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Copeptin as a Biomarker of Atherosclerosis in Type 1 Diabetic Patients

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Abstract

AIM: To evaluate copeptin as an early marker of atherosclerosis in adolescent type 1 diabetics.

METHODS: Sixty-two type 1 diabetic patients and 50 healthy volunteers were enrolled in the study. Serum copeptin, glycosylated haemoglobin (HbA1c), lipid profile, oxidised low-density lipoprotein (OxLDL), urinary albumin/creatinine ratio, carotid intimal medial thickness (cIMT), aortic intimal medial thickness (aIMT) and resistivity index were assessed for all participants in the study.

RESULTS: HbA1c, albumin/creatinine ratio, lipid profile, OxlDL, copeptin, cIMT and aIMT were significantly higher in diabetic patients. Copeptin was higher in patients with positive cIMT and aIMT. Copeptin correlated with cIMT and aIMT. Stepwise multiple regression analysis found that copeptin correlated with aIMT. ROC curve showed that copeptin had 100 % specificity with aIMT and cIMT and 95.2 and 60,7 sensitivity with aIMT and cIMT respectively.

CONCLUSION: Copeptin can be used as a marker for early detection of atherosclerosis of type 1 diabetic patients.

Introduction

Diabetic nephropathy (DN) and cardiac complication being considered the most important factor for morbidity and mortality in type 1 diabetes (T1D) [1], [2]. Early detection of the coronary artery plaque by using Coronary artery calcification (CAC) is an indication of endpoint coronary artery disease (CAD) [2].

As Arginine vasopressin (AVP) is small in size and had a short half-life, it can not be easily measured [3]. AVP is essential for renal and cardiovascular function as it regulates the volume status. Although Copeptin and AVP are derived from the same precursor molecule, copeptin is a more stable peptide and used for evaluation of fluid and osmosis status in various diseases [3], [4].

Type 1 diabetic patients had higher AVP and exaggerated response to AVP concentrations [5], [6], which stimulate V1a receptors leading to diabetic cardiovascular complications. Although the relationship between copeptin, CAD and DN have been studied in adults with type 2 diabetes (T2D) [7], [8], yet from our knowledge, very minimal studies were done on type 1 diabetic patients.

We aimed to study the association between copeptin and atherosclerosis and diabetic nephropathy.

Patients and Methods

This cross-sectional study was done on 62 type of 1 diabetic patient and 50 healthy volunteers. The diabetic patients were selected from the endocrine clinic, Medical Center of Excellence, National Research Centre and the controls among

healthy children attending the Medical centre of Excellence with their relatives. The ethical committee approval from National Research Centre, Registration number 19101 was taken. Also, written consent was received from diabetics or their parents and controls.

Diabetic patients (age > 14 and < 19 yrs) and duration of diabetes more than 5 years were selected. On the other hand, people with diabetes with acute diabetic complications, CVD, taking metformin or multivitamins or Smokers were excluded from the study. Demographic data of diabetic patients was taken. General, cardiac, chest and neurological examination were done for all diabetics and controls. Blood pressure was assessed for all diabetics and controls. It was measured three times after 5-minute rest in the sitting position by using automatic manometer (Omron M4 Plus, Omron Health care Europe, Hoof drop, and Holland). The mean value of the second and the third measurement was calculated.

Weight, height, waist circumference (WC), and hip circumference (HC) were assessed for diabetics and controls. Weight (by Seca Scale Standing Balance) and height (by Holtain Portable anthropometer, Holtain, Ltd, Crymmych, Wales, U.K) were measured. Body mass index, waist/hip ratio and waist/height ratio (cm/cm) were calculated [9], [10].

After 12 hr fasting, venous blood was collected for assessment of lipid profile [11]. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation. Triglycerides (Tg) was measured in a Techno Con AutoAnalyzer II, Tarrytown, NY, USA.

The mean value of glycosylated haemoglobin (HbA1c) of one year was recorded. Measurement of HbA1c every 3 was taken from files of patients.

Screening for microalbuminuria was assessed in fresh morning urine samples by measuring albumin/creatinine ratio. Microalbuminuria was measured 3 times (separated every 2 months), and it was considered positive if 2 from 3 samples were positive. If one sample was positive urine analysis was done to exclude urinary tract infection. Copeptin and OxLDL were measured by the ELISA method (quantitative sandwich enzyme-linked immunosorbent assay technique).

