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ORIGINAL ARTICLE

Aspirin resistance in patients with type II diabetes mellitus

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Abstract

Background. Diabetic patients exhibit platelet hyperreactivity, which renders them resistant to antithrombotic treatments. We aimed to investigate the prevalence and predictors of aspirin resistance in diabetic patients.

Material and methods. A total of 93 diabetic and 37 non-diabetic participants were included into the study. Aspirin resistance was measured with a whole-blood desktop platelet function analyzer (PFA-100) with an epinephrine agonist.

Results. Altogether 41.9% patients with DM were aspirin non-responders. Aspirin resistance was observed in 43.2% of non-diabetic patients ($p = 0.89$). Presence of diabetes mellitus had no effect on aspirin response (RR 0.95 (95% CI 0.44–2.05), $p = 0.89$) in the whole study population. Hypercholesterolemia was the only predictor of aspirin resistance in multivariate analysis in diabetic patients (RR 3.09 (95% CI 1.17–8.16), $p = 0.023$).

Conclusion. The prevalence of aspirin resistance is comparable in diabetic and non-diabetic patients. Hypercholesterolemia is the only independent predictor of aspirin resistance in diabetic patients.

Key words: *Aspirin resistance, diabetes mellitus, PFA-100*

Introduction

Cardiovascular events are still the leading cause of morbidity and mortality in patients with diabetes mellitus (DM) (1). Most patients with diabetes carry a risk for coronary heart disease (CHD) similar to that of patients with established CHD. Improved glucose control in diabetic patients has not been definitively shown to reduce CHD. Diabetes is a major, independent risk factor for CHD (2). However, certain antidiabetic drugs have been also implied to increase the risk of CHD further (3).

Antiplatelet agents are used for both the primary and secondary prevention of cardiovascular disease (4). However, there is little evidence supporting its efficacy in diabetics. The Primary Prevention Project trial reported that the cardiovascular risk reduction with aspirin was marginal and non-significant in patients with diabetes (5). In a meta-analysis of 287 randomized trials, aspirin reduced the risk of ischemic events by 22%, but the risk reduction in the subgroup with diabetes was only 7%, which was not statistically significant (6).

Here, we aimed to investigate the frequency of aspirin resistance in patients with diabetes as a potential explanation for the conflicting efficacy of aspirin in these patients.

Patients and methods

Patients

A total of 97 consecutive type II diabetic and 38 non-diabetic patients taking aspirin for any reason were recruited for the study. Patients with DM were enrolled in routine follow-up in the outpatient clinic of endocrinology; non-diabetic subjects were contacted in the outpatient clinics of internal medicine, hematology,

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Table I. Comparison of clinical and demographic characteristics.

