Family Medicine and Community Health
ORIGINAL RESEARCH

Relationship between fibroblast growth factor 21 and thyroid stimulating hormone in healthy subjects without components of metabolic syndrome

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Abstract

Objective: To determine the relationship between human fibroblast growth factor 21 (FGF21) and thyroid stimulating hormone (TSH) by testing the level of FGF21, lipid metabolism, and carbohydrate metabolism-related indices, as well as the level of TSH, among metabolic syndrome-free patients with normal physical examination results.

Methods: An enzyme-linked immunosorbent assay (ELISA) was used to test the levels of serum FGF21 and free fatty acids (FFA) in metabolic syndrome-free patients with normal physical examination results, and electrochemiluminescence (ECLIA) was used to measure TSH, thyroglobulin antibodies (TGAbs), and thyroid peroxidase antibody (TPOAb) levels.

Results: Three hundred fifty-six metabolic syndrome-free patients (116 males and 240 females; average age, 43±13 years) with normal physical examination results were enrolled. Among the patients with normal physical examination results, FGF21 had a weak relationship with obesity indices, such as the waist circumference (r=0.110, *P*=0.038), the waist-to-hip ratio (r=0.119, *P*=0.025), and the triglycerides level (TG; r=0.302, *P*=0.000), and a weak relationship with blood lipid levels, such as total cholesterol (TCHO; r=0.113, *P*=0.012) and low-density lipoprotein-cholesterol (LDL-C; r=0.175, *P*=0.001), but no relationship with TSH (r=–0.023, *P*=0.666). In addition, the FGF21 levels in thyroid autoantibody-positive and -negative groups were not significantly different.

Conclusion: Among the metabolic syndrome-free patients with normal physical examination results, FGF21 has no apparent relationship with TSH or thyroid autoimmunity.

Keywords: Human fibroblast growth factor 21 (FGF21), Thyroid stimulating hormone (TSH), Autoimmunity, Free fatty acids (FFA)

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Introduction

Human fibroblast growth factor 21 (FGF21), a newly discovered cell factor, is an important participant in regulating carbohydrate and lipid metabolism, and energy balance [1]. Some studies have shown that FGF21 has a close relationship with metabolic syndrome-related indices, such as the content of body fat, body mass index (BMI), waist-to-hip ratio, triglycerides (TG), free fatty acids (FFA), fasting blood glucose (FBG), fasting insulin (FIns), and insulin resistance [2, 3]. Different thyroid function states and thyroid stimulating hormone (TSH) levels also have an effect on carbohydrate and lipid metabolism [4–8], and an increase in TSH and FGF21 levels is closely associated with metabolic syndrome [9–11]. There

are no relevant reports focusing on whether TSH or another pathway plays a role in the relationship between FGF21 and metabolic syndrome, i.e., whether or not there is a relationship between TSH and FGF21. In addition, Xiao et al. [12] reported that FGF21 has a relationship with autoantibodies, such as glutamic acid decarboxylase antibody (GADA) and insulinoma-associated protein 2 autoantibodies (IA2As), thus it was suggested that FGF21 may also have a relationship with autoimmune diseases.

The purpose of the current study was to collect data from metabolic syndrome-free patients with normal physical examination results to determine the difference in FGF21 levels among patients with different TSH levels through comparison and to detect the relationship between FGF21 and lipid and carbohydrate metabolism, and to further determine the relationship between FGF21 and thyroid autoimmunity by testing thyroid-related antibodies.

