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Fibrinolytic, Platelets and Endothelial Microparticles Abnormalities among Obese Type 2 Diabetic Patients

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Abstract

Background: The prevalence of cardiovascular disorders is progressively increased among type 2 diabetic (T2DM) patients. While, the influence of association between obesity and T2DM on the level of platelets and endothelial micro particles remain to be fully elucidated.

Objective: The aim of this was to measure the abnormalities of fibrinolytic parameters, fibrinogen, platelets and endothelial Microparticles among obese T2DM patients.

Materials and Methods: Fifty non-smokers obese type 2 diabetic patients were included in this study. The mean age was47.13±5.42 year and mean body mass index was 33.34±4.11 kg/m^2 refers as the first group (A). Initially, a physician at King Abdulaziz University Hospital examined all participants. Their medical history was taken to collect information about general condition, physical activity and current medications if any. All subjects with any cardiovascular conditions (those with a known history of uncontrolled hypertension, congenital and rheumatic heart diseases), any pulmonary disease (obstructive or restrictive lung diseases), were excluded from the study. In the other hand another fifty non-diabetic subjects not suffering of any disease, were participated in the study as a control group refers as (B).

Results: Detailed baseline characteristics of the patients with T2DM and healthy controls showed a significant difference for all characteristics of the diabetic patient's vs controls, except in the age. However, the comparison between values of BMI, tPA: Ag, fibrinogen, PAI-1: Ac, PMP CD41$^+$ and EMP CD144$^+$ for group (A) and group (B), there were statistical significant differences. However, the relationship between tPA: Ag, fibrinogen, PAI-1: Ac, PMP CD41$^+$, EMPCD144$^+$ and BMI, both groups showed a strong direct relationship.

Conclusion: There was a positive association between obesity and the elevated biomarkers of endothelial, platelets micro particles and fibrinolytic parameters abnormalities among type 2 diabetic patients.

Keywords: Microparticles; Fibrinolytic; Obesity; Non-insulin dependent diabetes

Abbreviations: T2DM: Type 2 Diabetes Mellitus; Mps: Micro Particles; ELISA: Enzyme Linked Immunosorbent Assay; BMI: Body Mass Index; R: Pearson's Correlation Coefficient

Introduction

The prevalence of both diabetes associated with obesity is on the rise [1]. The worldwide estimation of diabetics was 171 million in 2000, however this number will be projected to 366 million by 2030 [2] along with increase in mortality rate among patients with diabetes [3]. However, the economic impact of diabetes is great which was 147 billion US dollars in 2008 [4,5].

Cardiovascular complications are more common among obese individuals with type 2 diabetes (T2DM) [6] which is the main cause of higher mortality rate among obese T2DM [7]. Moreover, level of micro particles (MPs) can be considered as an essential biomarkers of cardiovascular risk [8].

Endothelial micro particles are indicators for vascular tone, coagulation, endothelial inflammation and stress/damage of the endothelial cell [9]. However, platelet micro particles that released from activated platelets are indirect biomarker for endothelial dysfunction as it indicate increased inflammation and abnormal coagulation [10-17].

The aim of this was to measure the abnormalities of fibrinolytic parameters, fibrinogen, platelets and endothelial micro particles among obese T2DM patients.

Materials and Methods

Subjects

Fifty non-smokers obese type 2 diabetic patients visiting king Abdulaziz University Hospital, Jeddah, Saudi Arabia, were included in this study. The mean age was 47.13±5.42 year and mean body mass index was 33.34±4.11kg/m^2 refers as the first group (A). Initially, a physician at King Abdulaziz University Hospital examined all participants; their medical history was taken to collect information about general condition, physical activity and current medications if any. All subjects with any cardiovascular conditions (those with a known history of uncontrolled hypertension, congenital and rheumatic heart diseases), any pulmonary disease (obstructive or restrictive lung diseases), were excluded from the study. In the other hand another fifty non-diabetic subjects not suffering of any disease, were participated in the study as a control group refers as (B). The Ethics Committee of the Faculty of Applied Medical Sciences, King Abdulaziz University, approved this study. All participants assigned a written informed consent.

