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Association of Platelet-Activating Factor Acetylhydrolase with Ankle-Brachial Index in Patients with Type 2 Diabetes Mellitus

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Abstract: ***Background: Peripheral arterial disease (PAD) is a common cardiovascular complication in patients with type 2 diabetes mellitus (T2DM).Platelet-activating factor acetylhydrolase (PAF-AH) is a biomarker of vascular inflammation. The purpose of this study was to evaluate the influence of T2DMon PAF-AH activity in patients with or without PAD. Methods: cross sectional case control study included 180 subjects were stratified into control andT2DMgroup, the enzymatic activity of (PAF-AH) was determined by a colorimetric assay. Results: there were significant higher values of serum PAF-AH in patients with T2DM with moderate and sever PAD compared to patients with mild PAD. Regarding ankle-brachial index (ABI) there was highly significant lower values in moderate and sever diabetic patient with PAD compared to patients with mild PAD. By linear regression analysis test body mass index, HDL, LDL and fasting plasma glucose were independently correlated with PAF-AH. Receiver operating characteristic analyses (ROC) revealed that the sensitivity and specificity power of PAF-AH among T2DM patients were (97.5%, 60% respectively). Conclusion: plasma PAF-AH levels are significant high in T2DM patients as well as patients with severe PAD and strongly correlated with ABI as well as other lipid and metabolic disorders.***

Keywords: Peripheral arterial disease, PAF-AH, ABI

1. Introduction

Type 2 diabetes mellitus is a risk factor for atherosclerosis which is responsible for coronary heart disease, peripheral arterial disease, and cerebrovascular disease [1]. In Egypt, the prevalence of diabetes is around 15.5% among adults' population, with an annual death of 86, 478 related to diabetes [2].

Peripheral artery disease (PAD) is associated with an increased risk of cardiovascular Morbidity and mortality [3, 4], clinical manifestation of PAD, including functional decline, intermittent claudication, critical leg ischemia, and amputation, [5].Patients with diabetes mellitus often have extensive and severe PAD and a greater propensity for arterial calcification [6].

platelet-activating factor acetylhydrolase) is a member of the intracellular and secretory phospholipase enzyme family secreted by activated macrophages [7, 8]. The plasmatic PAF-AH is constitutively active and circulates bound to LDL, HDL and other lipoproteins and catalyses the hydrolysis of the sn2 acetate of PAF and PAF mimetics, which are early mediators of inflammation [9]. PAF activates a variety of cells of the innate immune system promoting migration, adhesion and inflammatory effects. Thus, PAF-AH while inactivating PAF is considered an important factor in preventing an exaggerated inflammatory response and in protecting cells from uncontrolled oxidative damage [10]. The ankle-brachial index is a useful tool for specific, cost-effective, noninvasive diagnosis for peripheral artery disease. [11, 12] a low ABI (≤0.9) is strongly associated with generalized atherosclerosis, cardiovascular mortality and all-cause death, regardless of the presence of symptoms. [13, 14]. In diabetic patients, the risk of peripheral vascular disease (PVD) is increased and occurs earlier and diffuse as well as more severe. ABI is still a relevant method because it is non-invasive as well as cheap; therefore the aim of our research was to estimate PAF-AH plasmatic activity and to clarify the possible correlation between PAF-AH and ABI, which reflect PAD as well as other clinical-laboratory features of type 2 diabetes.

2. Subjects and Methods

A cross-sectional case control study included 180unrelated subjects. One hundred thirty patients with type 2 diabetes mellitus recruited from Diabetes and Endocrinology outpatient clinic of Internal Medicine Department of Zagazig University Hospitals and50 healthy controls, who were matched to cases by age and ethnic origin. Diabetic patients were stratified into three subgroups according to ABI. All patients were subjected to thorough history taking and full clinical assessment including blood pressure, patients with history of respiratory disease, cancer, severe hepatic, renal diseases, acute illness, hormonal therapy, any active inflammatory diseases were excluded from the study. The ethical committee of Faculty of Medicine, Zagazig University approved our study protocol, and all participants assigned written informed consent. ABI is an easy way to compare the systolic pressure of the upper extremity with that of the affected lower extremity. The systolic pressure in the pedal arteries (dorsalis pedis or posterior tibial) was measured using a handheld 5-MHz. Doppler probe and a blood pressure cuff. The higher of these two measurements was compared with a similarly taken brachial artery systolic pressure. A ratio ankle/brachial of 0.9 or less is considered a sign of impaired flow to the extremity [15, 16]. Patients were classified according to ABI into three categories: I<

0.9-0.7 (mild PAD), II< 0.7-0.5 (moderate PAD) and III < 0.5-0.3 (severe PAD).

