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RESEARCH

Relationship between MPV and paraoxonase-1 activity, brachial artery diameter and IMT in patients with diabetes mellitus

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Aims: Higher mean platelet volume (MPV) in diabetic patients has been considered as an emerging risk factor for diabetes related micro- and macrovascular complications. Human paraoxonase 1/arylesterase (PON1), which has antioxidant and antiatherogenic properties, is documented in high oxidative stress conditions like uncontrolled diabetes. The present study aimed to evaluate the relationship between mean platelet volume (MPV) and paraoxonase-1 (PON-1) activity, brachial artery diameter (BAd) and intima media thickness (BA-IMT), in diabetic patients with regard to obesity and diabetic complications.
Methods: Two-hundred and one diabetic patients (mean age: 52.4 ± 13.4 years, 73.6% females) were grouped according to obesity and diabetic complications (microvascular and macrovascular). Data on demographics, anthropometrics, diabetic complications, MPV levels, BAd and BA-IMT, and serum paraoxonase and arylesterase activities were recorded. The correlation of MPV values to paraoxonase and arylesterase activities, BAd and BA-IMT was evaluated.
Results: Paraoxonase and arylesterase values were 119.8 ± 37.5 U/L and 149.0 ± 39.9 U/L, respectively, with no significant difference in respect of obesity and macrovascular complications. Significantly lower values for paraoxonase (107.5 ± 30.7 vs. 123.9 ± 38.8 U/L, $p = 0.007$) and arylesterase (132.1 ± 30.2 vs. 154.7 ± 41.2, U/L, $p = 0.001$) were noted in patients with microvascular complications. MPV values were 9.10 ± 0.87 fL, with no significant difference across the groups and no significant correlation with other parameters.
Conclusion: In conclusion, PON-1 activity is more significantly decreased in diabetic patients with microvascular than macrovascular complications with no effects on MPV values. On the other hand, no relationship was found between thrombogenic activity and PON-1 activity, BAd and BA-IMT regardless of obesity and diabetic complications.

Keywords: cardiovascular, diabetes, insulin resistance, obesity, vasculature

Introduction

Type 2 diabetes mellitus (T2DM) is a component of metabolic syndrome associated with dyslipidaemia, hypertension, impaired fibrinolysis, and increased pro-coagulation factors.[1–3] It ranks as the major risk factor for the development of coronary artery disease (CAD)[4,5] due to the central role of oxidative stress in the pathology of diabetes mellitus.[6,7]

In addition to cardiovascular manifestations, diabetes mellitus has been associated with an increased risk of micro- and macrovascular complications, which are a major cause of morbidity and mortality,[8] as oxidative stress is considered a link between diabetes mellitus and related complications.[9,10]

Human paraoxonase 1/arylesterase (PON1) is a calcium-dependent ester hydrolase with paraoxonase, arylesterase and dyazoxonase activities, and antioxidant and anti-atherogenic properties[11–14] shown to be inversely related to the risk of CVD.[15] Accordingly, a decrease in PON1 activity has been documented in states of high oxidative stress like metabolic syndrome, obesity, uncontrolled diabetes, and dyslipidaemia.[16]

It is suggested that decreased PON1 activity in patients with type 2 diabetes mellitus may lead to accelerated atherosclerosis, which causes increased mortality due to CAD.[17–19]

The early stages of atherosclerosis consist of functional impairment of endothelial surface with consequent impairment of arterial vasodilation capacity and thickening of the intima-media space.[20,21] In addition to carotid intima-media thickness (IMT), which was considered a validated parameter in detecting subclinical atherosclerosis and the severity of coronary atherosclerosis,[20,21] it was shown that brachial artery IMT (BA-IMT) correlated to carotid IMT. Consequently, it may serve as a marker of cardiovascular risk, and as initial steps of the atherosclerotic process.[22]