Subjects and methods

Subjects

Nine hundred three patients (438 males and 465 females; average age, 48±15 years) who had physical examinations between October 2012 and April 2013 at Peking University First Hospital were selected, and 356 patients (116 males and 240 females; average age, 43±13 years) who were free from any signs of metabolic syndrome and had no history of diabetes, hypertension, chronic kidney disease, polycystic ovary syndrome, autoimmune diseases, or pituitary and hypothalamic disease were enrolled. The metabolic syndrome was diagnosed as per the Chinese Society of Diabetes *2004 Recommendation on Metabolic Syndrome* [13]. Specifically, metabolic syndrome was diagnosed in any person who satisfies three or all four of the following features: (1) overweight and/or obesity, BMI ≥25 kg/m^2; (2) hyperglycemia, FBG ≥6.1 mmol/L and/or 2-h post-challenge plasma glucose (2-h PPG) ≥7.8 mmol/L and/or patients with a confirmed diagnosis of diabetes under treatment; (3) hypertension, blood pressure (BP) ≥140/90 mmHg and/or patients with a confirmed diagnosis of hypertension under treatment; (4) dyslipidemia, fasting plasma TG ≥1.7 mmol/L and/or high-density lipoprotein-cholesterol (HDL-C) <0.9 mmol/L (male) or <1.0 mmol/L (female). The authors received consent from all participants.

Methods

The age and gender were recorded, and the height, weight, waist circumference, hip circumference, and blood pressure were measured. The thyroid volume was estimated by palpation and the percentage body fat was determined using the biological impedance method (Tanita Company, Shanghai, China). Five millilitre fasting blood was drawn from the elbow vein, and examined using an automatic biochemical analyzer (Hitachi 7600/110, Beijing, China) to determine the alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine (Scr), uric acid (UA), FBG, TG, total cholesterol (TCHO), HDL-C, and low-density lipoprotein-cholesterol (LDL-C) levels. Another 2 mL of serum was stored in a –80°C freezer for uniform preservation to test TSH, thyroglobulin antibody (TgAb), thyroid peroxidase antibody (TPOAb), and Fins from the same batch. The ECLIA method (Siemens ADVIA Centaur® XP detector, Beijing, China) was used to test TSH (normal reference range, 0.55–4.78 mIU/L; between-run coefficient of variance, 2.857%–3.755%). The ECLIA method (Roche Cobas 601 detector, Shanghai, China) was used to test TPOAb, TgAb, and Fins (TPOAb >34 μIU/mL and TgAb >115 μIU/mL were judged to be positive). The ELISA method was used to determine the levels of serum FGF21 (between-run coefficient of variance, 13.64%; Li Ka Shing Faculty of Medicine, the University of Hong Kong, China) and FFA (between-run coefficient of variance, 13.22%; BlueGene Company, Shanghai, China). The BMI (kg/m^2) was calculated as the weight in kg/height in m^2, the estimated glomerular filtration rate (eGFR) (mL/[min*1.73 m^2]) was calculated as 175×(Scr in mg/dL)–1.234×(age in years)–0.179×(0.79 for females) [14], and the homeostasis model assessment for insulin resistance (HOMA-IR) was calculated as fasting insulin (mIU/L)×fasting blood glucose (mmol/L)÷22.5 [15].

Statistical analysis

All measurement data in conformity with a normal distribution are expressed as the $\bar{x} \pm s$. A t-test and variation analysis was used among the groups and Pearson correlation analysis was used for the correlation analysis between the two indices. Non-normal distribution data was subjected to logarithmic transformation. The same statistical methods was used for data in conformity with a normal distribution after logarithm

transformation, while the median was used to express those data which failed to conform to a normal distribution after logarithm transformation. The rank-sum test was used among the groups and Spearman correlation analysis was used for correlation analysis. Multiple linear regression analysis was used to analyze independent correlation factors for FGF21. All data were analyzed by SPSS 21.0 and a $P<0.05$ indicated statistical significance.

Results

TSH and thyroid autoantibody test results

Among 356 patients, 8 were in the decreased TSH group, 320 were in the normal TSH group, 28 were in the increased TSH group, 75 were TgAb- or TPOAb-positive, and 280 were TgAb- and TPOAb-negative; 1 patient was not tested for thyroid autoantibodies due to an insufficient blood sample.