Blood sampling: Blood samples were drawn from all subjects after an overnight fast. We measured fasting blood glucose using the glucose oxidase method (Spinreact, Girona, Spain). Total cholesterol, HDL cholesterol, and triglycerides were measured by routine enzymatic methods (Spinreact, Girona, Spain). LDL cholesterol was calculated using the Friedewald formula [17]. PAF-AH activity was analyzed using the colorimetric method with a commercial kit according to instructions provided by the manufacturer (Cayman Chemical Statistical analysis.

Data analyses were done with statistical package for the social sciences software (SPSS Version 21, Chicago, Illinois). Data were expressed as mean ± standard deviation (SD). The relationships of PAF-AH levels with clinical and laboratory parameters among T2DM patients were tested with the Pearson rank correlation. Receiver operating characteristic (ROC) analysis was performed to assess the potential accuracy of serum PAF-AH for diagnosis of PAD.A linear regression analysis was done to detect the main predictors of PAF-AH levels in T2DM patients. We considered P to be significant at <0.05 with a 95% confidence interval (CI).

Clinical and Biochemical Characteristics of the Studied Groups

In T2DM group, we found significant higher values of BMI, waist/hip ratio, FMI, systolic, diastolic pressure, TG, LDL, FPG andHbA1c compared to controls. On the contrary, we detected significant lower HDL cholesterol inT2DM patients than in those healthy subjects. (Table 1).

Table 1: Clinical, anthropometric and laboratory characteristics of all studied subjects

	Control group (n=50)	T2DM group (n=130)	P
Age (years)	45.8±11.14	44.4±10.35	0.07
Systolic pressure	127.14±6.0	136.5±14.1	<0.001*
Diastolic pressure	83.58±4.75	88.66±7.1	<0.001*
Waist /hip ratio	0.939±0.07	0.97±0.05	<0.001*
BMI	23.26±0.96	26.5±6.189	<0.001*
FMI (kg/m2)	4.65±0.192	7.3±1.139	<0.001*
TC (mg/dL)	168.88±9.9	176.7±29.7	0.06
TG (mg/dL)	135.8±13.3	178.3±37.2	<0.001*
LDL.C (mg/dL)	87.1±10.63	107.5±32.1	<0.001*
HDL.C (mg/dL)	50.9±5.53	48.81±6.41	<0.001*
FPG (mg/dL)	86.8±5.08	180.1±24.9	<0.001*
HbA1c (%)	5.33±0.382	7.37±0.53	<0.001*

Clinical and Biochemical Characteristics of Diabetic Groups

We classified T2DM groups according to severity of PAD to three subgroups. In group III, we found significant higher values of BMI, FMI, LDL, FPG and TC compared to group I. On the contrary, we detected significant lower HDL in group III patients than group I. Regarding group II, we observed significant higher values of BMI, LDL and TC compared to group I, (Table 2).

Table 2: Laboratory and anthropometric parameters in Type 2 DM group stratified according to ABI.

	Group I (n=69)	Group II (n=35)	Group III (n=26)
Age (years)	44.43±10.3	42.66±10.0	42.24±9.66
Waist /hip ratio	0.95±0.067	0.98±0.052	1.03±0.05
BMI	23.9±5.16*	24.6±4.81$	28.56±6.47
FMI (kg/m2)	6.64±1.186	7.55±0.86$	7.68±1.041
Systolic pressure	133.7±12.6	137.4±13.2	137.6±14.9
Diastolic pressure	87.58±5.83	89.05±7.79	89.12±6.32
TC (mg/dL)	168.3±11.1*	185.5±38.5$	187.2±42.3
TG (mg/dL)	178.1±11.2	169.8±47.9	190.8±58.8
LDL.C (mg/dL)	83.65±20.9*	128.5±18.2$	143.1±14.4
HDL.C (mg/dL)	49.7±4.8*	49.03±7.28$	45.96±8.11
FPG (mg/dL)	174.4±26.2*	184.2±21.1$	190.2±22.1
HbA1c (%)	7.25±1.31	7.34±1.36	7.45±1.64