Mean platelet volume (MPV) is a parameter of platelet size, which is easily determined on routine automated haemogram and is routinely available at a relatively low cost.[23] Higher MPV values, a marker of increased thrombogenicity and atherosclerosis, have been reported in patients with acute myocardial infarction, stroke, diabetes mellitus, congestive heart failure and in

hypertensive patients with evidence of target organ damage.[24–26] The volume of thrombocytes is increased with increased thrombocyte activation. It is known that large platelets have more thrombotic potential than smaller ones, they have more intense granules and are more effective metabolically and enzymatically.[27] Moreover, cytokines, such as interleukin-3 or interleukin-6, influence megakaryocyte ploidy and can lead to the production of more reactive, larger platelets at the level of progenitor cells such as megakaryocytes.[28] Altered platelet morphology, function and increased levels of MPV have been reported to lead to the synthesis of more thromboxane[1,29,30] in diabetic patients. This condition is currently considered an emerging risk factor for atherothrombosis[31–33] and is an accelerating factor in the development of micro- and macrovascular complications of diabetes.[29,30]

The present study was hence designed to evaluate the relation of mean platelet volume (MPV) levels with serum PON-1 activity and brachial artery diameter (BAd) and BA-IMT in diabetic patients with respect to obesity and diabetic complications.

Materials and methods

A total of 201 diabetic patients (mean age: 52.4 ± 13.4 years, 73.6% were females) were included in this study, and grouped with respect to obesity (obese: BMI ≥ 30 kg/m^2; n = 89 and non-obese: BMI ≤ 29.99 kg/m^2; n = 112) and diabetic complications (with [n = 50] or without [n = 150] microvascular complications and with [n = 91] or without [n = 108] macrovascular complications). Outpatients aged between 18 and 75 years, who were diagnosed and treated for T2DM (fasting blood glucose > 126 mg/dl or blood glucose level of > 200 mg/dl at random measurements or haemoglobin A1C > 6.5%), and who signed informed consents were included in the study. Patients with psychiatric disorders, cancer history, chronic renal failure, thrombocytopenia, myeloproliferative disease, chronic liver disease or hepatic failure, coronary artery disease or history of acute myocardial infarction were excluded from the study.

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study, which was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and approved by the institutional ethics committee.

Assessments

Data on demographic (age, gender) and lifestyle (smoking status, alcohol consumption, regular physical exercise) characteristics of patients, anthropometric measurements (height, weight, body mass index [BMI]), diabetes-related microvascular (neuropathy, retinopathy and nephropathy) and macrovascular (hypertension, CAD, past history of coronary artery bypass grafting [CABG], peripheral artery disease [PAD], stroke and past history of myocardial infarction [MI]) complications, MPV levels (fL), BAd and BA-IMT and serum paraoxonase and arylesterase activities were recorded. Correlation of MPV values to paraoxonase and arylesterase activities, as well as to BAd and BA-IMT, was evaluated in the study groups.

Mean platelet volume (MPV)

MPV, as a component of complete blood count test, was determined in a Coulter LH 750 auto analyser (Beckman Coulter, CA, USA). Blood samples collected in tubes with EDTA were transferred to the biochemistry laboratory within 30 minutes, and laboratory analysis was performed immediately so that time to analysis was not a confounding factor for MPV results. The expected normal range for Beckman Coulter LH 750 device was 6.9–16 fL.

Measurement of paraoxonase and arylesterase activities

Venous blood samples were collected in tubes from the antecubital vein, following an overnight fasting. The tubes were centrifuged at 2000 g (10 minutes) to remove plasma and serum. The plasma and serum samples were kept at –80°C until analysis of PON1 activity.

Paraoxonase and arylesterase activities were determined using a novel automated measurement method developed by Erel (Relassay®, Turkey). Briefly, the rate of paraoxon hydrolysis was measured by increased absorbance at 412 nm at 25°C. The PON activity is expressed as U/L serum. The coefficient of variation (CV) for individual samples was 1.8%. Arylesterase activity was measured spectrophotometrically using phenyl acetate. The reaction was initiated by the addition of the serum; the increase in absorbance was read at 270 nm. Enzymatic activity was calculated from the molar absorptivity coefficient of the produced phenol. One unit of arylesterase activity was defined as 1 µmol phenol generated/minute under defined assay conditions and expressed as U/L serum. The CV for individual serum samples was 3.3%.

