the incidence of clopidogrel HTPR increased gradually (P for trend =0.008), as shown in supplementary materials.

DISCUSSION

In this study, we found admission hyperglycemia was an independent predictor of clopidogrel HTPR and the glucose level was linearly correlated with MA_{ADP} in IS patients. Further analysis showed that with the increase of admission glucose level tertiles, the incidence of clopidogrel HTPR increased gradually. These results demonstrated that in IS patients taking clopidogrel, admission hyperglycemia is not only associated with increased platelet reactivity, but also with a low response to clopidogrel.

Association between hyperglycemia and clopidogrel HTPR

It is still controversial whether hyperglycemia can influence the effect of antiplatelet therapy by clopidogrel. In one previous study involving 60 patients with diabetes mellitus and ST-segment elevation myocardial infarction receiving clopidogrel and aspirin, admission hyperglycemia was found to be related to clopidogrel HTPR.[16] But another study showed that hyperglycemia had not modified the effect of clopidogrel on platelet function.[22] Moreover, some studies found glucose control was not related to clopidogrel HTPR.[23-25] On the one hand, prolonged protein glycation caused by hyperglycemia might reduce the biotransformation of clopidogrel and decrease the sensitivity of its receptors, leading to the occurrence of clopidogrel HTPR.[6] On the other hand, hyperglycemia was involved in platelet procoagulant response during IS[26,27], resulting in platelet activation, which might reduce the efficacy of clopidogrel on platelet function. In our study, we found that hyperglycemia was significantly associated with clopidogrel HTPR, and admission glucose level was linearly correlated with MA_{ADP},

Table 3: Baseline characteristics of hyperglycemia and normoglycemia group

	Normoglycemia (n=52)	Hyperglycemia (n=95)	P
Age, y, mean ± SD	64.97 ± 9.72	64.40 ± 10.45	0.744
Female, n (%)	26 (27.37%)	25 (48.08%)	0.012
Clopidogrel HTPR, n (%)	21 (22.11%)	21 (40.38%)	0.019
BMI, kg/m^2, mean ± SD	24.44 ± 2.97	23.57 ± 3.73	0.414
EMs, n (%)	31 (44.29%)	18 (43.90%)	0.969
Medical history, n (%)			
Smoking	40 (42.11%)	17 (32.69%)	0.263
Drinking	22 (23.16%)	14 (26.92%)	0.612
Diabetes mellitus	22 (23.16%)	33 (63.46%)	<0.001
Hypertension	63 (66.32%)	38 (73.08%)	0.398
Stroke	16 (16.84%)	12 (23.08%)	0.357
Coronary heart disease	13 (13.68%)	7 (13.46%)	0.970
Hyperlipemia	12 (12.63%)	4 (7.69%)	0.358
Medication history, n (%)			
Statins	91 (95.79%)	51 (98.08%)	0.656
Hypoglycemic agent	20 (21.05%)	33 (63.46%)	<0.001
PPIs	65 (68.42%)	41 (78.85%)	0.178
Baseline laboratory evaluation			
PLT, × 10^9/L, mean ± SD	247.83 ± 67.26	245.46 ± 57.27	0.830
PCT, 0/000, mean ± SD	228.95 ± 58.74	232.21 ± 49.07	0.733
MPV, fl, mean ± SD	9.27 ± 0.92	9.56 ± 1.06	0.085
PDW, %, mean ± SD	15.79 ± 1.06	15.72 ± 1.40	0.754
HDL-C, mmol/L, mean ± SD	1.10 ± 0.27	1.06 ± 0.28	0.525
LDL-C, mmol/L, mean ± SD	2.66 ± 1.05	3.02 ± 1.29	0.093
TG, mmol/L, mean ± SD	1.48 ± 0.78	2.10 ± 1.53	0.024
TC, mmol/L, mean ± SD	4.11 ± 1.12	4.61 ± 1.43	0.034
Creatinine, μmol/L, mean ± SD	83.74 ± 39.59	76.89 ± 27.34	0.272
AG, mmol/L, mean ± SD	5.50 ± 1.09	12.38 ± 5.50	<0.001
HbA1c, %, mean ± SD	6.25 ± 1.22	8.77 ± 2.13	<0.001
MA_{ADP}, mm, mean ± SD	32.82 ± 17.36	40.21 ± 16.72	0.013