Evaluated parameters

Overnight fasting venous blood samples were taken from anti-cubital vein-puncture were used for the study of lipid profile analysis, while the other two tubes contained EDTA for complete blood count, HbA1c and sodium citrate for coagulation and micro particles studies using a fully automated analyzer machine (Dimenition RxL, Diagnostics) at king Abdulaziz University Hospital.

Coagulation Parameters: Centrifugation of the whole blood at 1500xg for 10 min was done to have the platelet poor plasma which was then separated and stored at (-80°C) until analysis.

Analysis of Coagulation and Fibrinolytic Parameters: The PPP samples were processed with an enzyme linked immunosorbent assay (ELISA) kits for the determination of plasma tPA and PAI^{-1} activities and antigens and the measurement for activities was performed using Chromolize™ tPA and Spectrolyse® pL PAI Bio pool, Umea, Sweden). However, fibrinogen level was measured using Zymutest Fibrinogen, ELISA, Hyphen Biomed, and France.

Micro particle Preparation and Quantification: Flow cytometric analysis was used for the measurement of changes in platelets activities in type 2 diabetic patients. 50µ PPP was incubated with different monoclonal antibodies (5µl CD41 FITC and 5µl CD144 PE) for 30 min at 4°C in a dark place. The measurement of these markers was performed by using four color FACSC alibur® cytometer. Prior to flow cytometric analysis 30µl of flow Trucount Beads (BD Biosciences), was added to micro particle quantitation allowing the calculation of circulating endothelial and platelet derived micro particles (EMP) number / µl PPP [18,19].

Evaluation of Anthropometric Parameters: Measurements of weight and height for both participant groups were performed by using a digital staciometer (JENIX DS 102, S Korea), for the height and body weight were measured on a balance scale (HC4211, S Korea) then, Body Mass Index (BMI) was computed as Body weight/Height^2.

Statistical analysis

Independent "t" test was used to compare the investigated parameters between both groups (P<0.05). However, the degree of correlation body mass index and fibrinolytic, endothelial and platelets micro particles was calculated with Pearson's correlation coefficients (r).

Results

Table 1: The baseline characteristics of all participants.

Parameters	Mean±SD		p value
	Group (A)	Group (B)	
Age (years)	47.13±5.42	45.87±5.16	0.614
Waist circumference (cm)	108.65±7.22	88.15±6.40	<0.001
Hip circumference (cm)	112.45±5.21	100.62±4.87	<0.001
Waist to hip ratio	0.91±0.03	0.83±0.04	<0.001
Body weight (kg)	91.24±3.15	72.58±2.91	<0.001
Systolic blood pressure (mm Hg)	134.64±4.92	118.82±5.38	<0.001
Diastolic blood pressure (mm Hg)	85.52±3.85	71.22±4.16	<0.001
Fasting glucose (mg/dl)	125.46±6.62	88.51±5.40	<0.001
HbA1c %	7.84±1.15	4.96±1.01	<0.001
Total Cholesterol (mg/dl)	228.14±11.46	165.13±10.15	<0.001
HDL-Cholesterol (mg/dl)	31.16±5.81	45.62±4.22	<0.001
Ldl-Cholesterol (mg/dl)	172.54±8.95	97.86±8.87	<0.001
Triglyceride (mg/dl)	155.63±10.33	120.45±8.25	<0.001

BMI=Body Mass Index; HbA1c=Hemoglobin A1C; HDL=High Density Lipoprotein; LDL=Low Density Lipoprotein

Detailed baseline characteristics of the patients with T2DM and healthy controls were presented in Table 1. There was a significant difference for all characteristics of the diabetic patient's vs controls, except in the age (Table 1).Concerning the comparison between values of BMI, tPA: Ag, fibrinogen, PAI-1: Ac, PMP CD41$^+$ and EMP CD144$^+$ for group (A) and group (B),

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there were statistical significant differences as seen in Table 2. The relationship between tPA: Ag, fibrinogen, PAI-1: Ac, PMP CD41+, EMPCD144+ and BMI, both groups showed a strong direct relationship (Table 3).

