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Osteopontin for Early Detection of Microvascular and Macrovascular Type 1 Diabetic Complication

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Abstract

AIM: To evaluate the relationship between osteopontin and diabetes complication in type 1 diabetic patient.

PATIENTS AND METHODS: Seventy types 1 diabetic and 60 healthy volunteers were studied. Full history, examination, laboratory tests of glycosylated haemoglobin (HbA1c), serum lipids {cholesterol, triglyceride (Tg), high-density lipoprotein-cholesterol (HDL-c), low-density lipoprotein – cholesterol (LDL-c)}, oxidised low-density lipoprotein (OxLDL), Osteopontin and urinary microalbuminuria (albumin/creatinine ratio) were done. Image study in the form of a carotid intimal medial thickness (cIMT) and aortic intimal medial thickness (aIMT), renal doppler for resistivity index was also done for all participant included in the study.

RESULTS: Urinary albumin/creatinine ratio, lipid profile, osteopontin, cIMT and aIMT were higher in people with diabetes. Osteopontin was higher in people with diabetes with positive microalbuminuria and cIMT. Systolic blood pressure, microalbuminuria and cIMT had a positive correlation with osteopontin in people with diabetes. Stepwise multiple regression analysis showed that osteopontin had a significant correlation with cIMT. Receiver operating characteristic (ROC) curve showed that the cut off value of Osteopontin for detection of cIMT was > 60 with a specificity of 100% and sensitivity 80.5%, while that of albumin/creatinine ratio was > 64 with a specificity of 66.7 and sensitivity of 92.3.

CONCLUSION: Osteopontin is higher in type 1 diabetics and is useful for early detection of diabetic microvascular and macrovascular complication.

Introduction

Osteopontin (OPN) is an adhesive molecule, rich in phosphorylated sialic acid and is a way between cells and minerals [1]. It increases in autoimmune diseases and chronic inflammation and is important for cytokine production in macrophages, dendritic cells, and T-cells [2]. It has a role in the occurrence of adipose tissue inflammation and insulin resistance [3]. It increases in aortic atherosclerotic plaques and other cardiovascular diseases [4]. OPN is useful for early detection of coronary calcification [5], diabetic retinopathy [6] and nephropathy [7] in type 2 diabetes (T2DM).

cIMT and aIMT is an easy, useful, non-invasive method for early diagnosis of subclinical atherosclerosis in type 1 diabetic patients [8], [9]. From our knowledge, a very little publication was done for estimation of the relationship of OPN with a diabetic complication in adolescent type 1 diabetes. We aimed to assess the serum level of OPN in adolescent type 1 diabetes and to detect the association between OPN and diabetic complication (micro and macrovascular).

Patients and Methods

Seventy adolescent type 1 diabetics with duration of diabetes more than 5 years and 60 healthy volunteers from the endocrine clinic, Medical Center of Excellence, National Research Centre were enrolled in this cross-sectional study after taking approval from the ethical committee of the National Research Centre and a written consent from Patients

or their parents and healthy volunteers. Patients presented with any cardiac or vascular disease, hypertension, familial hyperlipidemia, receiving other medication rather than insulin were excluded from the study.

A detailed history was taken; the general and local examination was done for all diabetics and controls. Anthropometric assessment including weight, height, midarm circumference, waist circumference and hip circumference were done. Calculation of body mass index (kg/height (m^2), waist/hip ratio and waist/height ratio were done. Blood pressure was measured 3 times after 5-time rest in the sitting position by mercury sphygmomanometer. Venous blood samples were obtained from each subject in a sterile EDTA vacutainer tube for measuring glycated haemoglobin (HbA1c). It was measured using The NycoCard READER II (Alere Technologies AS, Kjelsåsveien 161, P.O. Box 6863 Rodeløkka, NO-0504 Oslo, Norway). Glycated haemoglobin (HbA1c) was done every 3 months, and the mean value was calculated per year.

A 2^{nd}-morning urine sample was taken for diagnosis of microalbuminuria by measuring albumin/creatinine ratio. Microalbuminuria was diagnosed if the albumin/creatinine ratio was 30-299 µg/g creatinine (measured by an immuno-nephelometric method) in 2 out of 3 samples (6 months period) done every 2 months. Fasting venous blood (12 hr) for determination of lipid profile was done [10]. LDL-c (by Friedewald equation) and Tg (in a Techno Con AutoAnalyzer II, Tarrytown, NY, USA) were calculated. Serum OPN and OxLDL determination by ELISA kit (PELO-BIOTECH GmbH, Germany) were also done.

Carotid intimal medial thickness cIMT

Carotid Doppler was done by ultrasound General Electric: Vivid 7 Pro, GE Vingmed ultrasound AS-Nl90, Horton-Norway, 7.5 – 10 MHz linear-array transducer. Doppler was done in the supine position with an extended neck and turned head 45° to contralateral side [11]. The average of 3 measurements each side was taken for calculation of cIMT [12], [13].