The relationship between FGF21 and various metabolic indices

As shown in Table 1, among 356 metabolic syndrome-free patients, FGF21 had a weak relationship with obesity indices, such as waist circumference (r=0.110, P=0.038) and waist-to-hip ratio (r=0.119, P=0.025); FGF21 had no relationship with BMI, hip circumference, and body fat percentage. FGF21 had a positive relationship with TG (r=0.302, P=0.000) and had a weak relationship with blood lipid levels, including TCHO (r=0.113, P=0.012) and LDL-C (r=0.175, P=0.001), but no relationship with HDL-C. In addition, FGF21 had no relationship with TSH (r=–0.023, P=0.666) and even no relationship with FBG, FIns, HOMA-IR, UA, FFA, and systolic and diastolic blood pressures. With FGF21 designated as the dependent variable and indices correlated with FGF21 as independent variables (waist circumference, TG, TCHO, and LDL-C), the results from multiple linear stepwise regression analysis after age and weight were entered showed that TG had an independent relationship with FGF21 (P=0.000), and the standardized regression equation was as follows: YFGF21=230.84×TG+5.26×age.

The relationship between TSH and various metabolic indices

The serum TSH level had a positive relationship with FFA (r=0.840, P=0.000) and no relationship with BMI, waist circumference, hip circumference, waist-to-hip ratio, body fat percentage, TG, TCHO, HDL-C, LDL-C, FBG, FIns, HOMA IR, UA, and systolic or diastolic blood pressure.

Table 1. The relationship between FGF21 and various metabolic indices

Variable items	r	*P*-value
Age (years)	0.324	0.000
BMI (kg/m^2)	0.074	0.163
Waist circumference (cm)	0.110	0.038
Hip circumference (cm)	0.064	0.228
Waist-to-hip ratio	0.119	0.025
Body fat (%)	0.06	0.256
SBP (mmHg)	0.055	0.300
DBP (mmHg)	0.004	0.935
Scr (μmol/L)	–0.017	0.757
UA (μmol/L)	0.018	0.742
FBG (mmol/L)	0.103	0.052
FIns (μIU/mL)	0.011	0.836
HOMA-IR	0.013	0.809
TG (mmol/L)	0.302	0.000
TCHO (mmol/L)	0.133	0.012
HDL-C (mmol/L)	–0.103	0.052
LDL-C (mmol/L)	0.175	0.001
FFA (μg/mL)	–0.006	0.917
TSH (μIU/mL)	–0.23	0.666
TgAb (IU/mL)	0.013	0.806
TPOAb (IU/mL)	0.057	0.284

Note: FGF21: human fibroblast growth factor 21; BMI: body mass index=weight/height; SBP: systolic blood pressure; DBP: diastolic blood pressure; UA: uric acid; FBG: fasting glucose; FIns: fasting insulin; HOMA-IR: homeostasis model assessment method insulin resistance; TG: triglycerides; TCHO: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL C: low density lipoprotein cholesterol; FFA: free fatty acid; TSH: thyroid stimulating hormone; TgAb: thyroglobulin antibody; TPOAb: thyroid peroxidase antibody.

Comparison of various metabolic indices of patients with different thyroid functions

As shown in Table 2, there was a significant increase in the serum FFA level of the increased TSH group when compared with the normal and decreased TSH groups; the medians were 338.8, 112.4, and 27.3 μg/mL (P=0.000), respectively. As shown

in Table 2, there was no significant difference in the FGF21 level among the three groups; the medians were 392.0, 317.0, and 327.0 pg/mL (P=0.441), respectively. As shown in Table 2, there was no significant difference in age, BMI, waist circumference, hip circumference, waist-to-hip ratio, body fat percentage, blood lipid levels, FBG, FIns, HOMA-IR, UA, and systolic or diastolic blood pressure level among the three groups. After matching age, gender, and BMI at a 1:3 ratio, the UA (mean values=315.0 and 114.0 μmmol/L, respectively; P=0.000) and FFA levels (averages=315.0 and 114.0 μmmol/L, respectively; P=0.000) were significantly higher in the increased TSH group than the normal TSH group; there was no significant difference in the FGF21 level, BMI, waist circumference, hip circumference, waist-to-hip ratio, body fat percentage, blood lipid profile, FBG, FIns, HOMA-IR, UA, eGFR, and systolic or diastolic blood pressure levels between the two groups.

