DIABETES MELLITUS INCREASES PLASMA CARDIOTHROPHIN-1 LEVELS INDEPENDENTLY OF HEART FAILURE AND HYPERTENSION

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ABSTRACT

***Aims**: Cardiothrophin-1 (CT-1) is a novel 201 amino acid cytokine that has pleiotropic protective effects in apoptosis, hepatic injury, myocardial infection and contrast nephropathy. CT-1 predicts a variety of disorders including atherosclerosis, heart failure, hypertension and cardiomyopathy. However, CT-1 has not been studied previously in diabetic patients without heart failure. The aim of this study was, therefore, to compare CT-1 levels in diabetic and non-diabetic patients.*

***Methods**: Thirty-eight patients with type 2 diabetes mellitus and 32 non-diabetic controls have been enrolled into the study. Subjects with severe hypertension, renal diseases, pregnancy and malignancy were excluded. The statistical analysis was performed with SPSS for Windows version 15.0.*

***Results**: There were no significant differences between the diabetic and non-diabetic groups with regard to age, hypertension, serum creatinine, systolic and diastolic blood pressure. Median plasma CT-1 was 9.05 (5.70-24.94) pg/ml in diabetic group and 7.16 (5.53-9.64) pg/ml in non-diabetic group (P<0.001).*

Conclusion: Plasma CT-1 levels increased in diabetic patients independently of hypertension (HT) and heart failure. Prospective studies with a larger cohort are now needed to observe the effects of CT-1 treatment in a diabetic population.

***Key words**: cardiothrophin-1, diabetes mellitus, hypertension, heart failure.*

***Received** Septemper 12, 2013; **Accepted** Septemper 20, 2013*

Introduction

Cardiothrophin-1 (CT-1) is a novel 201 amino acid cytokine that has pleiotropic protective effects[1]. Specifically, it exerts protective effects against apoptosis[2-4], ischaemic hepatic injury[5, 6], myocardial infarction[7, 8] and contrast nephropathy[9]. CT-1 also induces myocytes hypertrophy[10]. Although it is released from heart tissue in response to changes in wall tension[11], it is also expressed in the liver, brain, skeletal muscle, kidneys and lungs[12], and has been associated with energy balance, obesity and diabetes mellitus[13]. CT-1 reduces blood glucose levels and increases fat utilization and, thus, reduces appetite in animal models[13]. Specifically, Morena-Aliaga et al. showed that CT-1-deficient mice were obese, hyperlipidaemic and diabetic. Hypertension (HT), coronary artery disease and obesity, all cause an elevation in the plasma levels of CT-1[11, 12, 14, 15]. Several studies also revealed that plasma CT-1 levels in obese patients were increased compared with controls[14, 15]. The increased serum concentrations in these disorders may reflect a protective role for CT-1.

CT-1 predicts a variety of disorders including atherosclerosis, heart failure, hypertension and cardiomyopathy[16-20]. However, CT-1 has not been studied previously in diabetic patients without heart failure. The aim of this study was, therefore, to compare CT-1 levels in diabetic and non-diabetic patients.

Materials and methods

Subjects and definitions

Thirty-eight patients with type 2 diabetes mellitus and 32 non-diabetic controls were enrolled in the study. Informed consent was obtained from each

participant, and the study protocol was approved by the ethics committee of our institution. Subjects with severe hypertension, renal disease, pregnancy and malignancy were excluded. Blood pressure was measured using an aneroid sphygmomanometer in the sitting position on the right arm, and the mean of two readings taken 3 min apart was recorded. All study participants also underwent an echocardiographic evaluation.

Height and weight were measured for the calculation of the body mass index (BMI = weight (kg)/height2 (m2)). Hypertension was defined as systolic blood pressure ≥140mmHg and/or diastolic blood pressure ≥90 mmHg. DM was diagnosed using the 2010 American Diabetes Association criteria.

Blood Tests and Cardiotrophin-1 Measurement

Blood samples were collected from an antecubital vein after overnight fasting. Fasting blood samples (10 ml) were drawn into tubes containing ethylenediaminetetraacetic acid (EDTA). Fasting blood samples were obtained for analysis of creatinine, hemoglobin, HbA1c and glucose with standard methods.

Venous blood samples were centrifuged within 15 minutes of collection, at 3000 rpm for 10 minutes, and the supernatant plasma was then transferred into polypropylene tubes at-80 °C until the assays were determined. Serum CT-1 levels were assessed using a commercial specific enzyme-linked immunosorbent assay kit (Ray Biotech Inc., Norcross, USA).

Statistical analysis

All statistical analyses were performed using SPSS for Windows version 15.0. The normality of each variable distribution was studied by using Kolmogorov-Smirnov test. Normally distributed continuous data were expressed as mean ± standard deviation (SD) and non-normally distributed continuous variables were presented as median and min-max. Chi-square test was used to compare the categorical data. The relations between clinical data and CT-1 levels were evaluated using Spearman's correlation coefficients. P-values lower than 0.05 were considered to be statistically significant.

Results

The study consisted of 38 diabetic patients and 32 non-diabetic subjects divided in two groups.