Measurement of brachial artery diameter (BAd) and intima media thickness (BA-IMT)

Ultrasonography (US) examinations, IMT and brachial artery diameter measurements were performed by the same radiologist. After a five-minute rest in the supine position the brachial artery was examined in a longitudinal plane between the antecubital fossa and axilla by continuous grey-scale imaging with a linear, high resolution Dynamic Micro Slice (7–18 MHz) transducer. US examinations were performed by Toshiba Aplio 500 (Toshiba Medical Systems Corporation, Nasu, Japan). Measurement of IMT in the brachial artery was performed at the proper site, where IMT was considered the thickest, and where the clearest B mode image of the anterior and posterior intimal interfaces between the lumen and vessel wall was obtained above antecubital fossa. IMT was measured three times and the brachial IMT was defined as the mean of these three measurements. On the same image where the IMT was measured, the distance between the two intimal interfaces was measured and defined as the diameter of the brachial artery.

Statistical analysis

Statistical analysis was made using the MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013). The Mann–Whitney U test was used to analyse independent non-parametric variables, while the Pearson and Spearman correlation analyses were performed to determine correlations between parametric and non-parametric variables, respectively. Data were expressed as 'mean ± standard deviation (SD)', minimum–maximum and percentage (%) where appropriate. $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Overall, obesity was determined in 44.3% of the patients; at least one diabetic microvascular complication was evident in 50 (75.1%) patients, including neuropathy (19.4%), retinopathy

Table 1: Patient characteristics (n = 201)

Factor	No. (%)
Age (years), mean ± SD	52.4 ± 13.4
≤ 50 years, *n* (%)	85 (42.5)
> 50 years, *n* (%)	115 (57.5)
Gender, *n* (%)	
Female	148 (73.6)
Male	53 (26.4)
Anthropometrics, mean ± SD	
Height (cm)	164.1 ± 7.5
Weight (kg)	79.9 ± 14.9
BMI (kg/m^2)	29.8 ± 6.1
Obese (BMI ≥ 30 kg/m^2), *n* (%)	89 (44.3)
Non-obese (BMI ≤ 29.99 kg/m^2), *n* (%)	112 (55.7)
Diabetes-related complications	*n* (%)
At least one1 microvascular complication	50 (75.1)
Retinopathy	26 (12.9)
Neuropathy	39 (19.4)
Nephropathy	17 (8.5)
At least one macrovascular complication	91 (45.5)
Hypertension	86 (42.8)
Coronary artery disease	13 (6.5)
Past history of CABG	8 (4.0)
Peripheral artery disease	2 (1.0)
Stroke	1 (0.5)
Past history of MI	1(0.5)
Smoking status, *n* (%)	
Active smoker	28 (13.9)
Non-smoker	169 (84.1)
Ex-smoker	4 (2.0)
Alcohol consumption, *n* (%)	
Regular	10 (10.0)
None	179 (89.1)
Seldom	2 (1.0)
Physical exercise, *n* (%)	
Regular	57 (28.4)
None	143 (71.1)
Seldom	1 (0.5)
Family history for diabetes mellitus	96 (47.8)
Hypoglycaemia	15 (7.5)

(12.9%), and nephropathy (8.5%). At least one diabetic macrovascular complication was evident in 91 (45.5%) patients, including hypertension (42.8%), CAD (6.5%), past history of CABG (4.0%), PAD (1.0%), stroke (0.5%) and past history of MI (0.5%). Active smokers made up 13.9% of the study population, while regular alcohol consumption and physical activity were noted in 10% and 28.4% of patients, respectively (Table 1).

HbA1c was 7.4 ± 1.9% and blood glucose was 148.2 ± 61.6 mg/dL in the overall study population.