Variables	Non-diabetics	Diabetics	p	Non-diabetics		p	Diabetics		p
				Responder	Non-responder		Responder	Non-responder	
Total, *n* (%)	37 (28.5)	93 (71.5)		21 (56.8)	16 (43.2)		54 (58.1)	39 (41.9)	
Age									
Median (IQR)	59.5 (49.5–67)	59.5 (54.5–70)	0.22 [a]	60 (49–63)	59 (50–74)	0.30 [b]	60.5 (57–70)	57 (49–67)	0.06 [a]
≥60, *n* (%)	18 (50.0)	46 (50.0)	1.0 [c]	11 (52.4)	7 (46.7)	0.74 [c]	31 (57.4)	15 (39.5)	0.09 [c]
Gender									
Male, *n* (%)	18 (48.7)	38 (40.9)	0.42 [c]	9 (42.9)	9 (56.3)	0.42 [c]	21 (38.9)	17 (43.6)	0.65 [c]
BMI, kg/m^2									
Median (IQR)	26.4 (24.8–28.5)	31.3 (26.7–34.0)	0.001 [b]	26.4 (25.8–28.5)	26.4 (24.8–28.3)	0.79 [a]	30.9 (26.5–33.8)	31.3 (26.7–35.2)	0.60 [b]
≥30, *n* (%)	3 (15.8)	42 (61.8)	0.001 [d]	2 (15.4)	1 (16.7)	1.0 [d]	24 (60)	18 (64.3)	0.72 [c]
Cigarette									
Smokers, *n* (%)	2 (5.4)	18 (19.4)	0.06 [d]	1 (4.8)	1 (6.3)	1.0 [d]	13 (24.1)	5 (12.8)	0.20 [d]
Hypercholesterolemia									
Yes, *n* (%)	10 (35.7)	38 (44.2)	0.43 [c]	3 (20.0)	7 (53.9)	0.11 [d]	17 (33.3)	21 (60)	0.014 [c]
CHD									
Yes, *n* (%)	12 (32.4)	32 (34.4)	0.83 [c]	4 (19.1)	8 (50.0)	0.08 [d]	17 (31.5)	15 (38.5)	0.48 [c]
Duration of DM, years									
Median (IQR)	N/A	7 (4–12)	N/A	N/A	N/A	N/A	7 (4–10)	7.5 (3–14)	0.94 [b]
Medications, *n* (%)									
ACEI	11 (29.7)	28 (30.1)	0.97 [c]	6 (28.6)	5 (31.3)	1.0 [d]	19 (35.2)	9 (23.1)	0.21 [a]
Beta-blockers	14 (37.8)	43 (46.2)	0.38 [c]	5 (23.8)	9 (56.3)	0.09 [d]	27 (50)	16 (41.0)	0.39 [c]
Statins	12 (32.4)	35 (37.6)	0.58 [c]	5 (23.8)	7 (43.8)	0.29 [d]	23 (42.6)	12 (30.8)	0.25 [c]
Aspirin 300 mg	3 (8.1)	16 (17.2)	0.27 [d]	2 (9.5)	1 (6.3)	1.0 [d]	11 (20.4)	5 (12.8)	0.41 [d]
OAD	N/A	62 (66.7)	N/A	N/A	N/A	N/A	33 (61.1)	29 (74.4)	0.18 [c]
Glitazones	N/A	12 (12.9)	N/A	N/A	N/A	N/A	9 (16.7)	3 (7.7)	0.23 [d]
Laboratory data [e]									
WBC, $\times 10^3/\mu L$	7.7 (6.5–8.5)	8.6 (6.8–9.6)	0.08 [a]	7.3 (6.6–8.1)	7.8 (6.3–8.9)	0.44 [a]	8.5 (6.5–9.6)	8.8 (7.4–9.6)	0.32 [b]
Hb, g/dL	14.4 (13.3–15.6)	14.3 (13.1–15.4)	0.72 [a]	14.4 (13.6–15.5)	13.5 (13.1–16.0)	0.92 [a]	14.0 (12.8–15.1)	14.9 (13.6–15.5)	0.08 [a]
PLT, $\times 10^6/\mu L$	2.5 (1.9–3.0)	2.5 (2.0–3.0)	0.92 [a]	2.3 (1.9–2.9)	2.7 (2.2–3.1)	0.47 [b]	2.4 (1.9–3.0)	2.6 (2.2–3.1)	0.26 [a]
MPV, fL	7.5 (7.0–8.4)	8.1 (7.4–8.6)	0.06 [b]	7.5 (7.2–8.5)	7.8 (6.9–8.4)	0.47 [b]	8.1 (7.4–8.6)	7.9 (7.3–8.5)	0.31 [b]
pT, seconds	12.3 (12.0–12.9)	11.8 (11.4–12.9)	0.10 [b]	12.2 (12.0–12.8)	12.7 (11.9–13.2)	0.79 [a]	12.2 (11.5–13.3)	11.6 (11.2–12.3)	0.006 [b]
aPTT, seconds	27.8 (27.1–30.3)	27.9 (26.3–30.3)	0.67 [b]	27.8 (27.4–30.3)	27.6 (26.7–29.5)	0.59 [a]	28.4 (27.4–30.9)	26.9 (25.7–28.6)	0.014 [b]

Table I. (*Continued*).