BMI: body mass index, EMs: extensive metabolizers, PPIs: proton pump inhibitors, PLT: platelet count, PCT: plateletcrit; MPV (mean platelet volume); PDW, (platelet distribution width); HDL-C: high-density lipoprotein-cholesterol, LDL-C: low-density lipoprotein-cholesterol, TG: triglyceride, TC: total cholesterol; Cr: creatinine; AG: admission glucose; HbA1c: hemoglobin A1c; MA_{ADP}:ADP-induced clot strength

implying a lower response to clopidogrel in IS patients.

Potential mechanism between hyperglycemia and high platelet reactivity

The exact mechanisms between hyperglycemia and high platelet reactivity have not been fully elucidated. Some potential mechanisms are associated with hyperglycemia to increase platelet reactivity (Figure 3). The first mechanism is that hyperglycemia could increase platelet adhesion by impairing the fluidity of membrane, thereby increasing platelet reactivity.[28,29] Secondly, hyperglycemia could activate glycoprotein IIb/IIIa receptor, P-selectin and protein kinase C expression, which in turn to triggers platelet activation.[12,15,28,30] Thirdly, hyperglycemia could cause excessive accumulation of ADP and lead to the production of advanced glycation end products, which might underlie high platelet reactivity and induce a direct thrombogenic state.[31,32] Finally, a further contribution to high platelet reactivity was mediated by glycation of circulating LDL results caused by hyperglycemia, which increased the production of No and intracellular calcium concentration.[33]

The importance of monitoring clopidogrel HTPR

It is very important for IS patients with admission hyperglycemia to be performed with platelet function testing during clopidogrel treated. Clopidogrel HTPR was found to be an extremely

Table 4: Multivariate regression analysis

Model	Variable	OR (95% CI)	P
1	Normoglycemia	Ref	
	Hyperglycemia	2.39 (1.14, 4.98)	0.021
2	Normoglycemia	Ref	
	Hyperglycemia	2.20 (1.03, 4.72)	0.042
3	Normoglycemia	Ref	
	Hyperglycemia	8.36 (1.47, 47.55)	0.017

Model 1: crude model
Model 2: adjusted for age and gender
Model 3: adjusted for age, gender, BMI, EMs, smoking, drinking, diabetes mellitus, previous stroke, hypertension, coronary heart disease, statins, PPIs, PCT, LDL-C, TC, TG, HDL-C, Cr, PLT.

important independent risk factor for recurrent ischemic events, other vascular events and poor clinical outcomes.[6,8,34] Although clopidogrel is widely used, platelet function testing is only carried out in the larger hospital. Therefore, the prediction and identification of patients with clopidogrel HRTR is a significant issue. Our study indicates that admission glucose level was linearly correlated with MA_{ADP}, and hyperglycemia is an independent predictor of clopidogrel HTPR in IS patients. Consequently, for this type of patients, paying more attention to the correlation between admission glucose level and clopidogrel HTPR may help reduce the potential risk of stroke recurrence, as they may benefit from other antiplatelet drugs.

There were some limitations in this study. First, it was a retrospective study with a relatively small sample size, which may introduce bias into the primary findings. Second, TEG-defined clopidogrel HTPR was the primary efficacy outcome rather than clinical follow-up of cardiac death, nonfatal myocardial infarction and IS.

In conclusion, admission hyperglycemia was an independent predictor of clopidogrel HTPR, and the glucose level was linearly correlated with MA_{ADP} in IS patients. Meanwhile, with the increase of admission glucose level tertiles, the incidence of clopidogrel HTPR increased gradually. We highlight the importance that admission glucose levels should be considered and used as indicators of platelet reactivity testing to ensure the maximum efficacy of antiplatelet therapy.

