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Serum Level of Fibroblast Growth Factor 21 in Type 2 Diabetic Patients with and without Metabolic Syndrome

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Effect of FGF21 on metabolic syndrome patients is not exactly clear. In the present study, we assessed serum level of fibroblast growth factor 21 in type 2 diabetic patients with and without metabolic syndrome in Gorgan. The study groups consisted of 120 patients with type 2 diabetes and 60 healthy subjects. Diabetic patients divided into two groups. All subjects were matched according to age and sex. The mean waist circumference, systolic and diastolic blood pressure, triglyceride and fasting blood glucose levels and body mass index were significantly higher in the subjects with metabolic syndrome than control group, but the mean HDL-cholesterol was significantly lower ($p = 0.0001$). Mean serum level of FGF21 was higher in type 2 diabetic subjects with and without metabolic syndrome than that of control subject ($p = 0.0001$). There were significant negative correlation between FGF21 and BMI, diastolic blood pressure and HDL-cholesterol in subjects with metabolic syndrome ($p<0.05$). There were also significant negative correlation between FGF21 and cholesterol and HDL-cholesterol in control group ($p<0.05$). The findings of this study suggest that serum FGF21 are higher in patients with type 2 diabetes with and without metabolic syndrome than in age and sex matched control group. Our study shows that some of metabolic syndrome components (especially HDL-cholesterol) are associated with high serum FGF21 levels. Because of different effects of FGF21 in rodents, primates and in humans, it may require more investigating on metabolic effects of FGF21 in human's samples.

Key words: Fibroblast growth factor 21, type 2 diabetic patients, metabolic syndrome

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INTRODUCTION

The metabolic syndrome consisted of some metabolic abnormalities such as hypertension, dyslipidaemia, obesity, insulin resistance and high fasting plasma glucose (Miranda *et al*., 2005). It has been reported that genetic differences, diet, physical activity, age and sex affect the prevalence of metabolic syndrome and its components (Cameron *et al*., 2004). Many studies showed that metabolic syndrome changes in different ethnic and age groups and postmenopausal women (Marjani, 2005a, b, 2006a, b; Marjani *et al*., 2007a, b, c, 2008, 2010). The role of Fibroblast Growth Factor 21 (FGF21) was first reported in 2005. Glucose uptake was stimulated by FGF 21 in human and mouse adipocytes (Chen *et al*., 2011). The FGF 21 is encoded by chromosome 19. Production of this factor takes place in the liver, white adipose tissue, skeletal muscle and pancreas. Glucose and lipid metabolism regulation may depend on FGF21 (Iglesias *et al*., 2012). Some studies have shown that fasting and feeding may regulate FGF21 expression (Uebanso *et al*., 2011). This factor may be a risk factor for some diseases like insulin resistance, type 2 diabetes mellitus and metabolic syndrome (Mraz *et al*., 2009; Bobbert *et al*., 2013). Some studies have revealed that serum FGF21 influenced by high blood glucose, increased body mass index, uric acid level and low physical activity (Cuevas-Ramos *et al*., 2010). It has shown that FGF21 may effects endocrine pancreas function. Short-term treatment with FGF21 can reduce plasma insulin levels (Kharitonenkov *et al*., 2008). Some studies on rodents and primates have shown that FGF21 could have effect on carbohydrate and lipid metabolism (Badman *et al*., 2007; Inagaki *et al*., 2007; Lundasen *et al*., 2007). Studies on mice were indicated that FGF21 prevents hepatic glucose production, liver glycogen reduction and decrease glucagon level (Berglund *et al*., 2009). Several investigations on diabetic and obese rodents revealed that FGF21 reduces plasma triglyceride, free fatty acids and cholesterol levels (Kharitonenkov *et al*., 2005; Xu *et al*., 2009). Chronic therapy with FGF21 on diabetic rhesus monkeys showed that this factor causes a decrease in triglyceride and LDL-cholesterol levels and an increase in HDL-cholesterol level (Kharitonenkov *et al*., 2007). In studies on human have shown that lipolysis inhibition in adipocytes takes place by FGF21 (Arner *et al*., 2008), while other findings have indicated that high level of serum FGF21 associated with abdominal adiposity, insulin resistance, high level of triglyceride and type 2 diabetes (Jian *et al*., 2012; Chavez *et al*., 2009; Dushay *et al*., 2010; Galman *et al*., 2008; Li *et al*., 2012; Zhang *et al*., 2008). It is reported that FGF21 are associated with metabolic syndrome patients (Chen *et al*., 2008), type 2 diabetes (Li *et al*., 2010), impaired glucose tolerance (Chavez *et al*., 2009), nonalcoholic fatty liver disease (Dushay *et al*., 2010; Li *et al*., 2011; Yilmaz *et al*., 2010; An *et al*., 2012) and carotid artery disease (Yang *et al*., 2011; Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults, 2001). Effect of FGF21 in human on metabolic syndrome patients is not exactly clear. In the present study, we assessed serum level of fibroblast growth factor 21 in type 2 diabetic patients with and without metabolic syndrome in Gorgan.