MPV, paraoxonase and arylesterase levels in the study groups

Paraoxonase and arylesterase values were 119.8 ± 37.5 U/L and 149.0 ± 39.9 U/L, respectively in the overall population, with no significant difference with respect to obesity and macrovascular diabetic complications, whereas significantly lower values for paraoxonase (107.5 ± 30.7 vs. 123.9 ± 38.8 U/L, p = 0.007) and arylesterase (132.1 ± 30.2 vs. 154.7 ± 41.2 U/L, p = 0.001) were noted in patients with than in those without diabetic microvascular complications (Table 2).

Table 2: MPV, paraoxonase and arylesterase levels in study groups

Factor			MPV (fL)	Paraoxonase (U/L)	Arylesterase (U/L)
Overall (n = 201)		Mean ± SD	9.10 ± 0.87	119.8 ± 37.5	149.0 ± 39.9
		Median (min–max)	9 (7.3–12.2)	116.25 (46.6–262.0)	141.20 (90.7–279.2)
Obesity	Present (n = 89)	Mean ± SD	9.0 ± 0.9	119.5 ± 35.6	150.4 ± 39.0
		Median (min–max)	8.9 (7.3–11.8)	121 (55.8–195.5)	144 (90.7–229.8)
	Absent (n = 112)	Mean ± SD	9.1 ± 0.8	120.0 ± 39.1	147.9 ± 40.7
		Median (min–max)	9.2 (7.4–12.2)	112.3 (46.6–262)	141.2 (94.6–279.2)
		p-value[1]	0.282	0.879	0.464
Microvascular complications	Present (n = 50)	Mean ± SD	9.1 ± 0.9	107.5 ± 30.7	132.1 ± 30.2
		Median (min–max)	9 (7.3–11.8)	98.7 (63.1–177.2)	123 (90.8–201.3)
	Absent (n = 150)	Mean ± SD	9.1 ± 0.9	123.9 ± 38.8	154.7 ± 41.2
		Median (min–max)	9.1 (7.3–12.2)	121.4 (46.6–262)	153.9 (90.7–279.2)
		p-value[1]	0.792	0.007	0.001
Macrovascular complications	Present (n = 91)	Mean ± SD	9.0 ± 0.9	120.6 ± 36.1	147.5 ± 36.6
		Median (min–max)	9 (7.3–12.2)	117.2 (55.8–213.8)	140.5 (95.8–250.4)
	Absent (n = 108)	Mean ± SD	9.2 ± 0.8	119.6 ± 38.7	150.8 ± 42.3
		Median (min–max)	9 (7.3–11.6)	116.4 (46.6–262)	148.1 (90.7–279.2)
		p-value[1]	0.169	0.729	0.799

[1]Mann–Whitney U test.

Table 3: Correlation of mean platelet volume (MPV) values to paraoxonase and arylesterase activities in study groups

Factor			Paraoxonase		Arylesterase	
			r	*p*	r	*p*
MPV	Overall (n = 201)		–0.002	0.983	–0.040	0.577
	Obesity	Present (n = 89)	0.071	0.531	0.049	0.665
		Absent (n = 112)	–0.033	0.747	–0.067	0.515
	Microvascular complications	Present (n = 50)	–0.172	0.233	–0.159	0.270
		Absent (n = 150)	0.049	0.548	–0.003	0.974
	Macrovascular complications	Present (n = 91)	–0.145	0.189	–0.072	0.514
		Absent (n = 108)	0.111	0.251	0.049	0.617

Note: Spearman correlation analysis r: correlation coefficient.

MPV values were 9.10 ± 0.87 fL in the overall population, with no significant difference in respect of obesity and diabetic complications (Table 2).

Correlation of MPV values to paraoxonase and arylesterase activities in the study groups

No significant correlation of MPV values to paraoxonase and arylesterase activities was noted in the overall study population as well as in study groups of obese vs. non-obese patients, and in patients with vs. those without diabetic complications (Table 3).