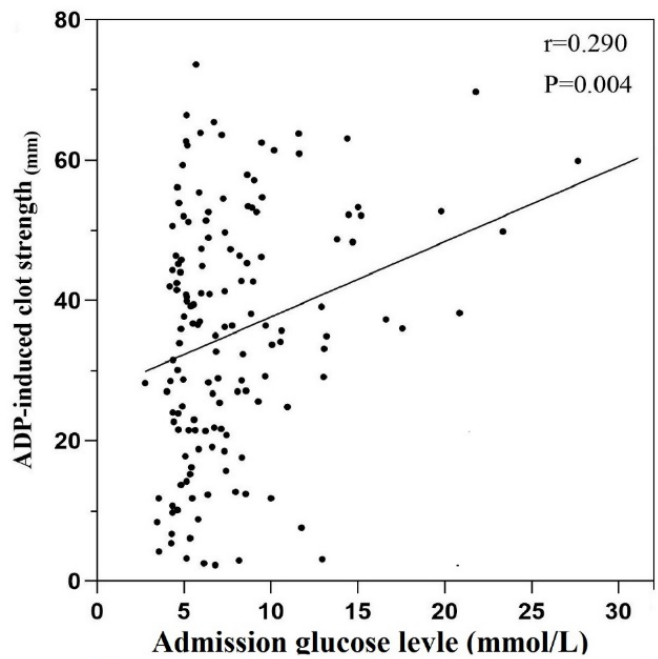

Figure 2. The correlation between ADP-induced clot strength and admission glucose level.

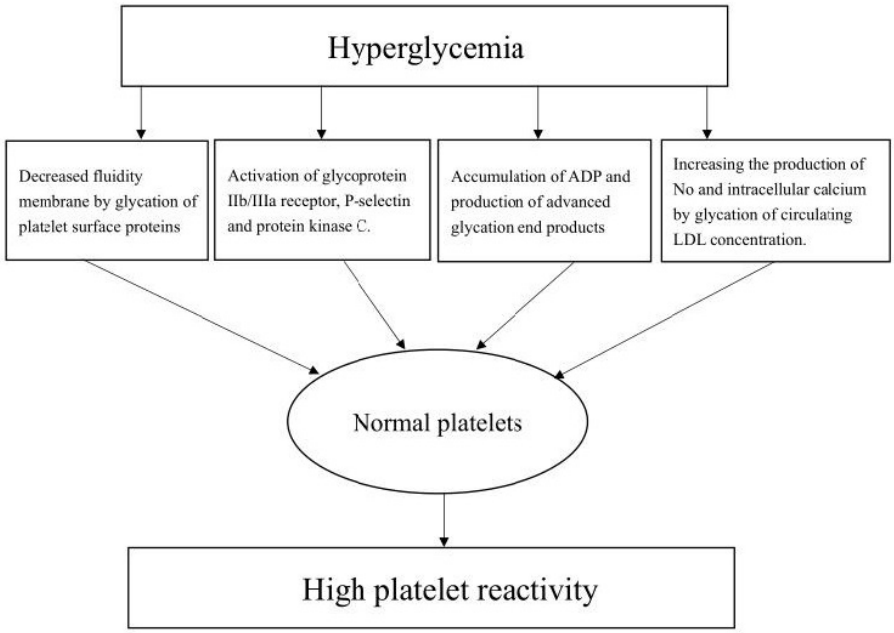

Figure 3. Schematic representation of various biochemical factors responsible for high platelet reactivity by hyperglycemia.