MATERIALS AND METHODS

The study groups consisted of 120 patients with type 2 diabetes and 60 healthy subjects. Diabetic patients divided into two groups. The control group had no hepatic, renal or any other diseases. All subjects were matched according to age and sex. All subjects gave informed consent to take part in the study. Blood samples were provided from all subjects after a 12 h fasting. Serum glucose, Total Cholesterol (TC) and High Density Lipoprotein Cholesterol (HDL-C), Low Density Lipoprotein Cholesterol (LDL-C), triglycerides (TG), were determined using commercial kits and spectrophotometer technique in the Metabolic Disorders Research Center, Gorgan Faculty of Medicine. Serum FGF21 was determined by ELISA kit. It provided from Bioassay Technology Laboratory (Shanghai Crystal Day Biotech Co., LTD, China). The metabolic syndrome diagnostic criteria were used as suggested by ATP III (Adult Treatment Panel III) (Altekin *et al*., 2005), including: (1) Waist circumference >102 cm in men and >88 cm in women, (2) Serum triglycerides level $\geq$150 mg dL^{-1}, (3) Low HDL-cholesterol: < 40 mg dL^{-1} in men and <50 mg dL^{-1} in women, (4) Systolic Blood Pressure (SBP) $\geq$130 mmHg and/or Diastolic Blood Pressure (DBP) $\geq$85 mmHg or on treatment for hypertension and (5) Serum glucose level $\geq$110 mg dL^{-1} or on treatment for diabetes. Subjects with any 3 or more of the above mentioned criteria specified as a metabolic syndrome subject. A digital scale was used to determine weight in all subjects, while they were minimally clothed without shoes. Height was measured in standing position using tape meter while the shoulder was in a normal position. Body Mass Index (BMI) was determined as weight in kilograms divided by height in meters squared. Overweight and obese were specified as BMI = 25.0-29.9 and $\geq$30 kg m^{-2}, respectively (WHO., 1998). Waist circumferences were measured at the point halfway between the lower border of ribs and the iliac crest in a horizontal plane (Ryden, 2009). Systolic and diastolic blood pressure was measured by using a standard mercury manometer with study groups in sitting position, from their right hands.

SPSS- 18 version software was used to calculate statistical analysis (as means and standard deviations). The association of serum FGF21 level and components of metabolic syndrome and other parameters was done by using Pearson's correlation test. One way analysis of variance (ANOVA) followed by Post Hoc Tukey's test was used to test the differences between groups. p-value lower than 0.05 was considered statistically significant.

RESULTS

Table 1 shows the clinical and biochemical data of type 2 diabetic subjects with metabolic syndrome and control group. The mean waist circumference, systolic and diastolic blood pressure, triglyceride and fasting blood glucose levels and BMI were significantly higher in the subjects with metabolic syndrome than control group, but the mean HDL-cholesterol was significantly lower ($p = 0.0001$). Mean serum level of FGF21 were higher in type 2 diabetic subjects with and without metabolic syndrome than that of control subject ($p = 0.0001$). Correlation between metabolic syndrome components and serum FGF21 in control group and subjects with and without metabolic syndrome are summarized in Table 2. There were significant negative correlation between FGF21 and BMI, diastolic blood pressure and HDL-cholesterol in subjects with metabolic syndrome ($p<0.05$). There were also significant negative correlation between FGF21 and cholesterol and HDL-cholesterol in control group ($p<0.05$).

