

Serum Progranulin Levels in Type 2 Diabetic Patients with Metabolic Syndrome

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Introduction. The role of progranulin in individuals with metabolic syndrome is not exactly clear. We aimed to assess the serum level of progranulin in type 2 diabetic patients with and without metabolic syndrome and compare them with healthy controls.

Methods. The study included 60 patients with type 2 diabetes and 30 healthy individuals as control groups. Biochemical parameters and progranulin levels were determined.

Results. Subjects with metabolic syndrome showed significantly higher levels of triglyceride, waist circumference, BMI, systolic and diastolic blood pressure than subjects without metabolic syndrome and the control groups, while HDL-cholesterol level was significantly lower in subjects with metabolic syndrome. Fasting blood sugar was significantly higher in type 2 diabetic patients than in the control groups. Serum level of progranulin was slightly increased in subjects with metabolic syndrome. Serum progranulin level had no significant relationship with metabolic syndrome components.

Conclusions. Serum progranulin was also not dependent on cardiometabolic risk factors for subjects with metabolic syndrome, but it could be considered for the management of type 2 diabetes mellitus. Further studies are recommended to explain the effect of progranulin on the pathogenesis of metabolic risk factors.

Key words: Diabetes mellitus, Type 2, Syndrome X, Metabolic, Diseases.

INTRODUCTION

Metabolic syndrome consists of metabolic risk factors such as hypertension, dyslipidaemia, obesity, insulin resistance and high fasting plasma glucose [1]. The prevalence of metabolic syndrome is influenced by dissimilarities in genetic factors, age, gender, diet and physical activity [2]. Studies of Marjani *et al.* indicated that metabolic syndrome is changed in different ethnic and age groups, different diseases and postmenopausal women [3-16]. Progranulin is known with different names such as granulin-epithelin precursor [17], proepithelin [18-19] and acrogranin [20]. Progranulin is found in yeast, arthropods, chordate and plants. It was purified as a growth factor from tissue culture media [21]. The progranulin precursor protein includes 593 amino acids [22] and plays an important role in many physiological and pathological processes such as cell growth, wound healing, tumorigenesis, neurodegenerative disease such as frontotemporal dementia,

embryogenesis, inflammation and tumor development [23]. Progranulin deficiency in mice leads to elevated neuro-inflammation, frontotemporal dementia [24-26], resulting in inflammation and progression of collagen-induced arthritis [27-28]. Progranulin has been also found in human blood and urine [28-33]. It has been recently used as a chronic inflammation marker in obesity and type 2 diabetes mellitus [34]. Progranulin may affect insulin signaling and block insulin-stimulated glucose uptake in adipocytes [31]. It was also revealed that serum progranulin levels in type 2 diabetic patients are higher than in normal subjects [34]. While inflammation plays an important role in the pathophysiology of metabolic syndrome and atherosclerosis, progranulin is thought to act as a modulator in different inflammatory processes with specific effects on target tissues [34]. Elevated serum progranulin levels are associated with impaired glucose tolerance rather than impaired fasting glucose [35]. Insulin resistance is a key characteristic of type 2 diabetes and obesity.

In a study on mice, it was showed that progranulin promotes insulin resistance [36]. The role of progranulin in subjects with metabolic syndrome is not exactly clear and only limited studies are available on its association with type 2 diabetes mellitus and metabolic syndrome. Therefore, this study aimed to assess the variations of serum progranulin levels in type 2 diabetic patients with and without metabolic syndrome and compare them with control groups in Gorgan, Iran.

MATERIALS AND METHODS

This study consisted of three groups (60 patients with type 2 diabetes and 30 healthy controls). Diabetic patients were divided into two groups and each group included 30 subjects with and without metabolic syndrome. All groups were matched according to age and gender. Exclusion criteria consisted of subjects with history of cardiovascular diseases, severe renal or hepatic and chronic inflammatory diseases. Blood samples were collected from all groups after a 12 hour overnight fast and then serum levels of glucose, total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and triglycerides (TG), were determined using commercial kits and spectrophotometry in the Metabolic Disorders Research Center, Golestan University of Medical Sciences. Serum progranulin was evaluated by ELISA kits (Bioassay Technology Laboratory, Shanghai Crystal Day Biotech Co., China). Diagnostic criteria of metabolic syndrome were defined according to ATP III (Adult Treatment Panel III) [37] which includes:

1. Waist circumference >102 cm in men and >88 cm in women
2. Serum triglycerides level ≥ 150 mg/dL
3. Low HDL-cholesterol: < 40 mg/dL in men and < 50 mg/dL in women
4. Systolic blood pressure (SBP) ≥ 130 mmHg and/or diastolic blood pressure (DBP) ≥ 85 mmHg or on treatment for hypertension.
5. Serum glucose level ≥ 110 mg/dL or on treatment for diabetes.