DISCLOSURES

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Conflict of interest: None

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Supplementary Table 1: Baselines characteristics according to admission glucose tertiles

Variable	Admission glucose tertiles			
	Q1(＜5.35) (n=49)	Q2(5.35-8.17) (n=49)	Q3(＞8.17) (n=49)	P
Age, y, mean ± SD	64.24 ± 11.13	65.61 ± 7.79	64.45 ± 10.75	0.980
Female, n (%)	11 (22.4%)	15 (30.6%)	25 (51.0%)	0.009
Clopidogrel HTPR, n (%)	9 (18.37%)	12 (24.49%)	21 (42.86%)	0.020
BMI, kg/m^2, mean ± SD	24.15 ± 3.26	24.58 ± 2.89	23.75 ± 3.58	0.664
EMs, n (%)	16 (42.1%)	16 (48.5%)	17 (42.5%)	0.835
Medical history, n (%)				
Smoking	18 (36.7%)	24 (49.0%)	15 (30.6%)	0.164
Drinking	9 (18.4%)	14 (28.6%)	13 (26.5%)	0.462
Diabetes mellitus	7 (14.3%)	16 (32.7%)	32 (65.3%)	<0.001
Hypertension	33 (67.3%)	32 (65.3%)	36 (73.5%)	0.663
Stroke	7 (14.3%)	9 (18.4%)	12 (24.5%)	0.432
Coronary heart disease	5 (10.2%)	9 (18.4%)	6 (12.2%)	0.471
Hyperlipemia	6 (12.2%)	6 (12.2%)	4 (8.2%)	0.755
Medication history, n (%)				
Statins	47 (95.9%)	47 (95.9%)	48 (98.0%)	1.000
Hypoglycemic agent	5 (10.2%)	15 (30.6%)	33 (67.3%)	<0.001
PPIs	36 (73.5%)	31 (63.3%)	39 (79.6%)	0.191
Baseline laboratory evaluation				
PLT, × 10^9/L	257.45 ± 69.71	240.06 ± 62.81	243.47 ± 58.06	0.423
HDL-C, mmol/L	1.10 ± 0.28	1.09 ± 0.26	1.06 ± 0.29	0.591
LDL-C, mmol/L	2.70 ± 1.24	2.64 ± 0.82	3.02 ± 1.32	0.287
TG, mmol/L	1.32 ± 0.67	1.66 ± 0.87	2.13 ± 1.56	0.012
TC, mmol/L	4.12 ± 1.29	4.12 ± 0.94	4.62 ± 1.46	0.129
Cr, μmol/L	84.43 ± 23.33	82.90 ± 50.52	76.61 ± 27.67	0.089
AG, mmol/L	4.63 ± 0.53	6.53 ± 0.78	12.65 ± 5.56	<0.001
HbA1c, %	5.86 ± 0.74	6.65 ± 1.45	8.97 ± 2.10	<0.001
MA_{ADP}, mm	31.52 ± 17.72	32.98 ± 17.38	41.81 ± 15.69	0.006

BMI: body mass index, EMs: extensive metabolizers, PPIs: proton pump inhibitors, PLT: platelet count, PCT: plateletcrit; MPV (mean platelet volume); PDW, (platelet distribution width); HDL-C: high-density lipoprotein-cholesterol, LDL-C: low-density lipoprotein-cholesterol, TG: triglyceride, TC: total cholesterol; Cr: creatinine; AG: admission glucose; HbA1c: hemoglobin A1c; MA_{ADP}:ADP-induced clot strength.

Supplementary Table 2: Multivariate regression analysis

Variable	Model1		Model 2		P for trend
	OR (95% CI)	P	OR (95% CI)	P	
Admission glucose tertiles					
Q1(＜5.35）	Ref		Ref		
Q2(5.35-8.17）	1.44(0.55-3.81)	0.461	3.98 (0.47, 33.94)	0.207	0.008
Q3(＞8.17)	3.33(1.33-8.35)	0.010	18.67 (2.07, 168.27)	0.009	

Model 1: Crude model

Model 2: adjusted for age, gender, BMI, EMs, smoking, drinking, diabetes mellitus, previous stroke, hypertension, coronary heart disease, statins, PPIs, PCT, LDL-C, TC, TG, HDL-C, Cr, PLT.