Comparison of PAF-AH (nmol/min/ml) and ABI values among the studied groups

Moderate and sever diabetic patient with PAD had significantly higher values of serum PAF-AH (24.21±2.78 and 31.44±4.08, respectively) compared to mid PAD group (21.68±3.36) (Fig.1). On the contrary, there was highly significant lower values of ABI in moderate and sever diabetic patient with PAD (0.57±0.062 and 0.43±0.056, respectively) compared to mid PAD group (0.87±0.049) (Fig.2).

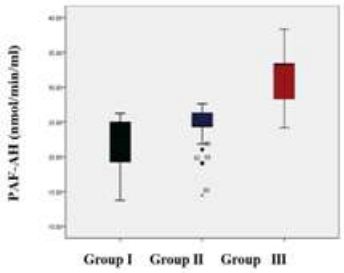

Figure 1: Comparison of PAF-AH (nmol/min/ml) levels among the studied groups

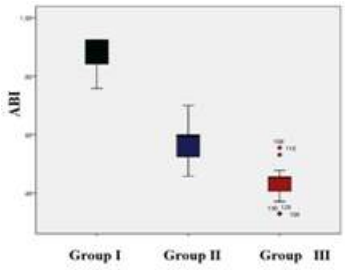

Figure 2: Comparison of ABI levels among the studied groups

Correlation between PAF-AH, ABI, and other parameters among T2DM groups

In T2DM group, PAF-AH levels were significantly positive correlated with waist /hip ratio, BMI, triglycerides, LDL and FPG, On the contrary, PAF-AH levels were significantly negative correlated with HDL (P<0.05).Regarding ABI, there were significantly positive correlated with HDL, On the contrary, ABI levels were significantly negative

correlated with BMI, TC, LDL, HDL, FPG, HbA1c and FMI (Table 3).

Table 3: Pearson correlations between ABI, PAF-AH (nmol/min/ml) and other parameters of studied groups

Variable	ABI		PAF-AH	
	r	p	r	p
Age (year)	-0.150	0.088	0.131	0.139
Systolic pressure	-0.063	0.475	0.153	0.083
Diastolic pressure	-0.060	0.498	0.033	0.706
FMI (kg/m2)	-0.261	<0.001*	0.020	0.819
Waist /hip ratio	-0.003	0.192	0.217	<0.01*
BMI	-0.380	<0.001*	0.190	<0.01*
TC (mg/dL)	-0.287	<0.001*	0.114	0.195
TG (mg/dL)	-0.035	0.693	0.205	<0.05
LDL.C (mg/dL)	-0.759	<0.001*	0.476	<0.001*
HDL.C (mg/dL)	0.202	<0.01*	-0.281	<0.001*
FPG (mg/dL)	-0.186	<0.01*	0.525	<0.001*
HbA1c	-0.218	<0.01*	0.055	0.531

Correlation between PAF-AH (nmol/min/ml) and ABI amongT2DM groups

In T2DM group, PAF-AH levels were significantly negative correlated with ABI (r=0.529, p<0.001) as demonstrated in figure3.

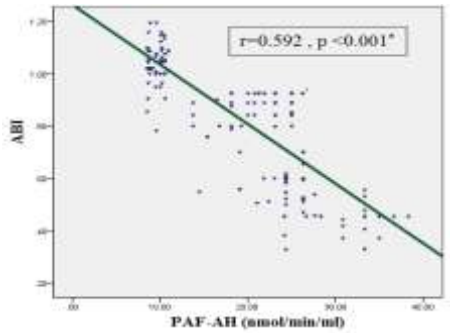

Figure 3: Pearson correlation between PAF-AH (nmol/min/ml) and ABI in studied groups

Linear regression analysis in T2DM groups

In T2DM group, linear regression analysis revealed that BMI, HDL, LDL and FPG were the main predictors of PAF-AH levels among other clinical and laboratory biomarkers (Table 4).

