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Original Article

Complement c1q tumor necrosis factor-related protein 3 a novel adipokine, protect against diabetes mellitus in young adult Egyptians

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ABSTRACT

C1q/TNF-related protein-3 (CTRP3) is a novel adipokine with anti-inflammatory and a multitude of biological effects on glucose and lipid metabolism however, the influence of CTRP3 on incidence of diabetes mellitus remain unclear. This study **investigated** the effects of CTRP3 levels in obese and normal body weight young adults on insulin resistance and occurrence of diabetes mellitus.

Subjects and methods: In this case control study, Serum levels of CTRP3, HbA1c, Lipid profile, glucose and insulin levels were determined in 75 obese and 68 normal body weight individuals.

Results: In obese young adults CTRP3 concentrations were decreased compared to normal body weight young adults (NBW). The association between reduction of CTRP3 concentrations and the presence of diabetes is statistically significant. CTRP3 showed significant negative correlation with BMI, HOMA-IR and triglycerides as well as positive correlations with HDL − cholesterol while there is no association between CTRP3 and BMI within the NBW group. Higher HbA1C, HOMA-IR, and risk of diabetes development within obese subjects were related to lower CTRP3 concentration.

Conclusions: This study shows that reduction of CTRP3 concentrations is likely to bring a concomitant increase in risk of diabetes in obese and normal body weight young adults. Decrease in CTRP3 concentration may have an essential role in the pathophysiology of metabolic disorders concomitant to obesity.

1. Introduction

Obesity has adverse effects on health as increase incidence of metabolic syndrome, diabetes, hyperlipidemia and heart disease [1,2]. The risk of T2DM increases as BMI increases in young individuals [3]. High risk and early onset of T2DM in young age individuals is associated with increased body weight than obesity between 40 and 55 years of age [4]. Adipocytes dysfunction caused by hyperplasia has been associated with the insulin resistance development [5]. Adipokines are fat-derived proteins that secreted from adipose tissue have a role in regulation of metabolic homeostasis. Weight gain lead to adipokines dysfunction and dysregulation of glucose and lipid metabolism [6,7]. Adiponectin is one adipokines play a role in the metabolic process of glucose and lipid [8,9]. CTRP3 is a novel adipokine mediate the unique biological function in metabolic diseases associated with obesity [10,11]. Decreased levels of CTRP-3 were found in females with polycystic ovarian syndrome and individuals with ischemic heart disease [12,13]. CTRP3 can act as anti-inflammatory [14–17] and cardioprotective factor [8]. The purpose of this research to study the changes in CTRP3 levels in obese young adults and identify the associations of insulin resistance with reduction of CTRP3 levels and the occurrence of diabetes mellitus.

1.1. Subjects and methods

A case control study conducted from January 2015 to November 2016 at the Zagazig University Hospital of Faculty of Medicine, Zagazig University, Egypt. We obtained informed consent from each individual shared in this research. This study included 143 patients (63 males and 80 females) with a mean age of 21.2 ± 4.2 years (range 18–23 years). Seventy five obese patients (40 diabetic and 35 non diabetic patients), 68 normal body weight individuals (37 diabetic and 31 non diabetic individuals) was included in this study, all diabetic patients were newly diagnosed according to American Diabetes Association Standards of medical care in

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diabetes 2014 [19] while diagnosis of obesity depend on data defined by National Heart, Lung, and Blood Institute [20]. Obese patients with a history of chronic diseases except diabetes and obesity due to secondary diseases were excluded.

Body mass index (BMI) calculated as weight/height2 (kg/m2). After eight to 10 h fast blood samples were obtained. Samples were centrifuged at 3200 r.p.m. for 10 min and serum was stored at −20 °C for laboratory analysis. Fasting (FBG) and postprandial glucose levels (2 hPG), lipid profile and hemoglobin A1c (HbA1c) were performed by Cobas c 502 analyzer (Roche Diagnostics GmbH). The insulin levels were measured by the electro-chemiluminescence immunoassay on Cobas e 601 analyzer (Roche Diagnostics GmbH). Homeostasis model assessment of insulin resistance (HOMA-IR) used for Insulin resistance evaluation [21]. Determination of CTRP3 levels by ELISA (NOVA, Keyuan Road, Daxing Industry Zone, Beijing, China).