Comparison of FGF21 levels among different thyroid antibody groups

The TgAb- or TPOAb-positive and double antibody groups were compared with the seropositive group and both seronegative groups; no significant difference in FGF21 levels was noted (median=331 and 318 pg/mL, respectively; P=0.755).

Reference range of the FGF21 level

The reference range for the FGF21 level was 49.47–1123.6 pg/mL (368.51±281.545 pg/mL) based on the FGF21 levels of 193 patients whose BMI, FBG, blood lipid, and TSH levels were within the normal ranges, the physical examination was normal, and who had no history of diabetes, hypertension, chronic kidney disease, polycystic ovary syndrome, and autoimmune diseases.

Table 2. Data of patients with different thyroid functions

Group	TSH decreasing group	TSH normal group	TSH increasing group	*P*-value
Cases (male/female)	8 (2/6)	320 (110/210)	28 (4/24)	
Age (years)	43.0±13.8	42.7±13.2	46.3±13.0	0.198
BMI (kg/m^2)	21.6±2.4	22.0±11.0	21.5±2.0	0.966
Waist-to-hip ratio	0.79±0.08	0.87±0.73	0.77±0.06	0.773
Body fat (%)	26.0±4.1	24.8±5.4	26.1±4.4	0.388
SBP (mmHg)	111.9±12.5	113.5±10.5	112.0±13.4	0.718
DBP (mmHg)	70.6±5.6	72.1±7.1	71.4±8.6	0.782
UA (μmol/L)	270.43±53.25	286.31±78.24	295.96±67.46	0.702
FBG (mmol/L)	4.89±0.35	4.84±0.43	4.86±0.36	0.930
FIns (μIU/mL)	4.76±1.96	4.93±2.49	4.47±1.71	0.620
HOMA-IR	1.20 (0.60–1.31)	0.96 (0.66–1.37)	0.96 (0.64–1.19)	0.742
TG (mmol/L)	0.97±0.29	0.94±0.33	0.94±0.34	0.951
TCHO (mmol/L)	4.49±0.83	4.69±0.91	4.87±0.89	0.482
HDL-C (mmol/L)	1.35±0.83	1.47±0.37	1.53±0.26	0.449
LDL-C (mmol/L)	2.70±0.65	2.82±0.73	2.94±0.74	0.605
FFA (μg/mL)	27.3 (5.9–48.6)	112.4 (76.3–168.1)	338.8 (256.1–285.9)	0.000
FGF21 (pg/mL)	327.0 (238.0–494.5)	317.0 (196.3–516.5)	392.0 (229.5–592.5)	0.441

Note: TSH: thyroid stimulating hormone; BMI: body mass index=weight/height; SBP: systolic blood pressure; DBP: diastolic blood pressure; UA: uric acid; FBG: fasting glucose; FIns: fasting insulin; HOMA-IR: homeostasis model assessment method insulin resistance; TG: triglycerides; TCHO: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; FFA: free fatty acid; FGF21: human fibroblast growth factor 21; the FFA, FGF21 and HOMA-IR which presented the nonnormal distribution were expressed in medians and interquartile range, and the other indexes in conformity with normal distributions were expressed in $\bar{x} \pm s$.

Discussion

A number of studies have suggested that the increase in FGF21 and TSH levels is directly related to metabolic syndrome, but the relationship between FGF21 and TSH is unclear [9–11]. To rule out the impact of metabolic syndrome on the relationship between FGF21 and TSH, the current study selected patients without metabolic syndrome and who had no history of diseases known to affect the FGF21 level, including polycystic ovary syndrome, chronic kidney disease, and autoimmune diseases [12, 16, 17].