	Diabetic subjects (n=38)	**Non-Diabetic subjects (n=32)**	**P**
Age (yr)	53.39 ± 7.13	50.84 ± 8.15	0.178
Gender (M/F)	21 / 17	25 / 7	0.046
Hypertension	18	13	0.571
Systolic blood pressure (mmHg)	132.5 (100-160)	130 (100-160)	0.965
Diastolic blood pressure (mmHg)	80 (60-100)	80 (65-100)	0.364
BMI (kg/m2)	31.92 (20.83-45.96)	27.93 (21.38-48.28)	0.039
Glucose (mg/dl)	147 (84-372)	97 (85-120)	<0.001
HbA1c (%)	7.80 (5.8-12)	5.70 (4.7-6.2)	<0.001
Creatinine (mg/dl)	0.75 (0.56-1.64)	0.71 (0.59-0.98)	0.089
Ejection fraction (%)	60 (50-70)	65 (50-70)	0.050
Cardiotrophin-1 (pg/ml)	9.05 (5.70-24.94)	7.16 (5.53-9.64)	<0.001

Table 1: Demographic and physical examination variables of the diabetic group and non-diabetic group.

The clinical characteristics of the subjects are shown in Table 1. There were no significant differences between the diabetic and non-diabetic groups with regard to age, hypertension, serum creatinine or systolic and diastolic blood pressure. The mean age of the diabetic group was 53.39 ± 7.13, of the non-diabetic group was 50.84 ± 8.15. The median plasma CT-1 was 9.05 (5.70-24.94) pg/ml in the

Variables	Cardiotrophin-1 (pg/ml)	
	R-value *	P Value
Gender	0.17	0.16
Hypertension	0.29 **	0.016
Systolic blood pressure	0.10	0.40
Diastolic blood pressure	0.05	0.71
BMI	0.11	0.37
Glucose	0.367 ***	0.002
HbA1c	0.44 ***	<0.001
Creatinine	0.18	0.14
Ejection fraction	-0.21	0.08

Table 2: Correlation between Cardiotrophin-1, gender, hypertension, clinical and biochemical variables.
**Spearman's correlation coefficient.*
***Statistically significant p<0.05, *** p<0.01*

diabetic group and 7.16 (5.53-9.64) pg/ml in the non-diabetic group (Table 1) (P<0.001; Figure 1). The plasma levels of CT-1 were also significantly correlated with plasma glucose, HbA1c and hypertension (Table 2). However, they were not correlated with gender, BMI and left ventricular ejection fraction.

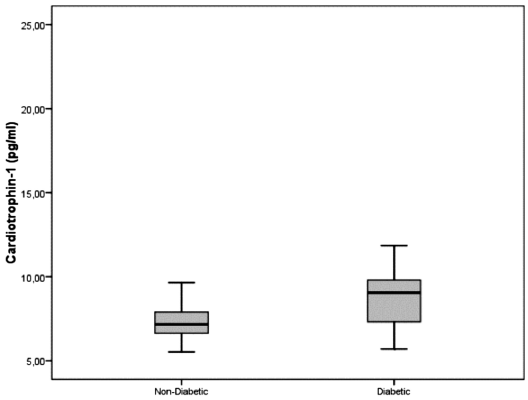

Fig. 1: Plasma Cardiotrophin-1 levels in diabetic and non- diabetic groups. P<0.001 diabetic subjects vs control values.

Discussion

In this study, we found that CT-1 levels were increased in patients with type 2 diabetes compared with non-diabetic controls. In addition, we showed that type 2 diabetes is a risk factor for CT-1 elevation independent of HT and heart failure. CT-1 has many different actions in humans. It causes left ventricular failure by inducing the structural modification of myocytes in the myocardium[12]. It also plays a role in energy metabolism. Despite this, elevated CT-1 levels are associated with an increased the risk of metabolic syndrome[14], and Moreno-Aliaga et al. reported that treatment with recombinant CT-1 improved metabolic parameters[13].

The association between obesity and CT-1 is controversial. Although the body mass index of individuals constituting the groups in our study were different, we do not think that this affected our observations. Whereas some studies have suggested that CT-1 levels are increased in obesity[14, 15], Jung et al. reported that CT-1 levels were comparable in overweight and normal-weight subjects[21]. Obstructive sleep apnoea syndrome is an obesity-associated disease. Kurt et al. studied the CT-1 levels of patients with obstructive sleep apnoea syndrome and healthy controls and found that, although obesity was significantly more common in patients with obstructive sleep apnoea syndrome than healthy controls, there was no significant difference in the CT-1 levels between groups[22].

There are several reasons why CT-1 levels may be increased in type 2 diabetes. Pancreatic beta cell volume and function deteriorates in patients with type 2 diabetes[23, 24]. Jimenez-Gonzales et al. reported that CT-1 protected pancreatic beta cells from apoptosis[2], and speculated that treatment with recombinant CT-1 may slow the progression of diabetes. The elevated CT-1 levels in our study may, therefore, be a consequence of protective mechanisms against apoptosis in diabetic patients.

Ravassa et al. found that CT-1 was associated with myocardial systolic dysfunction in patients with HT[25]. Therefore, we did not include patients with left ventricular systolic dysfunction in our study cohort. We also excluded patients with a left ventricular ejection fraction lower than 50%. Our results are important because they suggest an increase in the serum levels of CT-1 in diabetic patients without systolic dysfunction.

To date, many studies have revealed that hypertension and heart failure can cause elevated plasma CT-1 levels. In the present study we identified that an increase in plasma CT-1 is an additional independent risk factor for type 2 diabetes.

There are some limitations of this study. First, the study population was relatively small. Second, we did not exclude patients with HT to obtain more precise results, even though the incidence of HT in diabetic and non-diabetic subjects was comparable.

In conclusion, plasma CT-1 levels increased in diabetic patients independently of HT and heart failure. Prospective studies with a larger cohort are now needed to observe the effects of CT-1 treatment in a diabetic population.

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This study has been funded by "Scientific Research Supporting Fund" of Abant Izzet Baysal University, Bolu, Turkey. Approval number is: ABÜ.0.20.05.04-050.01.04-012"

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