1.2. Statistical analysis

The SPSS software (Inc, Chicago, IL, version 20.0) was used for all statistical analyses, data were presented as mean and standard deviation or median and range. The analysis of variance (ANOVA) was used for comparisons between multiple groups. Correlations between CTRP3 and various parameters were analyzed using Pearson's correlations. Linear regression analysis was done for each independent parameter with CTRP3. For evaluation the diagnostic performance of CTRP3, receiver operating characteristic (ROC) curve was constructed. The P-value of <0.05 was considered significant.

2. Results

BMI mean values of the normal body weight and obese groups were 23.2 ± 2.5 (range 17.6–26 kg/m^2), 34.5 ± 1.5 (range 30.6–37.6 kg/m2) respectively, every group subdivided into diabetic and non-diabetic. The obese group showed significantly increased BMI, fasting glucose, HbA1c, HOMA −IR, triglyceride levels, total cholesterol and HDL-cholesterol decreased. CTRP3 levels significantly lower in the obese individuals than the normal body weight individuals (median, 316 pg/ml, range112–653 pg/ml vs. 440 pg/ml, range 180–984 pg/ml). There was a significant reduction in circulating CTRP3 levels in obese diabetic compared with obese non diabetic groups (median, 265.5 pg/ml vs. 361 pg/ml), there was a significant change in circulating CTRP3 levels within diabetic or non-diabetic NBW individuals (median, 434 pg/ml vs. 499 pg/ml) (Table 1).

CTRP3 concentrations were negatively correlated with BMI, FBG, PPBG, HbA1C,TG, and HOMA-IR ($P < 0.001$) and positively correlated with HDL-cholesterol ($P < 0.001$) within an obese group (Table 2),.

Univariate linear regression analysis was conducted for prediction of DM within obese individuals; HbA1C ($P = 0.001$, OR = 1.135, 95% CI = 1.050–1.226), HOMA-IR ($P = 0.016$, OR = 1.204, 95% CI = 1.036–1.399), CTRP3 ($P = 0.001$, OR = 0.993, 95% CI = 0.990–0.997), lower CTRP3 concentration concomitant to risk of diabetes development within obese subjects (Table 3),. For discrimination between diabetic and non-diabetic obese subjects, at cutoff value 305.5 pg/ml, serum CTRP3 had 70% sensitivity, 75% specificity, PPV was 60%, NPV was 66.7% and accuracy was 62.5%, AUC was 0.705 (95% CI = 0.534–0.876); p = 0.0 27 (Fig. 1).

