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Relation of cartonectin (CTRP3) and dyslipedimia in adolescent type 1 diabetic patient

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To evaluate cartonectin (CTRP3) levels in adolescents type 1 diabetic patient. It is a cross sectional study, including 56 type 1 diabetic patients and 18 age and sex matched control group. Blood samples were taken for assessment of liver and kidney function, glycosylated hemoglobin (HbA1c), lipid profile and Serum cartonectin by ELISA. Urine samples were taken for assessment of albumin/creatinine ratio. Diabetic patients had a significantly higher diastolic blood pressure, lipid profile and cartonectin. Cartonectin had a significant negative correlation with waist/ hip ratio, total cholesterol/ HDL and triglyceride / HDL and negative correlation with HDL.CTRP3 increase in Egyptian adolescents with type 1DM, and showed significant correlation with lipoproteins risk ratios as total cholesterol /HDL and triglyceride /HDL, so it may act as biomarker of dyslipedimia in type 1DM.

Keywords:Cartonectin; dyslipedimia;adolescent; type 1 diabetic

INTRODUCTION

Children diagnosed with type 1 diabetes have a high risk of early subclinical and clinical cardiovascular disease (CVD) (Orchard et al, 2001 and Haller et al., 2004). The American Heart Association categorizes children with type 1 diabetes in the highest degree for cardiovascular risk and recommends both lifestyle and pharmacological treatment for those with decreased HDL cholesterol levels (Kavey et al, 2006 and McCrindle et al., 2007).

A novel family of secreted plasma proteins C1q complement/TNF related proteins (CTRPs), similar to adiponectin, plays important roles in regulating glucose and lipid metabolism (Peterson et al., 2012). New adipokine CTRP3 (also known as cartonectin, cartducin, CORS-26) demonstrated that its circulating levels are lower in diet-induced obese mice (Peterson et al., 2010). Furthermore, CTRP3 regulates gluconeogenesis and lipid metabolism in the liver (Peterson et al., 2013). Other investigators have determined that CTRP3 also has anti-inflammatory properties (. Murayama et al., 2014) and may be cardio-protective (Yi W et al., 2012).

Because of its role in metabolism and obesity in rodent models, there has been recent investigation of CTRP3 in adult humans. Two studies investigating CTRP3 levels and its association with diabetes and metabolic syndrome reported conflicting results. One study showed elevated CTRP3 levels in patients with type 2 diabetes (Choi et al., 2012), while a more recent study reported lower levels of CTRP3 in newly-diagnosed patients with type 2 diabetes (Ban et al., 2014). Women with Polycystic Ovarian Syndrome (PCOS) were found to have lower CTRP3 levels compared to their matched controls (Tan et al., 2013), and individuals with acute coronary syndrome or stable angina pectoris were also found to have decreased levels of CTRP-3 compared to control subjects (Choi et al., 2014).

In this study, our aim was to determine serum CTRP3 levels in Egyptian adolescent with type 1 diabetes mellitus (T1DM) and its relation to atherosclerosis. To our knowledge, this is the first study in humans examining CTRP3 levels in children with T1DM.

MATERIALS AND METHODS

Study design and protocol:

It is a cross-sectional observational study. Written informed consent was obtained from all patients or their parents and controls after full discussion about the aim of the study.

Patients:

The study included 56 adolescent type 1 diabetics (DM) among those attending to the endocrine clinic, Medical Center of Excellence, National Research Centre. The control group consisted of 18 age and sex matched healthy normal volunteers. Control group was the healthy friends or relatives of our patients.

Diabetic patients were receiving no treatments except of insulin at the time when their blood samples were obtained for this study. Exclusion criteria included a history of congestive heart failure, liver or kidney disease, malignancy, signs of inflammation, and any drugs influencing body weight like corticosteroids.

All the studied patients were subjected to:

History taking including: age of patients, sex, age of onset of diabetes, duration of diabetes, type and dose of insulin therapy and family history of diabetes.

We asked about presence of any symptoms of cardiac, renal, neurological affection or presence of any type of autonomic dysfunction. We also asked about history of taking drugs other than insulin.

Clinical examination:

I. Patients and controls were subjected to general, cardiac, chest and neurological examination.

II. Blood pressure was measured three times for patients and controls after 5-minute rest in the sitting position on both upper limbs with the use of 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. The measurements taken on the dominant limb were analyzed.