Variables	Non-diabetics	Diabetics	*p*	Non-diabetics		*p*	Diabetics		*p*
				Responder	Non-responder		Responder	Non-responder	
ESR, mm/h	12 (7–19)	20 (10–30)	0.03 [b]	14 (10–20)	10 (7–17)	0.24 [b]	18 (10–28)	20 (12–31)	0.71 [b]
Creatinine, mg/dL	0.86 (0.66–1.02)	0.84 (0.70–1.08)	0.71 [b]	0.85 (0.59–0.95)	0.88 (0.68–1.13)	0.24 [a]	0.80 (0.67–1.02)	0.89 (0.71–1.11)	0.41 [b]
T. cholesterol, mg/dL	193 (160–205)	190 (152–239)	0.54 [b]	164 (150–198)	203 (192–214)	0.03 [b]	182 (150–236)	213 (157–247)	0.140 [b]
F. glucose, mg/dL	101 (91–109)	164 (134–266)	< 0.001 [b]	102 (91–107)	99 (89–114)	0.89 [a]	162 (136–264)	169 (132–267)	0.77 [b]
HbA1C, %	N/A	7.7 (6.5–9.6)	N/A	N/A	N/A	N/A	7.6 (6.9–9.4)	7.8 (6.5–10.3)	0.56 [b]
CEPI, seconds	293 (127–301)	265 (126–301)	0.72 [b]	301 (301–301)	115.5 (98–138)	< 0.001 [b]	301 (289–301)	118 (102–137)	< 0.001 [b]

Hypercholesterolemia was defined as serum total cholesterol level ≥200 mg/dL according to National Cholesterol Education Program (NCEP)—Adult Treatment Panel III (ATP III) guideline (2).
[a]Student's *t* test.
[b]Mann–Whitney *U* test.
[c]Chi-square test.
[d]Fisher's exact test.
[e]Data were expressed as median (interquartile range).
ACEI = angiotensin-converting enzyme inhibitors; aPTT = activated partial thromboplastin time; BMI = body mass index; CEPI = collagen/epinephrine closure time; CHD = coronary heart disease; DM = diabetes mellitus; ESR = erythrocyte sedimentation rate; F. glucose = fasting glucose; Hb = hemoglobin; IQR = interquartile range; MPV = mean platelet volume; OAD = oral anti-diabetics; PLT = platelets; pT = prothrombin time; T. cholesterol = total cholesterol; WBC = white blood cell.

and endocrinology. Twelve out of 38 the non-diabetic patients were using aspirin prophylaxis for the previous history of coronary heart disease; two for vertebral basilar insufficiency; two women for essential thrombocytosis; one male with Reynaud phenomenon; and the remaining patients for primary prophylaxis of cardiovascular diseases (with no evidence of coronary heart disease). Inclusion criterion for the study was to take aspirin during at least the last 10 days and the last dose of aspirin had to have been taken within the last 24 hours. At least six of a total of eight laboratory tests had to have been performed recently for each patient: complete blood count, prothrombin time (pT), activated partial thromboplastin time (aPTT), erythrocyte sedimentation rate (ESR), serum creatinine, total cholesterol, fasting glucose, and HbA_1C levels (the last-mentioned was required in diabetic patients only). Patients with a history of bleeding diathesis, gastrointestinal bleeding, alcohol abuse, coagulopathy, major surgery within 6 weeks prior to study, platelet count <100,000/μL, hematocrit <25%, creatinine >4 mg/dL, current use of non-steroidal anti-inflammatory drugs, anticoagulants, or antiplatelet drugs other than aspirin were excluded. All patients were informed about the study, and a written and signed consent was obtained from each participant. The study was conducted in accordance with the Good Clinical Practice Guidelines, and the Institutional Board Review approved the study protocol (7).

Diabetes

Diabetes was present if at least one of the following criteria was present: a fasting glucose ≥126 mg/dL, treatment with oral hypoglycemic agents, or treatment with insulin (8).