Participants with three or more of the mentioned criteria were considered as a metabolic syndrome subject. Weight measurement was done with a digital scale and tape meter was used to measure height. Body mass index (BMI) was

determined as weight (in kilograms) divided by height (in meters) squared. Overweight (BMI = 25.0-29.9 kg/m²) and obesity (BMI ≥ 30 kg/m²) were determined in all subjects [38]. Waist circumference was measured from the halfway point between the lower border of ribs and the iliac crest in a horizontal plane [39]. Systolic and diastolic blood pressure was measured from subjects' right hand using a standard mercury manometer with subjects in sitting position. Data analysis was done using SPSS- version 18 statistical software. Differences between groups were assessed using one way analysis of variance (ANOVA) followed by Post Hoc Tukey's test. P-value of < 0.05 was considered as statistical significance.

RESULTS

The clinical characteristics of all groups are shown in Table 1. Subjects with metabolic syndrome showed significantly higher levels of triglyceride, waist circumference, BMI, systolic and diastolic blood pressure, in comparison with subjects without metabolic syndrome and control groups ($P < 0.001$). However, the level of HDL-cholesterol was significantly lower in subjects with metabolic syndrome ($P < 0.001$). Fasting blood sugar (FBS) was significantly higher in type 2 diabetic patients than in the control groups. There were no significant differences in age, FBS, cholesterol and LDL-cholesterol levels between diabetic subjects with and without metabolic syndrome. There were also no significant differences observed in age, systolic and diastolic blood pressure, cholesterol and HDL and LDL-cholesterol levels among the diabetic subjects without metabolic syndrome and control groups. There were no significant differences in the levels of cholesterol and LDL-cholesterol and age in diabetic subjects with metabolic syndrome when compared to the controls.

Although the serum level of progranulin had slightly increased in subjects with metabolic syndrome, this elevation was not statistically significant. There were no significant differences in serum progranulin levels in all the tested groups. Study findings showed no significant differences in serum levels of progranulin between men and women of all test groups (data not shown). Serum progranulin levels were not correlated with any components of metabolic syndrome (data not shown).

Table 1
Clinical Characteristics of different study groups

Parameters	Control groups (n=30)	Diabetic Subjects with metabolic syndrome (n=30)	Diabetic Subjects without metabolic syndrome (n=30)	P-value between all groups	* P value between 2 groups
Age (years)	47.5±10	50.60±6.20	50.50±6.10	0.21	P1:0.998 P2:0.291 P3:0.261
Waist circumference (cm)	83.70±9.10	103.80±10.60	91.10±6.20	0.0001	P1:0.0001 P2:0.005 P3:0.0001
BMI (kg/m ²)	25.20±3.40	31.30±4.20	27.50±2.90	0.0001	P1:0.0001 P2:0.038 P3:0.0001
Systolic blood pressure (mmHg)	115.90±10.40	133.40±13.10	120.30±16.10	0.0001	P1:0.001 P2:0.428 P3:0.0001
Diastolic blood pressure (mmHg)	76.80±5.60	86.30±8.20	78.10±6.70	0.0001	P1:0.0001 P2:0.773 P3:0.0001
Fasting blood sugar (mg/dL)	86.10±8.90	167.80±63.91	144.60±61.90	0.0001	P1:0.196 P2:0.0001 P3:0.0001
Triglyceride (mg/dL)	87.80±29.20	203.4±83.3	150.30±46.20	0.0001	P1:0.002 P2:0.0001 P3:0.0001
Cholesterol (mg/dL)	178.80±37.70	179.80±38.30	178.30±35.70	0.987	P1:0.986 P2:0.998 P3:0.994
HDL-Cholesterol (mg/dL)	52.30±9.80	42.40±10.50	55.50±110	0.0001	P1:0.0001 P2:0.471 P3:0.001
LDL-Cholesterol (mg/dL)	97.10±23.30	96.40±38.0	94.0±33.10	0.926	P1:0.954 P2:0.926 P3:0.996
Progranulin (ng/mL)	250.90±152	254.50±167	251.7±201.80	0.269	---

P1: Diabetic Subjects with and without metabolic syndrome, P2: Control groups and Diabetic Subjects without metabolic syndrome, P3: Control groups and Diabetic Subjects with metabolic syndrome.