Assessment of Carotid intima-media thickness (cIMT) was done by using General Electric medical ultrasonographic machine model: Vivid 7 Pro, GE Vingmed ultrasound AS-Nl90, Horton-Norway equipped with 7.5–10 MHz linear-array transducer) [12].

Measurement of the aortic intimal medial thickness (aIMT)

The transducer (7.5 MHz) was put in the upper abdomen for evaluation of abdominal aorta and aortic bifurcation. The aortic intima-media complex was assessed (10 MHz linear array transducer). For the assessment of aIMT, the image was focused on the far wall (dorsal arterial wall of the most distal 15 mm of the abdominal aorta), and gain settings were used to optimise image quality [13]. The average of 3 measurements of each patient was taken for evaluation of aIMT.

Renal colour duplex scan by Toshiba, Xario ultrasound machine (3-6 MHz transducer) was done in Rt and Lt renal arteries for measurement of the peak systolic velocities and excluded renal artery stenosis in all patients by assessment of different segments starting from their origins to renal hila. Right, and left resistivity indices in segmental, interlobar and arcuate arteries were also measured [14].

Statistical Analysis

Statistical Package for Social Science (SPSS) program version 20.0 (Chicago, Illinois, USA) was used. T-test for quantitative variables was done. We evaluate the correlation between copeptin with demographics, laboratory data, anthropometric data, and image study of diabetic patients. Pearson's correlation, followed by stepwise multiple regression analysis, were also done. Receiver Operating Characteristic curve (ROC curve) was used for detecting sensitivity and specificity of copeptin with cIMT and aIMT. Stepwise multiple regression analysis of copeptin about demographics, anthropometric data, laboratory data and image study in type 1 diabetic patients

Results

Glycosylated haemoglobin, albumin/ creatinine ratio, lipid profile OxLDL, copeptin, cIMT and aIMT were significantly higher in people with diabetes (Table 1).

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

Variables	Patients		Controls		P-value
	Mean	SD	Mean	SD	
Age of diabetic patients (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
Copeptin (Pg/ml)	9.43	1.70	4.38	1.28	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

HDL-c: High-density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol; OxLDL: Oxidized low-density lipoprotein.

Copeptin was significantly higher in diabetic patients with positive aIMT and cIMT (Table 2).

Table 2: Comparison between copeptin concerning aortic intimal medial thickness and carotid intimal medial thickness in type 1 diabetic patients

	Negative aIMT		Positive aIMT		P-value
	Mean	SD	Mean	SD	
	6.65	0.49	9.54	1.65	0.02
Copeptin (Pg/ml)	Negative cIMT	Positive cIMT	Negative cIMT	Positive cIMT	0.0001
	Mean	SD	Mean	SD	
	8.08	0.98	8.08	0.98	

aIMT: Aortic intimal medial thickness; cIMT: carotid intimal medial thickness.

Copeptin had a positive correlation with age of diabetic patients, cIMT and aIMT (Table 3).

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

Variables	Copeptin	
	r	P-value
Demographic data		
Age of diabetic patients (yrs)	0.32	0.01
Duration of diabetes (yrs)	0.11	0.39
Onset of disease (yrs)	0.23	0.07
Insulin dose (u/kg)	0.04	0.75
Blood pressure (mmHg)		
Systolic blood pressure (mmHg)	0.02	0.85
Diastolic blood pressure (mmHg)	0.06	0.65
Anthropometric data		
Midarm circumference (mm)	0.18	0.17
Body mass index (kg/m2)	0.12	0.37
Waist/ hip ratio	0.13	0.32
Waist/height ratio	0.17	0.18
Laboratory data		
HbA1c (%)	0.02	0.87
Albumin/ creatinine ratio (µg/ g creatinine)	0.05	0.78
Total cholesterol (mg/dl)	0.10	0.47
Triglyceride (mg/dl)	0.14	0.30
HDL-c (mg/dl)	0.08	0.57
LDL-c (mg/dl)	0.03	0.82
OxLDL (mg/dl)	0.06	0.62
Image study		
carotid intimal medial thickness(mm)	0.40	0.0001
Aortic intimal medial thickness (mm)	0.86	0.0001
Resistivity index	0.11	0.40

HbA1c: Glycosylated haemoglobin; HDL-c: High-density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol; OxLDL: Oxidized low-density lipoprotein.