Hypercholesterolemia

Hypercholesterolemia was defined as serum total cholesterol levels ≥200 mg/dL according to the National Cholesterol Education Program (NCEP)—Adult Treatment Panel III (ATP III) guideline (2).

Measurements

Demographic and recent laboratory data were obtained from the medical chart records. Past and current medical histories were taken from both patient and hospital records. Participants had blood drawn into tubes containing 0.105 mol/L (3.2%) sodium citrate in a ratio of 9 volumes of blood to 1 volume of citrate. Blood was processed and testing completed within 2 hours of collection. Aspirin resistance was

measured with a whole-blood desktop platelet function analyzer (PFA-100) with an epinephrine agonist (9). The PFA-100 is a Food and Drug Administration-approved device used to evaluate platelet dysfunction (10,11). The PFA-100 device measures the time (CT) required for platelets to plug an orifice simulating an injured vessel, after platelet activation by relevant stimuli, by collagen and epinephrine (CEPI), or collagen and ADP (CADP). Aspirin influences the CT_{CEPI} value, whereas the CT_{CADP} remains unaffected (11). Definition of aspirin resistance used was CT_{CEPI} <193 seconds, as defined previously (12).

Statistical analysis and study end-points

Primary end-point of this study was the prevalence of aspirin resistance in diabetic subjects. A secondary end-point was the investigation of potential predictors for aspirin resistance both in diabetic and non-diabetic participants. Power sample estimation revealed that at least 94 subjects in the diabetic and 38 in the non-diabetic group were needed in a 2:1 study design to show a 25% difference with the assumptions overall of type I error of 5%, type II error of 20%, and aspirin prevalence in non-diabetic populations of 15% (13). Descriptive data were expressed as median and interquartile range (IQR). Continuous variables were compared by Student's *t* test if normally distributed. Comparison of skewed data was made by means of Wilcoxon rank-sum test. Statistical analysis of categorical variables was performed by chi-square or Fisher's exact test, when appropriate. Variables predicting the aspirin resistance in univariate analyses were included into the multivariate analysis. A p Value < 0.05 was arbitrarily defined as an inclusion criteria for the multivariate analysis. Two-tailed p Value of less than 0.05 was defined as statistically significant. Univariate and multivariate analyses of potential variables were performed by simple and multivariate logistic regression analyses, respectively. Before performing these analyses, variables were dichotomized by use of median values or cut-off values obtained by receiver-operating curve analysis. Risk of aspirin resistance attributed to each variable was expressed as relative risk (RR) and 95% confidence interval (95% CI). All analyses were performed by Stata Special Edition v. 11.2 for Macintosh OSX (Texas, USA).

Results

Patients

Four diabetic subjects and one non-diabetic subject were excluded due to having no recent laboratory test results. Finally, 93 diabetic and 37 non-diabetic participants were included into the study. Median age for all study population was 59.5 years. A total of 56 out of 130 participants (43.1%) were male. All participants received aspirin 100 mg/day. Only 3 (8.1%) non-diabetic and 16 (17.2%) diabetic subjects used aspirin 300 mg/day. Diabetic patients were more overweight and/or obese (61.8% versus 15.8%, respectively, p = 0.001), had higher ESR (median 20 (IQR 10–30) versus 12 (IQR 7–19) mm/h, respectively, p = 0.03), and serum fasting glucose concentrations (median 164 (IQR 134–266) versus 101 (IQR 91–109) mg/dL, respectively, p < 0.001). Although not statistically significant, there was a trend favoring diabetic patients as more frequent smokers (19.4% versus 5.4%, respectively, p = 0.06) and to have higher mean platelet volume (MPV) (mean 8.1 (IQR 7.4–8.6) versus 7.5 (IQR 7.0–8.4) fL, respectively, p = 0.006). Groups were comparable in terms of other demographic and laboratory parameters including past/current history of coronary heart disease and hypercholesterolemia (Table I).