3. Discussion

C1q/TNF-related proteins (CTRPs) secreted by adipose tissue that affect glucose metabolism and increasing the risk of diabetes in obese patients [22,23]. This study showed that reduction of CTRP3 levels in young obese compared to younger age persons with NBW, as well as young diabetic patients relative to non-diabetic individuals, there were associated between CTRP3 and glucose levels, lipid profile and HOMA-IR. Hua et al., reported that CTRP3 rises in obese and diabetic patient than healthy subjects [24]. Ban et al., found CTRP3 levels were significantly higher in healthy individuals compared to patients with early onset of diabetes [11]. CTRP3 concentrations were reduced in the presence of obesity and hypertension [25,26], but other studies showed increases in CTRP3 concentrations in metabolic syndrome and diabetes alone, they explained this as a defensive response to neutralize the metabolic stress or resistance to CTRP-3 action, which is reminiscent of insulin resistance [10,27]. Using animal models, CTRP3 can reduce glucose output and lower glucose levels in normal and insulin-resistant stat via suppressing the hepatic gluconeogenic gene and enzyme expression also changed IL-6 and TGF-β levels [28,29]. Obesity lead to down regulation of anti-inflammatory effects of CTRP3 so present association of insulin resistance [30]. Our results showed that CTRP3 levels were inversely associated with BMI, triglycerides and blood glucose levels in obese subjects these results are unlike to results reported by Yoo et al. who demonstrated that, in the presence of metabolic syndrome there is no change in CTRP3 levels [30]. Wong et al., found that an inverse correlation between CTRP3 and waist circumference, but not BMI [27]. CTRP3 acts as a regulator of triglyceride metabolism as well as glucose metabolism, obesity changes the normal metabolic homeostasis as decreases CTRP3 production and function [12,26,31,32]. CTRP3 is a beneficial metabolic hormone secreted by adipose tissue, leucocytes and vascular cells, acts as mediators in lipid metabolism, decreased CTRP3 concentration was related to the degree of body mass index which points to a major inflammatory/cardiovascular effect so there is a significant relation between CTRP3 and obesity [14,22]. Nishimoto et al., demonstrated that CTRP3 can decrease adipogenesis, as well as extracellular signal-regulated protein kinase 1/2 and Akt are simultaneously phosphorylated by CTRP3 treatment in mature 3T3-L1 adipocytes [33]. Our results revealed that HOMA-IR was increased and had inversely associated with CTRP3 in young obese individuals. Insulin resistance is caused by the expansion of adipose tissue, which stimulates a sustained inflammatory response accompanied by adipokine dysregulation. CTRP3 can increase insulin sensitivity and improving glycolipid metabolism [13]. Cellular injury associated with obesity recruit and activate immune cells that contribute to the pathogenesis of insulin resistance in different body tissue [34]. In obese individuals the main determinant of insulin resistance is waist circumference, that is, visceral adiposity, whilst in thin subjects, it is BMI and subcutaneous fat [35]. Visceral obesity associated with diabetes and atherosclerosis as an extension of visceral adipocytes stimulates the inflammatory cytokines, leading to a chronic low-grade inflammatory state [22]. Excess fatty acids from excess visceral adipocytes draining into the portal vein results in accumulation of lipid in the liver lead to the release of inflammatory cytokines by macrophages, which obstacles insulin action [36]. CTRP3 is a secreted protein structurally homologous to adiponectin, which has insulin-sensitizing, anti-inflammatory, and anti-atherogenic properties [7,8,37]. Previous studies identified CTRP3 a metabolic hormone with anti-inflammatory properties, whose circulating levels are down-regulated in the pro-inflammatory obese state [14,15,18,38]. CTRP3 decreases the release of interleukin-6 (IL-6) and TNF-α, that increase the insulin sensitivity through inhibit the inflammatory response. Moreover, CTRP3 increases protein expression of phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) and Akt, as well as increase the glucose transporter type 4 (GLUT-4), thereby enhancing insulin signal transduction; the result is improved insulin sensitivity [39].

Table 1
BMI and biochemical parameters of the studied groups.