DISCUSSION

Progranulin was originally discovered by Anakwe and Gerton in 1990 [20]. The physiological and pathophysiological functions of progranulin are complex [24]. It has been reported that progranulin is a component of human HDL [40], while others indicated otherwise [41]. Earlier studies showed increased progranulin levels in insulin resistance states, both *in vivo* and *in vitro*. It is also suggested that progranulin in adipose tissues may be associated with insulin resistance and obesity [31]. Our findings showed that progranulin levels have no significant association with any components of metabolic syndrome (data not shown). Contrary to our results, other studies have shown a significant association between progranulin levels with waist circumference, diastolic blood pressure, elevated fasting glucose levels, lipid profile [42], BMI, total

body fat mass, visceral fat area, total cholesterol [34] and dyslipidemia [34]. However, similar to our study findings, a study has reported the serum progranulin level increase in type 2 diabetic subjects. An increased level of progranulin is thought to be associated with insulin resistance [34]. It has been revealed that fasting blood sugar regulation is more related to waist circumference [43]. Another study has exhibited that plasma progranulin levels were positively correlated with fasting plasma glucose, waist circumferences and LDL-cholesterol and triglyceride levels and negatively correlated to HDL-cholesterol, with HbA1c acting as an independent predictor of plasma progranulin levels [44] which was not in agreement with our findings (data not shown). Progranulin levels found in this study were higher than in the study done on a Chinese population [44]. Various other studies also represented the positive association between progranulin and

components of the metabolic syndrome including insulin resistance, obesity and dyslipidemia [34, 45 and 35]. Weak correlation of serum progranulin level with components of the metabolic syndrome may be associated with the wide tissue distribution of progranulin. Some previous studies indicated that serum progranulin levels were also increased significantly in subjects with type 2 diabetic patients and metabolic syndrome [34, 46-47]. Similar to the mentioned studies, our results showed the elevation of progranulin in type 2 diabetic patients, although this increase was not statistically significant ($P > 0.05$). A study has revealed that serum levels of progranulin increased 1.4-fold in patients with type 2 diabetes [34]. Another study has found that plasma progranulin levels were 1.3 and 1.5 fold ($P < 0.01$) higher than in normal-weight and obese type 2 diabetes patients when compared to healthy subjects [34] which is not in accordance with our results. It has been indicated that type 2 diabetes and obesity could elevate plasma progranulin levels. The Progranulin levels may increase by reduction of glucose metabolism. Obesity and abnormal glucose tolerance may cause the increase in plasma progranulin levels [34]. Similar to other studies, serum progranulin levels showed no significant difference between men and women (data is not shown), which suggests that serum level of progranulin is not gender-dependent [48]. However, some findings showed that serum progranulin levels are higher in obese children than in the controls, which was in agreement with a study on adults [30]. Our study result may suggest

that progranulin is not used as a suitable biomarker for diagnosis of type 2 diabetes mellitus. It may be useful for prediction of different diabetic complications such as increased IL-6 expression, impairing insulin signaling [39], promoting inflammatory response [35] macro and microvascular complications. Intensity and duration of hyperglycemia may cause kidney, eyes, nerves, heart and blood vessels dysfunction [49-50]. Progranulin also seems to be a reason for diabetic microangiopathy and its severity [51], renal damage, decreasing glomerule filtration rate and increasing albuminuria [52]. The small number of diabetic subjects was a limitation in our study, therefore it is thought that associations between progranulin and metabolic syndrome components may become statistically significant in larger samples populations.

In conclusion, our study showed that serum progranulin levels have no significant relationship with metabolic syndrome components and it is not dependent on cardiometabolic risk factors (obesity, glucose levels, lipid parameters) in metabolic syndrome subjects, but it can be considered for the management of type 2 diabetes mellitus. Further studies are necessary to explain the effect of progranulin on the pathogenesis of metabolic risk factors.

Conflict of interest. The authors confirm that this article content has no conflict of interest.

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Introducere. Rolurile progranulinei la pacienții cu sindrom metabolic nu este foarte clar. Scopul studiului a fost de a analiza nivelurile serice ale progranulinei la pacienții cu diabet zaharat tip 2 ce au sau nu sindrom metabolic comparând expresia cu martori sănătoși.

Materiale și metode. Studiul a inclus 60 de pacienți cu diabet zaharat tip 2 și 30 de martori sănătoși. Au fost analizați mai mulți parametri biochimici și nivelurile progranulinei.

Rezultate. Pacienții cu sindrom metabolic au avut valori semnificativ statistic mai mari ale nivelurilor trigliceridelor serice, ale BMI, ale circumferinței abdominale și ale valorilor presionale sistolice și diastolice comparativ cu martorii sănătoși. Nivelurile HDL colesterolului au fost semnificativ mai mici la pacienții cu sindrom metabolic. Nivelul glicemiei a jeun a fost semnificativ statistic mai mare la pacienții cu diabet tip 2. Nivelul seric al progranulinei a fost ușor mai mare la pacienții cu sindrom metabolic însă nu a fost corelat cu niciunul dintre componentele acestuia.

Concluzii. Nivelurile serice ale progranulinei nu au fost asociate cu factorii de risc cardiometabolici, dar ar putea fi utilizate pentru managementul pacienților cu diabet zaharat tip 2. Studii ulterioare sunt necesare pentru explicarea efectului progranulinei asupra patogenezei sindromului metabolic.

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