Prevalence of aspirin resistance

Of patients with DM, 39/93 (41.9%) were aspirin non-responders. Aspirin resistance was observed in 16/37 (43.2%) of non-diabetic patients. The prevalence of aspirin resistance in diabetic patients was similar to that in non-diabetics (p = 0.89) (Figure 1).

Predictors of aspirin resistance

In diabetic patients, hypercholesterolemia, pT (<12 s), and aPTT (<28 s) were found to be a

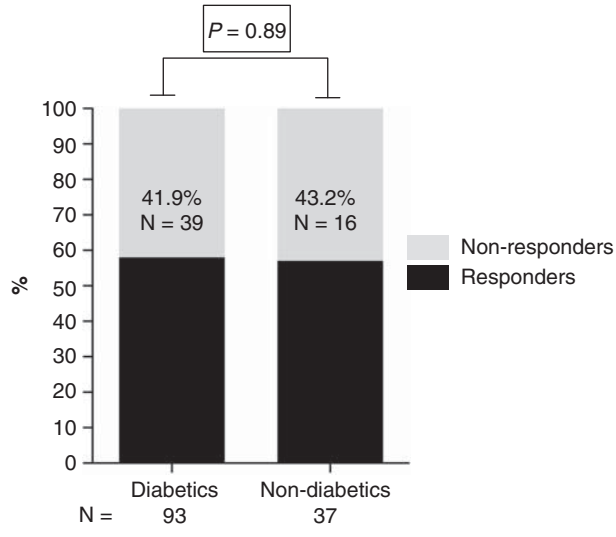

Figure 1. Frequency of aspirin resistance prevalence in diabetic and non-diabetic subjects.

Table II. Univariate and multivariate analysis of potential predictors of aspirin resistance in diabetics and non-diabetics.

Variables	Relative risk	95% Confidence interval	*p*
Diabetics			
Univariate			
Hypercholesterolemia	3.00	1.23–7.32	0.016
Prothrombin time ≥12 s	0.29	0.11–0.78	0.014
Activated thromboplastin time ≥28 s	0.32	0.12–0.88	0.027
Multivariate			
Hypercholesterolemia	3.24	1.07–9.80	0.037
Prothrombin time ≥12 s	0.49	0.16–1.52	0.22
Activated thromboplastin time ≥28 s	0.48	0.16–1.46	0.20
Non-diabetics			
Univariate			
Total cholesterol ≥192 mg/dL	6.67	1.24–35.71	0.027
Hypercholesterolemia	4.67	0.88–24.80	0.071
All study population			
Univariate			
Hypercholesterolemia	3.22	1.48–7.01	0.003
Prothrombin time ≥12 s	0.43	0.19–0.96	0.038
Activated thromboplastin time ≥27.8 s	0.36	0.15–0.83	0.017
Multivariate			
Hypercholesterolemia	3.09	1.17–8.16	0.023
Prothrombin time ≥12 s	0.78	0.29–2.12	0.62
Activated thromboplastin time ≥27.8 s	0.46	0.17–1.21	0.12

Hypercholesterolemia was defined as serum total cholesterol levels ≥200 mg/dL according to National Cholesterol Education Program (NCEP)—Adult Treatment Panel III (ATP III) guideline (2).

potential predictor of aspirin resistance in univariate analyses. However, multivariate logistic regression analysis revealed that the presence of hypercholesterolemia was the only independent predictor of aspirin resistance (RR 3.24 (95% CI 1.07–9.80), $p = 0.037$) (Table II).

Hypercholesterolemia was more frequent in non-diabetic non-responders (53.9% versus 20%, respectively, $p = 0.11$); and relative risk of aspirin resistance in subjects with hypercholesterolemia was 4.67 (95% CI 0.88–24.80). This difference did not reach statistical significance ($p = 0.071$). However, serum total cholesterol concentration ≥192 mg/dL was related to aspirin resistance in non-diabetic patients (RR 6.67 (95% CI 1.24–35.71), $p = 0.027$) (Tables I and II).