Table 2: The mean value and the significance values of different parameters in both groups.

Parameters	Mean±SD		T-value	p value
	Group (A)	Group (B)		
BMI (kg/m^2)	33.17±2.11	23.13±2.42	6.95	<0.001
t-PA: Ag (mg/ml)	7.12 ±1.25	4.36 ±1.32	5.53	<0.001
Fibrinogen (ng/dl)	315.66±9.92	223.17±7.15	9.71	<0.001
PAI-1: Ac (ng/ml)	0.58 ±0.17	0.31±0.14	5.92	<0.001
PMP-CD41+ (count/µl)	438.17±15.26	226.24±17.42	8.24	<0.001
Plasma				
EMP-CD144+ (count/µl)	7.94±1.14	4.13±0.98	8.35	<0.001
Plasma				

BMI=Body Mass Index; t-PA: Ag=Tissue Plasminogen Activator Antigen; PMP=Platelet Microparticle; PAI-1: Ac=Plasminogen Activator Inhibitor-1 Activity; EMP=Endothelial Microparticle.

Table 3: The relationship between the grade of tPA: Ag, fibrinogen, PAI-1:Ac, CD41+, EMPCD144+ and BMI in the diabetic group (A).

Test	Pearson's value	Relationship to BMI kg/m^2
t-PA: Ag (ng/ml)	0.87	Strong direct relationship
Fibrinogen (mg/dl)	0.81	Strong direct relationship
PAI-1: Ac (ng/ml)	0.78	Strong direct relationship
PMP-CD41+ (count/µl)	0.85	Strong direct relationship
Plasma		
EMP-CD144+ (count/µl)	0.89	Strong direct relationship
Plasma		

t-PA: Ag=tissue Plasminogen Activator Antigen; PMP=Platelet Microparticle; PAI-1: Ac=Plasminogen Activator Inhibitor-1 Activity; EMP=Endothelial Microparticle.

Discussion

The cardiovascular disorders are three times more frequent among diabetics and mortality rate may reach about 50–75% of diabetic population due to coronary artery disease [20,21]. MPs are biomarkers that can be of value in prediction of risk factors of cardiovascular disease, and as potential targets of therapy [22]. Therefore, this study was a trial to measure the coagulation parameters, platelet and endothelial MPs in T2DM patients compared to control subjects.

The principal findings of in this study included an increased BMI that were positively correlated with higher values of t-PA: Ag, PAI-1: Ac, EMP-CD144+ and PMPCD41+ levels in obese T2DM patients. These findings agreed with many previous studies [23-29]. The obtained results in this study, indicated that PMP-CD41+ were significantly increased among T2DM patients compared to the healthy control group which agreed with Tan et al. [30] who are the first to prove that the symptomatic atherosclerosis is usually associated with increased PMPs in T2DM patients. In addition, results in this study illustrated a significant increase in the circulating levels of EMP-144+ among T2DM compared to the healthy subjects. Moreover, Meigs et al. [31] found that CD62E+ (E-selection) EMPs are elevated among T2DM patients [31]. However, Tramontano et al. [19] and Helal et al. [32] stated that diabetic patients have relatively high level of CD31+ EMPs than non-diabetic subjects [19,32]. Moreover, MP levels have been shown in multiple studies to be higher in diabetics than non-diabetics [19,23,24]. While, Koga et al. [23] conducted a study on 232 diabetics and 102 non-diabetics in Japan, endothelial MP levels were about twice as high among the diabetics [23]. In addition, Jung et al. [25] reported an association between endothelial MPs with macro-vascular complications among diabetics [25].

Our study founded a positive association between BMI and EMP & PMP, which may be caused by the deleterious impact of visceral fat depot in over production of the MP as obesity induce a state of low systemic inflammatory state and causing chronic oxidative stress that, trigger release of MP [26-29]. Finally, our results proved that levels of PAI-1 and t-PA were significantly increased among T2DM patients in comparison to healthy subjects [30-36].

Conclusion

There was a positive association between obesity and the elevated biomarkers of endothelial, platelets micro particles and fibrinolytic parameters abnormalities among type 2 diabetic patients.

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