Aortic intimal medial thickness aIMT

Abdominal aorta till aortic bifurcation was assessed by using 7.5 MHz pediatric phased array transducer. Aortic intimal medial thickness was measured by 10 MHz linear array transducer [14], [15]. The average of 3 measurements was taken to calculate the aIMT.

Renal Doppler

Renal colour duplex ultrasound scans using 3-6 MHz convex array transducer (Toshiba, Xario ultrasound machine). Patients were scanned in the supine position. The transducer was placed in a longitudinal position just to the Lt. of the midline, recording colour flow and Doppler spectrum from the abdominal aorta where peak systolic velocity of the abdominal aorta was recorded. Then, the transducer was placed in transverse position just distal to the origin of superior mesenteric artery, to achieve transverse view of the aorta at the origins of both renal arteries where peak systolic velocity of both renal arteries was recorded, and renal artery stenosis was ruled out in all patients by tracing and examining different segments of both renal arteries from origin to renal hilum. Then, resistivity indices were recorded in the segmental, interlobar and arcuate arteries, on both sides [16], [17].

Statistical Analysis

Statistical analysis was conducted using Statistical Package for Social Science (SPSS) program version 20 (Chicago, Illinois, USA) t-tests for independent variables was done. Pearson's correlation, followed by stepwise multiple regression analysis, was done. Receiver operating characteristic curve (ROC curve) was also done to detect sensitivity and specificity of OPN about cIMT and albumin/creatinine ratio.

Results

Diabetic patients had higher urinary albumin/ creatinine ratio, lipid profile (total cholesterol, Tg, LDL-c), OxLDL, osteopontin, cIMT and aIMT (Table 1).

Table 1: Comparison between demographics, laboratory data, anthropometric and image study of diabetic patients and controls

Variables	Patients N = 70		Controls N = 60		P-value
	Mean	SD	Mean	SD	
Age of diabetics (yrs)	17.99	2.59	17.50	2.67	0.6
Systolic blood pressure (mmHg)	118.45	13.33	123.75	10.61	0.30
Diastolic blood pressure (mmHg)	76.55	10.06	80.00	10.69	0.40
Midarm circumfrence (mm)	75.14	379.53	25.79	4.41	0.30
Body mass index (kg/m^2)	24.44	3.89	21.86	6.47	0.30
Waist/hip ratio	0.88	0.08	0.88	0.07	0.90
Waist/height ratio	0.51	0.07	0.48	0.10	0.40
Albumin/creatinine ratio (µg/g creatinine)	71.94	73.49	11.27	4.28	0.0001
Total cholesterol (mg/dl)	194.86	63.65	159.94	22.20	0.0001
Triglyceride (mg/dl)	106.59	53.12	88.21	30.37	0.03
HDL-c (mg/dl)	49.31	16.35	48.78	10.01	0.40
LDL-c (mg/dl_)	116.49	39.10	100.74	28.60	0.03
OXLDL (mg/dl)	4.33	1.42	2.66	1.37	0.0001
Osteopontin (mg/ml)	75.12	20.90	18.71	3.17	0.0001
Carotid intimal medial thickness (mm)	0.52	0.06	0.41	0.03	0.0001
Aortic intimal medial thickness (mm)	0.72	0.11	0.46	0.04	0.0001
Resistivity index	0.67	0.04	0.65	0.05	0.30

LDL: Low-density lipoprotein; HDL: high-density lipoprotein; OxLDL: Oxidized low-density lipoprotein.

Diabetic patients with higher urinary

albumin/creatinine ratio and cIMT had a higher level of serum osteopontin (Table 2).

Table 2: Comparison between osteopontin about microalbuminuria and to a carotid intimal medial thickness in type 1 diabetic patients

Osteopontin (mg/ml)	Negative microalbuminuria		Positive microalbuminuria		P-value
	Mean	SD	Mean	SD	0.01
	63.20	16.44	83.38	23.48	
Osteopontin (mg/ml)	Negative cIMT		Positive cIMT		
	Mean	SD	Mean	SD	0.0001
	53.25	7.23	77.20	20.55	

cIMT: carotid intimal medial thickness.

Osteopontin had a relationship with albumin/creatinine ratio, systolic blood pressure and cIMT (Table 3).

Table 3: Correlation between Osteopontin with demographics, laboratory data, anthropometric data and image study of diabetic patients

Variables	Osteopontin	
	r	P-value
Demographic data:		
Age of diabetic patients (yrs)	0.10	0.44
Duration of diabetes (yrs)	0.09	0.52
Onset of disease (yrs)	0.22	0.10
Insulin dose (u/kg)	0.08	0.55
Blood pressure:		
Systolic blood pressure (mmHg)	0.28	0.03
Diastolic blood pressure (mmHg)	0.01	0.92
Anthropometric data:		
Midarm circumference (mm)	0.07	0.62
Body mass index (kg/m2)	0.03	0.85
Waist/ hip ratio	0.10	0.45
Waist/height ratio	0.12	0.40
Laboratory data:		
HbA1c (%)	0.19	0.16
Urinary albumin/ creatinine ratio (µg/g creatinine)	0.48	0.0001
Total cholesterol (mg/dl)	0.04	0.76
Triglyceride (mg/dl)	0.17	0.25
HDL-c (mg/dl)	0.04	0.80
LDL-c (mg/dl)	0.06	0.70
OxLDL (mg/dl)	0.01	0.92
Image study:		
carotid intimal medial thickness(mm)	0.64	0.0001
Aortic intimal medial thickness (mm)	0.1	0.6
Resistivity index	0.15	0.26

HbA1c: glycosylated haemoglobin; LDL: Low-density lipoprotein; HDL: high-density lipoprotein; OxLDL: oxidised low-density lipoprotein.