Presence of diabetes mellitus did not affect the aspirin response (RR 0.95 (95% CI 0.44–2.05), $p = 0.89$) in the whole study population. Hypercholesterolemia, pT (<12 s), and aPTT (<27.8 s) were associated with aspirin resistance in univariate analysis. Hypercholesterolemia was the only predictor of aspirin resistance in multivariate analysis (RR 3.09 (95% CI 1.17–8.16), $p = 0.023$).

Discussion

This study showed that the prevalence of aspirin resistance is comparable in diabetic and non-diabetic patients. The only predictor of aspirin resistance in patients with or without DM is hypercholesterolemia.

Two percent to 57% of patients have been reported to have a suboptimal antiplatelet response to aspirin therapy (14-16). Definition of aspirin resistance in various studies, heterogeneity of laboratory methods used to assess platelet function, characteristics of study population, and non-compliance rates cause this discrepancy. Commonly used platelet function assays are flow cytometric markers of platelet activation, soluble P-selectin, urine or serum thromboxane-B_2, light transmission aggregometry (LTA), VerifyNow, and PFA-100. All assays have certain advantages and limitations. A comparison of six different platelet function assays including PFA-100 showed that there was a poor correlation between them (12,17). Both clinically and experimentally there is no consensus on how to define aspirin resistance, making interpretation difficult. Definition of aspirin non-responsiveness as post-aspirin CTs ≤193 s may overestimate the prevalence of aspirin non-responsiveness in both diabetic and non-diabetic patients (13). Nonetheless, aspirin resistance measured using the PFA-100 is associated with 2.35 times more vascular events in comparison to aspirin responders (18).

Diabetes mellitus was regarded as a coronary heart disease risk equivalent in the Third Report of the National Cholesterol Education Program (Adult Treatment Panel III) (2). In diabetic patients, aspirin therapy is recommended for the secondary prevention of coronary heart disease and for primary prevention in patients at increased cardiovascular risk (19). Together with increased platelet turnover, increased protein glycosylation has been suggested as the possible mechanisms of aspirin resistance in diabetic patients (20). Increased protein glycosylation reduces aspirin-mediated acetylation and inhibition of COX-1, possibly through a competitive mechanism (21). However, our analysis has failed to demonstrate the effect of DM on aspirin resistance.

Abaci et al. performed an analysis, by use of PFA-100, setting a cut-off value ≤193 s in patients

with coronary artery disease and DM. They reported an aspirin resistance prevalence of 28/184 (15.2%) in the whole study population. The only predictor of aspirin resistance in that study was the presence of DM (13). In the ASPECT study, aspirin resistance was measured by serum and urine thromboxane B_2 levels, PFA-100, LTA, and VerifyNow. Aspirin resistance was higher at low (81 mg/day) doses of aspirin in diabetic patients. At higher doses, diabetic and non-diabetic patients had similar resistance rates (22). Later, interindividual variability of the recovery of platelet cyclo-oxygenase activity has been suggested as an explanatory mechanism for this difference with lower doses of aspirin (23).

The role of hyperlipidemia on aspirin resistance was demonstrated by *in-vivo* and *in-vitro* studies (24,25). Platelet response to aspirin is reduced in patients with chronic hyperlipidemia (24). High levels of low-density lipoprotein cholesterol and triglyceride diminish aspirin responsiveness in diabetic patients with suboptimal glycemic control (26). Infusion of reconstituted high-density lipoprotein cholesterol is highly effective in reversing the excessive accumulation of cholesterol in platelet membranes. This results in reduced platelet hyperreactivity. Increased cholesterol content within the platelet membranes probably reduces membrane fluidity in diabetic patients. This is one of the potential mechanisms of platelet sensitivity (27). Furthermore, high-dose statin therapy reduces *in-vitro* aspirin resistance in 65% of the patients (28).

In conclusion, the prevalence of aspirin resistance is comparable in diabetic and non-diabetic patients. Hypercholesterolemia is the only independent predictor of aspirin resistance in diabetic patients.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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