Correlation of MPV values to BAd and BA-IMT in the study groups

No significant correlation of MPV values to BAd and BA-IMT was noted in the overall study population, or in study groups of obese vs. non-obese patients and patients with vs. without diabetic complications (Table 4).

Discussion

The study results revealed significantly lower PON-1 activity in diabetic patients with microvascular complications than in those without microvascular complications, while no difference in MPV values was observed in obese vs. non-obese patients, or in patients with vs. those without diabetic complications. No significant correlation was found between MPV values and PON-1 activity or BAd or BA-IMT in our study population, regardless of the obesity or diabetic complication status.

Lower PON1 activity was also shown in diabetic patients with complications,[34] including macrovascular[35,36] and microvascular[37] complications, and especially in those with neuropathy and nephropathy, leading to a higher risk for atherosclerosis.[16]

No difference was noted with regard to macrovascular complications. However, significantly lower paraoxonase and arylesterase activities in our diabetic patients with microvascular complications compared with those without microvascular complications were found to be consistent with the more pronounced decrease in PON1 activity reported in patients with, than in those without diabetic nephropathy, when compared with controls.[37–41] This relationship was also reported in patients with, than in those without diabetic retinopathy[39,42,43] as well as in the data on the lowest levels of paraoxonase specific activity in patients with peripheral neuropathy.[42] In this regard, our findings suggested that decreased PON1 activity in patients with type 2

Table 4: Correlation of mean platelet volume (MPV) values to brachial artery diameter and intima media thickness (IMT) in study groups

Factor		MPV values					
		Obesity		Microvascular complications		Macrovascular complications	
		(+)	(−)	(+)	(−)	(+)	(−)
Brachial artery IMT							
Right	r	−0.209	0.140	−0.011	−0.061	0.046	−0.063
	p	0.150	0.318	0.952	0.610	0.771	0.634
Left	r	−0.232	0.114	−0.077	−0.064	0.012	−0.010
	p	0.108	0.415	0.687	0.590	0.938	0.943
Brachial artery diameter							
Right	r	−0.131	−0.042	−0.204	−0.084	−0.274	0.109
	p	0.369	0.764	0.280	0.484	0.079	0.412
Left	r	−0.094	−0.068	−0.361	0.008	−0.205	0.054
	p	0.522	0.627	0.050	0.944	0.193	0.685

Note: Spearman correlation analysis. r: correlation coefficient.

diabetes mellitus was probably playing a role in the development of diabetic vascular complications.[38–41]

Following the first data on decreased PON1 paraoxonase activity and increased lipid peroxidation levels in isolated HDL from obese adult patients,[44] a decreased serum PON1 arylesterase activity was consistently reported in obese adults.[45,46] Although data on PON1 paraoxonase activity in obesity revealed inconsistent findings with decrease in activity as shown in some studies,[47,48] similar to our study no significant change was reported in the others.[49–51]

Enhanced platelet activity has been documented,[3,54] in relation to the fact that abnormal platelet–endothelial interaction is an essential pathogenic mechanism in the development of atherosclerosis.[52,53] Larger platelets are younger, more reactive, contain denser granules, and secrete more serotonin and β-thromboglobulin. They have been reported to produce more thromboxane A2 than smaller platelets. All these can produce a pro-coagulant effect and cause thrombotic vascular complications. This suggests a relationship between platelet function, especially with MPV and diabetic vascular complications, thus indicating changes in MPV and reflecting the state of thrombogenesis. High MPV has currently therefore emerged as a new risk factor for the vascular complications of DM.[54–56]

Significantly higher values for MPV in diabetic patients as opposed to non-diabetic subjects have consistently been reported in previous studies, with regard to an increased thrombotic state.[3,29,30,57–59] Data from different cohorts of type 2 diabetes mellitus patients in Turkey revealed significantly higher values for MPV in diabetics compared with age- and sex-matched non-diabetic healthy controls,[29,60] and also in diabetics and subjects with impaired fasting glucose compared with the non-diabetic group, along with a positive correlation of MPV with HbA1c and fasting blood glucose (FBG) levels.[60]