III. Anthropometric measurements in the form of weight, height, waist circumference (WC), and hip circumference (HC) were taken for each participant. The weight and height of the participants were measured up to 0.01 kg and 0.1 cm using a Seca Scale Standing Balance and a Holtain Portable Anthropo meter (Holtain, Ltd, Crymmych, Wales, U.K.). Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. Waist circumference was measured at the level of the umbilicus with the participant standing and breathing normally; hip circumference was measured at the level of the iliac crest, using non stretchable plastic tape to the nearest 0.1 cm. The waist / hip ratio and waist / height ratio (cm/ cm) were calculated. Each measurement was taken as the mean of three consecutive measurements, using standardized equipment (Tanner et al., 1969 and Cameron N, 1986).The landmarks, instruments used, and techniques followed were those recommended by the international biological program (Tanner et al., 1969 and Cameron, 1986).

Laboratory investigation:

Simultaneously all patients and controls underwent the following tests:

All patients and controls underwent the following tests: For cholesterol measurements, venous blood was sampled after a 12-h fast. Serum total cholesterol was determined by a commercial kit (Boehringer-Mannheim, Germany) (Flegg, 1973). High-density lipoprotein (HDL) cholesterol was separated from the serum by precipitation of the other lipoproteins with a heparin/manganese procedure (Marques et al., 1999). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation. The concentration of triglycerides (Tg) was measured in a Techno Con Auto Analyzer II (Techno Con Instruments, Tarrytown, NY, USA). . The TCH/HDL and TG/ HDL ratios were calculated as indices of dyslipidemia and cardiovascular risk in children with T1DM (Hassan et al., 2015).

ALT, AST and Creatinine measurement was carried out using an auto analyzer (Olypus- Au-400).

Glycosylated hemoglobin (HbA1c) was done every 3 months and the mean value was calculated per year. It was measured using high pressure liquid chromatography (Nichols Institute, Van Nuys, CA, USA) (Danilova et al., 1986).

Screening for micro albuminuria was assessed in fresh morning urine samples by measuring albumin/creatinine ratio by enzyme linked immune osorbent assay (ELISA) kit provided by Orgentec Diagnostika, Gmbh (Mainz, Germany) (Mogensen, 1984).

Serum cartonectin was measured using a commercially available ELISA kit (MyBiosource, Inc., Wuhan, China) according to manufacturer's protocol, with an intra-assay coefficient of variation of less than 8% and inter-assay coefficient of variation of less than 10%.

Statistical analysis

Statistical Package of social science (SPSS) version 16 was used for analysis of data. Data was summarized as mean + SD. t test used for comparison of 2 independent variables. Pearson's correlation was used for correlation of 2 variables. P – Value was consider significant if < 0.05.

RESULTS

The average age of the studied diabetic patients was 15.18±.2.07 years, and their average BMI was 23.36±4.25 kg/m^2 (Table 1). Descriptive, demographic and laboratory data of diabetic patients and controls were shown in (Table 1, 2). Comparison between demographic and laboratory data of diabetic patients and controls included in the study (Table 3). Diabetic patients had a significantly higher diastolic blood pressure, lipid profile and cartonectin. Cartonectin (CTRP-3) had a significant negative correlation with waist/ hip ratio and HDL-c, and positive correlation with total cholesterol/ HDL-c and triglyceride / HDL-c (table 4).

Table 1: Descriptive statistics of diabetic patients included in the study

	Minimum	Maximum	Mean	SD
Age (yrs)	12.00	19.00	15.18	2.07
Age of onset of disease (yrs)	1.00	14.00	7.89	3.17
Duration of disease (yrs)	5.00	15.00	7.29	2.49
Insulin dose (U/kg)	0.50	1.95	1.19	0.43
BMI (kg/m2)	16.60	30.90	23.36	4.25
Waist (cm)	58.00	101.00	73.95	12.36
Hip (cm)	61.00	104.00	77.29	11.30
Waist / hip ratio	0.79	1.22	0.96	0.08
Systolic blood pressure (mmHg)	80.00	140.00	110.71	18.44
Diastolic blood pressure (mmHg)	40.00	100.00	70.71	17.41
HbA1c (%)	5.80	13.00	7.73	1.39
Cholesterol (mg/dl)	107.00	249.00	184.43	30.08
Triglyceride (mg/dl)	25.00	140.00	85.21	21.79
HDL-c (mg/dl)	34.00	84.00	51.53	11.25
LDL-c (mg/dl)	54.00	160.00	114.66	23.82
Albumin/ Creatinine ratio	6.00	60.00	19.11	10.65
ALT	8.00	222.00	67.80	90.24
AST	14.00	81.00	47.50	47.38
Creatinine (mg/dl)	0.50	0.74	0.62	0.11
CTRP3	3.04	53.40	16.29	15.02