Table 4: linear regression analyses in elderly patients to test the influence of the main independent variables against PAF-AH (mm) (dependent variable

Model	Unstandardized Coefficients		Standardized Coefficients	t	p	95% C.I.	
	B	SE	Beta			Lower Bound	Upper Bound
Constant	1.669	7.634		0.219	0.827	16.78	13.447
BMI	0.189	0.062	0.235	3.025	<0.001*	0.312	0.065
FPG	0.069	0.013	0.346	5.105	<0.001*	0.042	0.096
LDL.C	0.056	0.010	0.363	5.506	<0.001*	0.036	0.076
HDL.C	-0.144	0.056	-0.186	-2.559	<0.001*	-.256	-0.033
TG	0.019	0.009	0.139	2.071	<0.05*	0.001	0.036
Waist /hip ratio	14.791	5.531	0.177	2.674	<0.001*	3.839	25.742

Accuracy of circulating PAF-AH levels for assessment of PAD severity by ROC analysis

The power of PAF-AH levels to assess the severity of PAD among T2DM studied subjects was evaluated using ROC analysis. When we compared our patients (n=130) with healthy subjects (n=50), the AUC was 0.981 (95% CI = 0.899-0.986) with sensitivity = 88.3%, specificity = 70%, and the cutoff values (19.16) (Fig. 4).In attempt to differentiate between mild and moderate PAD, the cutoff values were (17.4375) and the AUC was 0.954 (95% CI = 0.901–0.988). Additionally, the sensitivity and the specificity were (97.5%, 60% respectively). (Fig. 5). Regarding sever PAD, the AUC was 0.899 (95% CI = 0.839-0.958) with sensitivity = 91.4%, specificity = 60%, and the cutoff values (24.22). (Fig. 6).

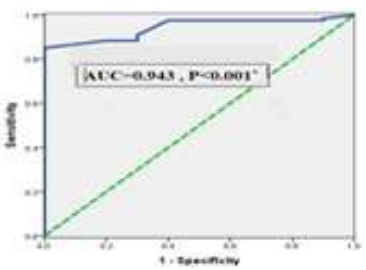

Figure 4

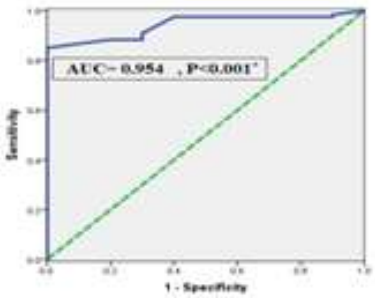

Figure 5

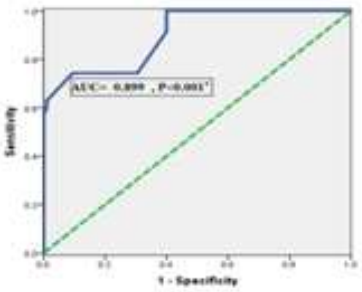

Figure 6

3. Discussion

Peripheral arterial disease (PAD) is a public health problem across the world with a significant impact on healthcare and a high economic burden [18-22]. It is associated with an increased risk of cardiovascular disease [23-25], and is particularly common in patients with type 2 diabetes [26-29]. PAD affects 9% - 23% of people over 55 years of age [30, 31] among them, only 10% reveal the typical symptoms of intermittent claudication, whereas 50% have other leg symptoms and the remaining 40% are asymptomatic [22, 23].

The main cause of death in patients with PAD is associated with CV and/or cerebrovascular events, rather than complications related to PAD itself, as PAD is mostly a powerful indicator of progressive, systemic atherosclerotic disease, the results of limited studies regarding the influence of PAF-AH plasmatic activity on PAD are unclear, thus the purpose of our study was to evaluate the influence of type 2 diabetes and cardio metabolic markers on PAF-AH activity in patients with or without PAD.