Parameters	NBW (N = 68)		Obese (N = 75)		P
	Non diabetic N = 31	Diabetic N = 37	Non diabetic N = 35	Diabetic N = 40	
BMI (k/m^2)	23.2 ± 2.58	23.30 ± 2.7	34.53 ± 5.1^{a**,c**}	37.2 ± 11.75^{b**}	0.001
F BG (mg/dL)	90.4 ± 11.6	165.9 ± 53.1^{f*}	92.7 ± 10^{c**,e*}	168.85 ± 61.3^{b**}	0.001
2 h PG (g/dL)	123.5 ± 6.3	282.8 ± 73.1^{f*}	118 ± 11.5^{c**,e*}	244.7 ± 73.2^{b**,d*}	0.001
HBA1C (%)	4.4 ± 0.36	7.78 ± 1.5	4.63 ± 0.43^{c**,e*}	8.22 ± 1.7^{b**,d**}	0.001
Fasting insulin (mIU/L)	8.6 ± 2.53	14.17 ± 4.2	16.5 ± 4.88	15.35 ± 5.8	0.524
HOMA-IR	1.8 ± 0.66	7.22 ± 2.6^{f*}	3.884 ± .59^{a**e*}	6.825 ± 2.3^{b*}	0.010
T. cholesterol (mg/dL)	158 ± 17.1	44.1 ± 11.1	51.252 ± 8.45	44.68 ± 8.1^{b*}	0.001
Triglyceride (mg/dL)	114 ± 30.7	181.6 ± 62.6	123.05 ± 40.21	137.35 ± 45.2^{b*}	0.001
HDL-C (mg/dL)	56.9 ± 10.4	44.1 ± 11.1	51.25 ± 8.45	44.68 ± 8.1^{b*}	0.001
LDL- C (mg/dL)	74 ± 13.5	105 ± 30.2^{f*}	107 ± 27.23^{a*}	128.5 ± 31^{b**,d**}	0.001
CTRP3 (pg/ml)	499	434^{f*}	361^{a*,c*,e*}	265.5^{b*,c*,d*}	0.001
Median Range	212–984	180–736	197–653	112–521	

a: Non diabetic NBW vs non diabetic obese.
b: Non diabetic NBW vs diabetic obese.
c: Diabetic NBW vs non diabetic obese.
d: Diabetic NBW vs diabetic.
e: Diabetic vs non-diabetic obese.
f: NBW diabetic vs non-diabetic.
*Significant P < 0.05, **Highly significant P < 0.001.

Table 2
Correlations between CTRP3 and all studied parameters.

Parameters	NBW N = 68		Obese N = 75	
	r	*p*	*P*	*r*
Age (years)	0.096	0.532	0.861	0.029
Weight (kg)	−0.102	0.504	0.007	−0.419
Height (cm)	0.259	0.086	0.720	0.059
BMI (kg/m2)	0.026	0.867	<0.001	−0.710
Fasting B G (mg/dL)	- 0.522	<0.001	<0.001	−0.505
2 h PG, (mg/dL)	−0.774	<0.001	0.012	−0.393
HBA1C (%)	−0.623	<0.001	<0.001	−0.569
Fasting insulin (mIU/L)	−0.654	<0.001	<0.001	−0.850
HOMA-IR	−0.669	<0.001	<0.001	−0.831
Total cholesterol (mg/dL)	−0.267	0.077	0.460	−0.120
Triglycerides (mg/dL)	−0.144	0.345	0.042	−0.324
HDL- C (mg/dL)	0.176	0.248	0.004	0.446
LDL − C (mg/dL)	−0.108	0.481	0.477	−0.116

BMI, body mass index; HOMA-IR, homeostasis model assessment for insulin resistance; 2 h PG, Postprandial blood glucose; HbA1c, hemoglobin A1c; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

CTRP3 has important role in lipid metabolism by improving insulin sensitivity and regulating the expression and secretion of other adipokines, thus protecting against obesity and associated diseases [9]. CTRP-3 is an inhibitor of inflammatory signaling molecules mediated proinflammatory response in adipocytes and in monocytes so it represents a novel and promising role in treating adipoinflammation and obesity-linked metabolic diseases [14,15]. In the current study CTRP3 can predict diabetes within young age obese individuals, as CTRP3 is a beneficial hormone that regulates lipid and glucose metabolism, but in case of obesity CTRP3 level decreases may play a pivotal role in the etiology of IR, which progress to diabetes and in other pathophysiological conditions such as cardiovascular disease [11,13,25]. Ban et al., identified that CTRP3 is a promising biomarker for the prediction and early diagnosis of T2DM patients. Additionally, CTRP3 and/or pharmacological agents that increase circulating CTRP3 levels can represent a new therapeutic field in the treatment of T2DM patients [11]. This study showed that, at cutoff value 305.5 pg/ml, serum CTRP3 had 70% sensitivity, 75% specificity so we suggested that CTRP3 may be differentiated between diabetic and non-diabetic obese individuals. Our study had some obstacles, such as high price of investigations and decreased number of patient group as select obese/diabetic young adult age need longer time.