Table 2: Descriptive statistics of demographic and laboratory data of controls

	Minimum	Maximum	Mean	SD
age	11.00	17.00	13.09	2.17
BMI	15.97	29.07	21.00	4.08
waist	60.00	94.00	71.04	12.07
hip	66.50	88.00	74.20	7.18
Waist/hip ratio	0.80	1.27	0.96	0.12
Systol B.P	70.00	120.00	102.73	14.21
Diastol B.P	40.00	80.00	59.09	11.36
CTRP3	2.70	11.20	6.26	3.02

Table 3: Comparison between demographic and laboratory data of diabetic patients and controls included in the study

Variables	Patients		Controls		P-value
	Mean	SD	Mean	SD	
Age	15.18	2.07	14.09	2.17	0.1
BMI	23.36	4.25	21.00	4.08	0.10
Waist	73.95	12.36	71.04	12.07	0.38
Hip	77.29	11.30	74.20	7.18	0.27
Waist/Hip ratio	0.96	0.08	0.96	0.12	1.00
Systol	110.71	18.44	102.73	14.21	0.20
Diastol	70.71	17.41	59.09	11.36	0.02
Cholesterol	184.43	30.08	100.54	20.41	0.001**<**
Triglycerides	85.21	21.97	68.89	28.39	0.01
HDL-c	51.53	11.25	52.21	11.12	0.82
LDL-c	144.66	23.82	62.50	19.88	0.001**<**
CTRP3	16.29	15.02	6.26	3.02	0.04

CTRP3 was significantly increased in diabetic patients than controls (p=0.04), diastolic B.P significantly increase in diabetic patients than controls (p=0.02). Diabetic children in comparison with control showed extreme significance difference of cholesterol and LDL-c the P value in both was < 0.001 and statistically significant in triglycerides p=0.01.

Table 4: Correlation between demographic and laboratory data with CTRP3 in diabetic patients included in the study

Variables	CTRP3	
	r	P-value
CTRP3	0.52	
age	0.13	0.52
onset	0.07	0.72
duration	0.02	0.94
Insulin U/kg	0.18	0.40
BMI	-0.20	0.39
Waist	-0.10	0.65
Hip	0.12	0.54
Waist/hip ratio	-.379*	0.05
Systol	-0.10	0.61
Diastol	-.047-	0.81
HbA1c	0.35	0.07
Cholesterol	0.04	0.85
TG	0.08	0.67
HDL-c	-.400*	0.04
LDL-c **TCH/HDL** **TG/HDL ratio**	-.016- 0.4 0.8	0.94 0.05 0.009
Album. /Creat.	0.15	0.46
ALT	-.068-	0.91
Creatinine	-0.10	0.78

CTRP3 was negatively correlated with HDL-c and Waist/hip ratio value respectively(r= - 0.400, p=0.04 and r = -0.379, p= 0.05) and also CTRP3 were correlated with, TCH /HDL-c ratio and TG/HDL-c ratio value respectively(r =0.4 , p=0.05 and r = 0.8 , p = 0.009). CTRP3 has no correlation with HbA1c r = 0.35, p=0.07 or with BMI r = -0.20, p=0.39. CTRP3 has no significance with sex p=0.6

DISCUSSION

Cartonectin is a new adipokine belonging to the CTRP family , it is a paralogue of adiponectin (Ban et al., 2014).It is an anti-inflammatory adipokine which inhibits toll-like receptor (TLR) and nuclear factor κB (NF-κB) signaling pathway and also reduces IL-6 and TNF-α secretion (Choi et al., 2012).Also, It has glucose lowering effects achieved by suppressing hepatic gluconeogenesis and it is protective against hepatic steatosis by reduce liver triglycerides synthesis (Ban et al., 2014). Peterson et al. have shown an immunomodulatory role for CTRP3 in systemic and chronic inflammation associated with insulin resistance and obesity.