Stepwise multiple regression analysis of copeptin concerning demographic, anthropometric data, laboratory data and image study in type 1 diabetic patients were shown in Table 4.

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

	Unstandardized coefficent		Standardized coefficent		P-value
	B	SE	Beta	t	
(Constant)	2.14	1.59		1.35	0.19
aIMT (mm)	10.23	2.06	0.76	4.97	0.0001

Dependent variables are copeptin; aIMT: aortic intimal medial thickness.

ROC curve of copeptin for detection of atherosclerosis in relation to carotid intimal medial thickness and aortic intimal medial thickness in type 1 diabetic (Table 5).

Table 5: ROC curve of copeptin for detection of atherosclerosis concerning carotid intimal medial thickness and aortic intimal medial thickness in type 1 diabetic patients

Variables	Cut off	AUC	SE	95%C.I	Sensitivity	Specificity
cIMT	> 9	0.8	0.07	0.7 – 0.9	60.7	100
aIMT	> 7	1.0	0.02	0.9 – 1.0	95.2	100

ROC: Receiver operating characteristic curve; aIMT: Aortic intimal medial thickness; cIMT: Carotid intimal medial thickness; AUC: Area under the curve; SE: Standard error; CI: Confidence interval.

Discussion

In our study, adolescent type 1 diabetic patients had higher HbA1c, microalbuminuria, dyslipidemia and higher aIMT and cIMT. aIMT was found to be higher than cIMT in diabetic patients. This result is comparable with previous studies [15], [16]. Järvisalo et al., [17] revealed that young type 1 diabetic patients had an increased incidence of subclinical atherosclerosis. McGill et al., [12] found that intima of the abdominal aorta is affected before intima of the carotid artery and aIMT is an early diagnosis of preclinical atherosclerosis in children [18].

In the current study, copeptin was higher in adolescent type 1 diabetics and patients with higher cIMT and aIMT. Stepwise multiple regression analysis revealed that copeptin had a significant correlation with aIMT. Our results are comparable with the result of [19]. Copeptin had a strong relationship with atherosclerosis and diabetic kidney disease in adult's type 1 diabetic patient [19].

In the present study, copeptin had no significant correlation with albumin/creatinine ratio. As Copeptin and AVP are secreted from neurohypophysis, their level increase in many medical conditions in type 2 diabetic patients such as acute myocardial infarction [20], cardiovascular mortality [3] and diabetic kidney disease.

Vasopressin may lead to an increase in blood pressure (systemic and glomerular) as it leads to an increase in vasoconstriction of blood vessels, enhancing gluconeogenesis, glucagon release and leads to fat accumulation. Vasopressin aggravates kidney disease in animals and leads to an increase in proteinuria in humans [2].

Bjornstad et al., [19], revealed that copeptin is high in adult type 1 diabetic patients and is related to albuminuria, impaired glomerular filtration rate (GFR) and increase in coronary calcium calcification. Increase copeptin level is associated with cardiorenal complications irrespective to the control of blood glucose, lipid profile and blood pressure. Also, Schiel et al., [21] reported that copeptin might be considered as a marker of renal function in children and adolescents with type 1 diabetes mellitus. Moreover, the concentration of copeptin may also be related to stress, behavioural and lifestyle factors as well as

inflammatory activity and the lipid profile.

In the current study, ROC curve of copeptin showed that the cut off level of copeptin for detection of aIMT was > 7 with specificity and sensitivity 100% and 95.2% respectively and for cIMT cut off was > 9 and specificity and sensitivity 100% and 60.7%. Copeptin has better sensitivity and specificity with aIMT, which is early affected before cIMT and can be used as early detection of atherosclerosis.

In conclusion, copeptin is high in adolescent type 1 diabetic patients irrespective of control of blood glucose, dyslipidemia and hypertension. It can be used for early detection of atherosclerosis. Copeptin has no relation to diabetic nephropathy. AVP (Vapans) can be given to adolescent type 1 diabetic patients with cardiorenal complications. A follow-up study and increase number of patients is recommended to detect if copeptin is a cause of occurrence of diabetic atherosclerosis.

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