Similarly, in another study from Turkey, MPV levels were reported to be significantly higher in type 2 diabetic patients with HbA1c levels > 7% than in patients with HbA1c levels ≤ 7% and in non-diabetics,[3] which is consistent with the statement that glycaemic control reduces MPV levels and hence the possible role of platelets in cardiovascular events observed in type 2 diabetic patients.[61] Hyperglycaemia can increase platelet reactivity by inducing nonenzymatic glycation of proteins on the platelet surface, through the osmotic effect of glucose and activation of protein kinase C. Such glycation decreases membrane fluidity and increases the propensity of platelets to activate.[54–57]

Higher levels for MPV were shown in diabetic patients than in the control group, and also in diabetic patients with, than in those without retinopathy, along with a positive correlation with FBG and HbA1c levels, in another study from Turkey.[62] Moreover, MPV has been suggested to be a simple and cost-effective tool to monitor the progression and control of T2DM, and a useful prognostic marker of cardiovascular complications in patients with T2DM.[3,60]

Notably, a difference between platelet volume indices in terms of their association with macrovascular and peripheral neuropathy complications was also reported in a previous study on type 2 diabetic patients, which indicated that both MPV and platelet distribution width (PDW) were significantly associated with vibration perception threshold (VPT), while only PDW, but not MPV, was significantly associated with carotid IMT in a multivariate analysis.[63]

In this regard, and although the lack of a control group limits the interpretation of our findings in relation to the above findings, MPV values were within the normal non-diabetic range in our diabetic patients with no difference in MPV values, with regard to presence of obesity or diabetic complications. Accordingly, aside from the lack of an increased platelet activity, which is one of the mechanisms deemed responsible for the pathogenesis of atherosclerosis,[24–26] no correlation of MPV levels to BAd and BA-IMT was noted in our study population.

In addition, on the basis of mean HbA1c (7.4%) and blood glucose (148.2 mg/dL) in our study population, it should be noted that platelet hyper-reactivity and increased baseline activation in patients with diabetes mellitus has been considered to be multifactorial and related to certain biochemical factors including hyperglycaemia, insulin resistance and hyperlipidaemia.[56] Several limitations to this study should be considered. First, the cross-sectional nature of the study and lack of a non-diabetic control group along with the relatively small sample size precluded the possibility of drawing extensive causal conclusions and generalising our findings to the overall diabetic population. Second, no data are available considering surrogate serum biomarkers of oxidative stress alterations, which could have impacts on PON1 protein

expression or activity, along with the lack of data on other platelet volume indices, which may have varying associations with complications of vascular and peripheral neuropathy in type 2 diabetes mellitus. Third, while drugs such as statins, fibrates, aspirin, glucocorticoids, and phenobarbital are amongst the classical inducers of PON1 activity[16] and MPV values are significantly higher in diabetic patients receiving oral hypoglycaemic agents than in those patients on insulin therapy,[23] no data have been collected on these treatments approaches. Lastly, study data were not analysed in subsets according to platelet size such as lower MPV, normal MPV or higher MPV, to investigate correlations with micro- and macrovascular complications. More detailed analysis could have revealed additional information about the MPV value and its possible correlations.

Accordingly, further larger-scale prospective studies with consideration of glycaemic control and anti-diabetic therapy, and the duration of diabetes would make a valuable contribution to the literature regarding the role of MPV as a prognostic marker of cardiovascular complications in diabetes mellitus.

In conclusion, our findings indicate a decreased PON1 activity and thus an increased atherosclerotic burden in diabetic patients with microvascular rather than macrovascular complications, No increase in thrombogenic activity along with no correlation of thrombogenic activity to PON-1 activity or BAd and BA-IMT was reported in diabetic patients regardless of obesity status or diabetic complications. Nonetheless, further larger-scale prospective case control studies are needed to draw a concrete conclusion regarding the role of MPV as a prognostic marker of cardiovascular complications in diabetes mellitus.

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