There is enough evidence showing reasonable role of CTRPs in the pathogenesis of T2DM and coronary artery disease, since the expression of members of this family are dysregulated in metabolic diseases and obesity (Yuasa et al., 2014).

To the best of our knowledge we reported for the first time that serum cartonectin concentration was significantly higher in adolescent type 1 diabetic patients. We referred that to (alteration of glucose metabolism, insulin therapy, metabolic stress or ongoing inflammatory and autoimmune process that seen in this type of DM). It had no significant correlation with glycemic control. Our result agree with the results of Choi et al., 2012 who reported that plasma cartonectin was significantly higher in adult patients with T2DM (Kopp et al., 2010). Their explanation was that increase in the cartonectin level may be due to possible compensatory effect of cartonectin as it is considered a beneficial hormone. On the contrary, Bo Ban et al., 2014 had found lower

cartonectin in newly diagnosed patients with T2DM and they proposed that due to changes in glucose metabolism and insulin sensitivity.

Our results showed no difference in cartonectin with age and this coincides with results of Risa et al., 2015.Also it has no correlation with sex which disagreed with results of Risa et al., 2015 that found male sex had significant lower cartonectin than female sex. This was attributed to sex hormones as female sex has subcutaneous adipose tissue while male sex has visceral and hepatic adipose tissue. These sex differences in Cartonectin were similar for adiponectin and other adipokines (Choi et al., 2013).

In the present study, cartonectin was negatively correlated with waist to hip ratio, as waist/ hip ratio is a measure of obesity (Bacopoulou et al, 2015) and this agree with results of Denge et al, 2015 and Risa et al., 2015 which found down regulation of cartonectin in obesity as obese state alter metabolic homeostasis and leads to dysregulation of adipokine production and function (Risa et al., 2015).

Also cartonectin showed positive correlation with cholesterol /HDL and triglyceride /HDL ($p=0.05$, 0.009) respectively in our study. This means that Cartonectin increase with dyslipedimia indices as lipoproteins risk ratio is a predictive value for cardiovascular risk in Egyptian children with T1DM (Hassan et al., 2015), this agree with results of Choi et al., 2013 that found cartonectin decrease in patient with acute coronary syndrome or stable angina pectoris (Reza et al., 2016) and disagree with results of (Petersen et al., 2016) that say cartonectin has no relation with Metabolic syndrome and dyslipedimia. Also it showed negative correlation with HDL-c ($p=0.04$, $r= -0.400$) which disagree with Risa et al., 2015 that showed cartonectin positively correlated with HDL-c ($P<0.01$). This explained by when metabolic parameters reach unhealthy levels, there develops an inverse relationship with Cartonectin, further supporting that Cartonectin is a beneficial hormone that decrease in adults with T2DM, obesity and cardiovascular disease.

Cartonectin is similar to adiponectin and several studies in adults showed decrease adiponectin in T2DM, obesity, coronary artery disease and metabolic syndrome (Jaber Al-Ahmed, 2012) and increase adiponectin in T1DM due to insulin treatment not by T1DM itself (Kazushige et al, 2005) or related to development of microvascular complications or represent a beneficial counter-regulatory response (Frystek et al., 2005). Also studies of cartonectin in T2DM, obesity and coronary artery disease showed its decrease and this coincides with adiponectin, so it might explain increase cartonectin level in T1DM as adiponectin due to insulin therapy, development of micro vascular complication or a beneficial counter-regulatory response.

CONCLUSION

CTRP3 increase in Egyptian adolescents with type 1DM, and showed significant correlation with lipoproteins risk ratios as total cholesterol /HDL and triglyceride /HDL, so it may act as biomarker of dyslipedimia in type 1DM. To the best of our knowledge, no previous studies have evaluated the influence of exercise on cartonectin along with changes in cardio metabolic risk factors as lipoprotein risk ratio in type 1 DM, so we recommend exercise program as it will improve this cardio metabolic disorder and decrease cartonectin level as observed by Choi et al., 2013.

CONFLICT OF INTEREST

The authors declared that the present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

AG and AAM designed and performed the experiments.SMA performed data analysis as well as samples collection. RMH performed data collection and reviewed the manuscript. EAM wrote the manuscript. AAA performed chemical and laboratory analysis. All authors read and approved the final version.

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