Table 1: Clinical and biochemical data of type 2 diabetic subjects with and without metabolic syndrome and control group

Parameters	Control groups	Diabetic subjects with metabolic syndrome	Diabetic subjects without metabolic syndrome	p-value between all groups	p-value between 2 groups
Age (years)	48.51±6.78	52.18±9.80	49.91±10.19	0.085	P1:0.071
					P2:0.675
					P3:0.358
Waist circumference (cm)	84.85±8.07	103.12±13.78	92.70±8.70	0.0001	P1:0.0001
					P2:0.0001
					P3:0.0001
BMI (kg m^{-2})	26.19±3.40	30.60±3.89	28.19±3.98	0.0001	P1:0.0001
					P2:0.011
					P3:0.002
Systolic blood pressure (mm Hg)	116.40±10.34	125.50±23.79	116.80±11.45	0.003	P1:0.008
					P2:0.992
					P3:0.011
Diastolic blood pressure (mm Hg)	76.76±7.08	80.63±11.14	74.80±8.55	0.002	P1:0.054
					P2:0.463
					P3:0.002
Fasting blood glucose (mg dL^{-1})	87.65±9.59	131.46±54.78	159.38±57.81	0.0001	P1:0.0001
					P2:0.0001
					P3:0.003
Triglyceride (mg dL^{-1})	99.61±33.41	200.43±84.49	143.68±61.06	0.0001	P1:0.0001
					P2:0.001
					P3:0.0001
Cholesterol (mg dL^{-1})	170.45±37.05	179.80±38.88	175.75±42.57	0.432	P1:0.400
					P2:0.744
					P3:0.841
HDL-Cholesterol (mg dL^{-1})	54.06±10.08	44.22±11.10	53.21±13.04	0.0001	P1:0.0001
					P2:0.914
					P3:0.0001
LDL-Cholesterol (mg dL^{-1})	101.17±48.15	99.28±47.14	95.52±38.85	0.784	P1:0.972
					P2:0.772
					P3:0.892
FGF21	533.90±55.39	772.96±62.85	622.00±61.34	0.0001	---

P1: Comparison between control group and diabetic subjects with metabolic syndrome, P2: Comparison control group and diabetic subjects, without metabolic syndrome and P3: Comparison of diabetic subjects with and without metabolic syndrome, BMI: Body mass index

Table 2: Fibroblast growth factor 21 correlated with metabolic syndrome components of control group, type 2 diabetic subjects with and without metabolic syndrome

Groups	Age (years)	Waist circumference (cm)	BMI (kg m^{-2})	Systolic blood pressure	Diastolic blood pressure	Triglyceride	Cholesterol	HDL-C (mg dL^{-1})	LDL-C	Glucose
Control group	p = 0.840	p = 0.701	p = 0.317	p = 0.701	p = 0.128	p = 0.836	p = 0.036	p= 0.033	p = 0.052	p = 0.396
	r = 0.026	r = -0.051	r = -0.131	r = 0.051	r = 0.198	r = 0.027	r = -0.271	r= -0.275	r = 0.252	r = 0.111
Diabetic subjects with metabolic syndrome	p = 0.221	p = 0.875	p = 0.040	p = 0.308	p = 0.028	p = 0.814	p = 0.704	P=0.046	p =0.283	p = 0.241
	r = 0.160	r = 0.021	r = -0.266	r = -0.134	r = -0.284	r = -0.031	r = 0.050	r= -0.259	r = 0.142	r = -0.154
Diabetic subjects without metabolic syndrome	p = 0.858	p = 0.467	p = 0.797	p = 0.312	p = 0.412	p = 0.547	p = 0.424	p=0.645	p = 0.484	p = 0.288
	r = 0.024	r = -0.096	r = 0.034	r = 0.133	r = 0.108	r = 0.079	r = -0.105	r= 0.061	r = -0.093	r = 0.140

DISCUSSION

Fibroblast Growth Factors (FGFs), as new proteins, include FGF19, FGF21 and FGF23. Endocrine FGFs can bind weakly to heparin/heparin sulfate, which allows them to function as endocrine factors (Coskun *et al*., 2008). It is not clear that the elevations of FGF21 levels are related to FGF21 resistance or to the metabolic disorders. Many studies reported that FGF21 shows functions such as metabolic regulator or as a biomarker of metabolic diseases. The metabolic effects of FGF21 were first recognized in murine studies (Li *et al*., 2008). The FGF21 causes stimulation of insulin-independent glucose uptake by increasing GLUT-1 expression, reduce blood glucose and triglyceride levels in obese mice and reduce body weight (Kharitonenkov *et al*., 2005). Serum FGF21 shows metabolic effects in different animal models of obesity and diabetes mellitus. It has reported that expression and regulation of FGF21 in human seems to be different when compare to animal models. This may open an idea for discussions about the possible clinical roles of FGF21. In our study, no significant differences in age, BMI and systolic and diastolic blood pressures, cholesterol and HDL-cholesterol were seen between the patients without metabolic syndrome and control group. The mean Body Mass Index (BMI) was lower in the control group than the patient groups. The FGF21levels of the patients were significantly higher than those of the control group ($p = 0.0001$ for all). There was a significant negative correlation between serum FGF21 and BMI, diastolic blood pressure and HDL-cholesterol in the group of patients with metabolic syndrome ($r = 0.266$ $p = 0.040$, $r = 0.284$ $p = 0.028$ and $r = 0.259$ $p = 0.046$ $r = 0.498$, resp).