4. Conclusion

Present study shows that lower levels of CTRP3 are concomitant to increased risk of diabetes in obese young age individuals. Decrease in CTRP3 concentration may have a role in the pathophysiology of metabolic disorders related to obesity.

Table 3
Regression analysis for prediction of DM within obese subjects.

	Univariate				Multivariate			
	OR	*p*	95% CI		*p*	OR	95% CI	
Age (years)	1.041	0.167	0.983	1.103				
Males	0.276	0.079	0.106	1.721				
BMI (kg/m2)	1.009	0.706	0.962	1.058				
HBA1C (%)	1.135	0.001	1.050	1.226	0.017	1.150	1.025	1.291
HOMA-IR	1.204	0.016	1.036	1.399	0.387	0.987	0.958	1.017
Total cholesterol (mg/dL)	1.025	0.010	1.006	1.044	0.858	0.999	0.985	1.012
Triglycerides (mg/dL)	1.019	0.001	1.008	1.031	0.851	1.000	0.996	1.005
HDL −C (mg/dL)	0.905	<0.001	0.860	0.954	0.862	0.998	0.975	1.021
LDL −C (mg/dL)	1.030	0.001	1.012	1.048	0.740	1.002	0.990	1.015
CTRP3(pg/ml)	0.993	<0.001	0.990	0.997	0.018	0.645	0.109	0.987

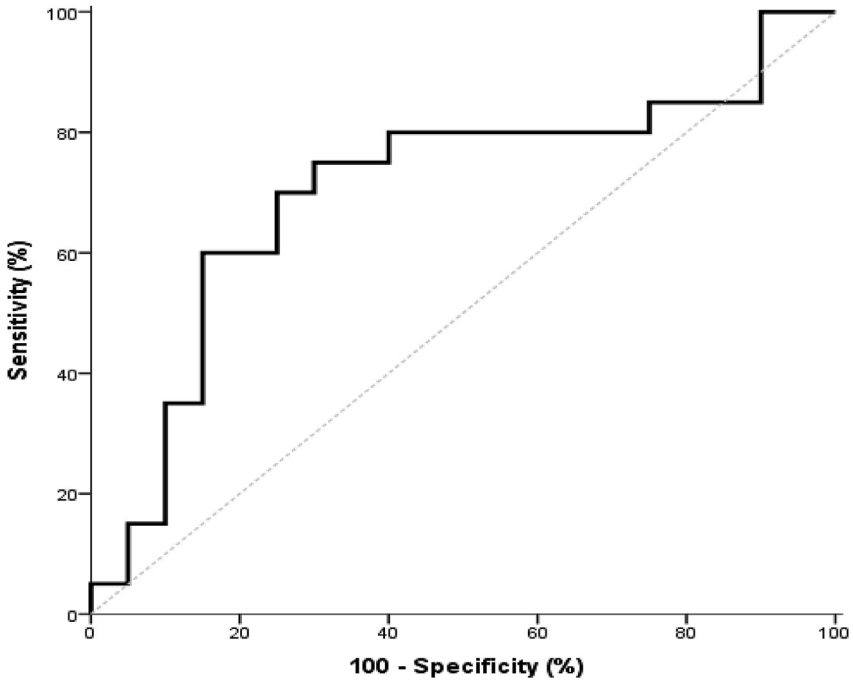

Fig. 1. ROC Curve for discrimination between diabetic and non-diabetic subjects within obese group.

Conflicts of interest

There is no conflict of interest.

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