Our results revealed that, there were significant higher values of BMI, waist/hip ratio, FMI, systolic blood, diastolic blood pressure, triglycerides, LDL, FPG and HbA1c in T2DM groups compared to controls group. Moreover, there were significant higher values of BMI, FMI, LDL, TC and FPG. In patients with severe PAD compared to patients with mild PAD.

In agreement with our results Aboleineen et al. [33] study found that, there was significant difference between the groups regarding TC and TG being higher among group. The same results were perceived in a study of Liang et al. [34]

The main finding of our research that, there were significant higher values of serum PAF-AH in diabetic patients with moderate and sever PAD compared patients with mild PAD. Regarding ABI there was highly significant lower values in moderate and sever diabetic patient with PAD compared to patients with mild PAD.

The finding of our present study consistent with our previous researches [35, 36] which demonstrated that diabetic patients, cardiovascular risk patients, and the general patient population with borderline ABI had a poorer prognosis than those with normal ABI [35, 36]. The same results were conducted by a study of Natsuaki et al. [37] and Tanaka et al. [38]. Also Serban et al noticed that the PAF-AH levels were significantly higher in patients with both NIDDM and dyslipidemia, as compared to healthy subjects.

Concordance with our finding, Aboleineen et al. found that, there was difference between diabetic and non-diabetic patients regarding the distribution of arterial tree affection in the lower limbs; diabetic patients had more severe arterial affection in the below knee arteries (popliteal, anterior tibial, peroneal, posterior tibial) than non-diabetic patients [33].

Similar to our findings Jude et al observed greater severity of arterial disease in diabetic patients in the all arterial segments below the knee [39].

These results were supported previously by de Castro et al who studied on type 1 DM and they found that higher enzyme activity of PAF-AH in patients with DM 1 than in control subjects [40], It seems probable that hyperglycemia causes endothelial dysfunction, vascular inflammation, arterial wall hypertrophy and fibrosis, which are all interrelated processes that lead to vascular damage with arterial stiffness [41, 42].

Several lines of evidence provide information about the relationships of Lp-PLA2 biomarkers with coronary heart disease and ischemic stroke. To our knowledge, no previous studies reported associations of PAF-AH activity as a member of Lp-PLA2 family with PAD in diabetic as well as non-diabetic subjects. Our study found that, there was positive correlation between PAF-AH levels with waist /hip ratio, BMI, triglycerides, LDL and FPG.

Meanwhile, according to our results ABI levels were significantly negative correlated with BMI, total cholesterol, LDL, HDL, FPG, HbA1c and FMI. For further evaluation of the main effectors of PAF-AH among T2DM group, linear regression analysis test was done. Our results showed that, BMI, HDL, LDL and fasting plasma glucose were independently correlated with PAF-AH.

These results agree with those reported in Garg et al. they detected that higher Lp-PLA2 mass and activity were associated with development of both incident clinical PAD and low ABI [45].

In line with the current knowledge of Serban et al found positive correlation between PAF-AH activity and LDL-ch/HDL-ch ratio in patients with NIDDM [46].

Similar results obtained by de Castro et al they observed that, in patients with DM 1, a direct correlation between PAF-AH activity and LDL, and an inverse correlation between PAF-AH and high-density lipoprotein (HDL) were found [42].

In line with the current knowledge of Serban et al found positive correlation between PAF-AH activity and LDL-ch/HDL-ch ratio in patients with NIDDM [44].

Similar results obtained by de Castro et al they observed that, in patients with DM 1, a direct correlation between PAF-AH activity and LDL, and an inverse correlation between PAF-AH and high-density lipoprotein (HDL) were found [40].

We analyzed our data by ROC to estimate the cut off, sensitivity and specificity of PAF-AH in differentiating between different degrees of PAD. The sensitivity and specificity were (97.5%, 60% respectively). Thus PAF-AH could be useful diagnostic test discriminate different degrees of PAD especially moderate PAD from mild PAD.

In conclusion, plasma PAF-AH levels are high in T2DM patients as well as patients with severe PAD compared to mild group. PAF-AH levels are correlated with ABI as well as other lipid and metabolic disorders thus plasma PAF-AH could be used as marker of vascular inflammation and atherosclerosis. We recommend further studies on a population to support these findings.

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