In the present study, we showed that serum FGF-21 levels in humans are increased in diabetic subjects and are negatively correlated with some components of metabolic syndrome. This is in agreement with the results of other findings (Chen *et al*., 2011; Zhang *et al*., 2008) that indicated increased plasma FGF-21 level in obesity and type 2 diabetes mellitus. Our study is also in agreement with previous findings in Asian populations, in which elevated plasma FGF-21 levels were observed in treated type 2 diabetic subjects (Li *et al*., 2008, 2009; Zhang *et al*., 2008; Chavez *et al*., 2009). Study of FGF-21 level in rodent models showed that FGF-21 increases GLUT4 expression in adipocytes. Findings of Arner *et al*. (2008) indicated that FGF-21 inhibits lipolysis in human adipocytes. They mentioned that this may help to cause the protein's insulin-sensitizing effect in humans. Study in animal models of FGF-21 has been indicated that FGF-21 has glucose-lowering effects which are mediated by its actions on liver (Eto *et al*., 2010; Kharitonenkov *et al*., 2005). The different findings of many studies in humans and in animal models may express difference in the metabolic influences of FGF-21 in humans and animals studies. No significant correlation was found between serum FGF-21 levels and age, waist circumference, fasting glucose, triglyceride, cholesterol, LDL-cholesterol levels in subjects with metabolic syndrome. In our study, we did not also find any correlation between serum FGF-21 and serum fasting glucose levels in all groups, which is in accordance with the results of the Galman *et al*. (2008). This means that FGF21 may has no effect on glucose metabolism which is especially important in type 2 diabetic subjects. The serum FGF21 levels were significantly higher in diabetic subjects with metabolic syndrome and correlated negatively with HDL cholesterol (Zhang *et al*., 2008; Li *et al*., 2009), while some other studies showed that serum FGF21 level was associated with triglycerides (Eto *et al*., 2010; Stein *et al*., 2010). Study of Chen *et al*. (2008) showed a negative correlation between serum FGF21 levels and fasting plasma glucose levels. Our results are not in agreement with the findings of other studies (Eto *et al*., 2010; Stein *et al*., 2010; Chen *et al*., 2008). The elevation of FGF21 levels in type 2 diabetic patients may be associated with a compensatory response, FGF21 resistance (Chavez *et al*., 2009; Chen *et al*., 2011).Studies on animal models have indicated that FGF21 is expressed in the pancreas (Tacer *et al*., 2010) to protect the mass and function of pancreatic beta-cells (Wente *et al*., 2006). The increased serum FGF-21 level in diabetic patients may prevent the abnormal metabolic process by causing to improve lipid profile. (Titan *et al*., 2011). Studies in human subjects suggested that FGF-21 may be a metabolic regulator that plays an important role in metabolic process such as lipid and energy metabolism. Some studies showed increased FGF-21 levels in patients with obesity and T2DM (Zhang *et al*., 2008; Chen *et al*., 2008). The FGF-21 level was indicated to be associated with several symptoms of metabolic syndrome (Zhang *et al*., 2008). However, other studies revealed that FGF-21 was positively associated with metabolic disorders, including dyslipidemia, obesity, high plasma glucose level and insulin resistance (Dostalova *et al*., 2008; Mai *et al*., 2011; Chavez *et al*., 2009). The cause of these discrepancies is still unclear. There are different findings about FGF-21 in human and other mammals. The results of our study differed considerably from those obtained in mice, suggesting that the physiologic role of FGF-21 in humans may differ from that in animals. In this study, we found that FGF-21 level negatively correlated with HDL-C level, which was inconsistent with the beneficial metabolic function of FGF-21 in rodents (Coskun *et al*., 2008).

CONCLUSION

The findings of this study suggest that serum FGF21 are higher in patients with type 2 diabetes with and without metabolic syndrome than in age and sex matched control group. Our study shows that some of metabolic syndrome components (especially HDL-cholesterol) are associated with high serum FGF21 levels. Because of different effects of FGF21 in rodents, primates and in humans, it may require more investigating on metabolic effects of FGF21 in human's samples.

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