Stepwise multiple regression analysis of osteopontin as a dependent factor with demographic, anthropometric, laboratory data and image studies as an independent variable of diabetic patients revealed that osteopontin had a relationship with cIMT (Table 4).

Table 4: Stepwise multiple regression analysis of osteopontin about demographics, anthropometric data, laboratory data and image study in type 1 diabetic patients

	Unstandardized coefficent		Standardized coefficent		
	B	SE	Beta	t	P-value
(Constant)	-76.75	42.13		-1.82	0.09
cIMT (mm)	290.23	76.43	0.67	3.80	0.0001

Dependent variables are osteopontin; cIMT: carotid intimal medial thickness.

ROC curve of osteopontin demonstrate that the area under the curve (AUC) of cIMT was 0.9 with cut off value > 60 and high specificity and sensitivity (100, 80.5% respectively), on the other hand, AUC of urinary albumin/creatinine ratio was 0.8 with cut off value > 64, specificity and sensitivity (66.7 and 92.3 respectively) (Table 5).

Table 5: ROC curve of osteopontin about carotid intimal medial thickness and albumin/ creatinine ratio in type 1 diabetic patients

Variables	Cut off	AUC	SE	95%CI	Sensitivity	Specificity	+LR	-LR
cIMT	> 60	0.9	0.05	0.8 -1.0	81.5	100	0.2	100
Albumin/creatinine ratio (µg/g creatinine)	> 64	0.8	0.1	0.7 – 0.9	92.3	66.7	2.8	0.1

Discussion

In the current study, diabetic patients had higher albumin/creatinine ratio, lipid profile (cholesterol, Tg, LDL-c), OxLDL and aIMT were higher than cIMT which is comparable with [15], [18] who revealed that dyslipidemia is a risk factor of cardiovascular disease. Several previous studies revealed that cIMT and aIMT are increased in type 1 diabetic patients indicating the early occurrence of subclinical atherosclerosis [19], [20].

In our study, all diabetic patients had higher OPN, and it is particularly higher in those with a diabetic complication in the form of diabetic nephropathy (positive microalbuminuria) or atherosclerosis (in the form of increased cIMT) which is comparable with the previous study [19].

Gordin et al., [21] demonstrated that adult type 1 diabetic patient with diabetic nephropathy had higher OPN and in follow up study patients who had higher baseline OPN level develop diabetic nephropathy (microalbuminuria or macroalbuminuria), cardiovascular or retinal disease later on.

OPN had a relationship with systolic blood pressure, albumin/creatinine ratio and cIMT in our diabetic patients and no relation was found with glycemic control and stepwise multiple regression analysis revealed that the most important factor related to OPN is the cIMT.

On the contrary, Abo El-Asrar et al., [19], reported that uncontrolled diabetes, microalbuminuria is associated with high OPN level. Also, a previous study revealed that high serum level of OPN is associated with long duration of diabetes, increase in waist/ hip ratio, high systolic blood pressure, microalbuminuria and increase high sensitive CRP (hs CRP) level and no relation was found with glycemic control (HbA1c) [21].

ROC curve of OPN in our study was done to estimate the cut off level at which we can early predicate patients with complication (cIMT and microalbuminuria). The area under the curve (AUC) of cIMT and microalbuminuria were 0.9 and 0.8 respectively with cut off value > 60 and high specificity

and sensitivity (100, 80.5% respectively) for cIMT and cut off value > 64, specificity and sensitivity (66.7 and 92.3 respectively) for urinary albumin/creatinine ratio. Our study is comparable with Abo EL Asrar et al., [19] study which found that 90 is a cut-off value of OPN for detection of microvascular complications with a sensitivity and specificity of 81.7, 95.8% respectively and AUC is 0.8.

Yan et al., [22] revealed that OPN is associated with the development and degree of nephropathy and coronary affection in diabetic patients and can be used as a predictor of diabetic vasculopathy while Berezin and Kremzer [5] found that OPN can be used in coronary heart disease type 2 diabetic patients as an early marker of coronary artery calcification.

In conclusion, type 1 diabetic patients had subclinical atherosclerosis that can be diagnosed easily by non-invasive and an easy method cIMT and aIMT. OPN is increased in adolescent type 1 diabetic patients and can be used as an early marker for the diagnosis of diabetic nephropathy and subclinical atherosclerosis.

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