The current study grouped patients on the basis of different TSH levels; no relationship existed between FGF21 and TSH. FGF21 had a positive relationship with TG, with the exception of patients with an elevated TG level, suggesting that FGF21 can still participate in TG metabolism when TG and TSH levels are within the normal range. Lee et al. [18] showed that the FGF21 level of patients with elevated TSH (hypothyroidism) was increased when compared with euthyroid patients. FGF21 has a positive relationship with TSH, and the difference is significant, even after TG correction [18]. A relationship between FGF21 and TSH was not observed in this study, and possible reasons were as follows: (1) Small sample size; there were only 8 patients in the decreased TSH group and 28 patients in the increased TSH group. (2) Patients with known diseases which have an impact on FGF21 were not selected as subjects in this study to rule out the impact of abnormal glucose metabolism, hypertriglyceridemia, and obesity on FGF21, and to rule out pathologic states induced by the effect of polycystic ovary syndrome, chronic kidney disease, and autoimmune diseases on the FGF21 level. Lee et al. [18] did not screen out known diseases. To summarize, the relationship between FGF21 and TSH was not observed in the current study, and further studies on the relationship and mechanism of action are needed for clarification.

The current study indicated that among the metabolic syndrome-free patients, FGF21 had a relationship with TG, a weak relationship with blood lipid levels (TCHO and LDL-C), and a weak relationship with obesity indices (waist circumference and waist-to-hip ratio); however, a relationship between FGF21 and carbohydrate metabolism was not observed. Li and others [19] reported that FGF21 has a relationship with TG and TCHO, but no relationship with the secretion and sensitivity of insulin when patients with abnormal glucose tolerance and healthy patients were compared. Li proposed that FGF21 has a much closer relationship with abnormal lipid metabolism and obesity, and the difference in expression among people with different glucose metabolism levels may be secondary to obesity. The relationship between FGF21 and glucose metabolism was also not observed in the current study, which indicated that FGF21 has a much closer relationship with TG metabolism.

The study also suggested that the serum FFA level of the increased TSH group was higher than the normal TSH group, and the serum FFA level of the normal TSH group still had a positive relationship with TSH among the normal TSH patients, which is quite similar to the results reported by Yu et al. [20]. It has been confirmed that there is a TSH receptor on the surface of fat cells [21], and TSH accelerates intracellular lipolysis to increase the generation of FFA in the human body through downstream protein kinase C [22, 23].

Xiao et al. [12] reported that the serum FGF21 level increased in patients with type 1 diabetes and latent autoimmune diabetes in adults (LADA) and had a positive relationship with GADA and IA2A. Xiao et al. [12] proposed that FGF21 may be involved in the autoimmune process. A relationship between the FGF21 level and thyroid autoantibody titers was not observed in the current study, thus additional studies are needed to verify the relationship between the FGF21 level and other autoimmune diseases.

A number of studies have suggested that FGF21 has a relationship with a variety of metabolic diseases, but there are no domestic or international studies involving the normal reference range of FGF21. Li et al. [19] studied 353 Chinese Han people (including patients with normal carbohydrate metabolism, impaired fasting glucose, impaired glucose tolerance, and diabetes), and demonstrated that the fluctuation range of FGF21 was 11.0–930.0 pg/mL. In the current study, the reference range for FGF21 level was 49.47–1123.6 pg/mL using a typical ELISA method based on the FGF21 level of 193 patients with BMI, FBG, blood lipids and TSH were within normal ranges, normal physical examinations, and no history of polycystic ovary syndrome, diabetes, hypertension, fatty liver, autoimmune diseases, or chronic kidney disease. The current study suggested that there is a large difference in FDG21 levels, even amongst the metabolic syndrome-free patients, which is consistent with the FGF21 fluctuation range reported by Li et al. [19]. Therefore, the above-mentioned facts might need to be considered when the relationship between FGF21 and diseases is studied.

In conclusion, among metabolic syndrome-free patients, we observed that FGF21 has no significant relationship with the TSH level, and thus may be unrelated to thyroid autoimmunity. FGF21 may participate in maintaining metabolic balance in humans through a mechanism different from TSH.

Conflict of interest

The authors declare no conflict of interest.

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