

Serum Fibroblast Growth Factor 19 Levels Are Decreased in Chinese Subjects With Impaired Fasting Glucose and Inversely Associated With Fasting Plasma Glucose Levels

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OBJECTIVE—Fibroblast growth factor 19 (FGF19), a hormone secreted from the small intestine, has recently been shown to stimulate glycogen synthesis and inhibit gluconeogenesis through insulin-independent pathways. This study investigated the change of FGF19 in prediabetes and newly diagnosed type 2 diabetes mellitus (T2DM) and explored the association of serum FGF19 levels with parameters of glucose metabolism in Chinese subjects.

RESEARCH DESIGN AND METHODS—Fasting serum FGF19 levels were determined by ELISA in 81 normal glucose tolerance (NGT), 91 impaired fasting glucose (IFG), 93 impaired glucose tolerance (IGT), and 104 newly diagnosed T2DM subjects, and their association with parameters of glucose metabolism was studied. An ordinal logistic regression analysis was performed in subjects with NGT, IFG, and T2DM. Serum FGF19 levels at 2 h after a 75-g oral glucose tolerance test in the different glucose tolerance categories were studied in a subgroup.

RESULTS—Fasting serum FGF19 levels in subjects with IFG (210 pg/mL [142–327]) (median [interquartile range]) and T2DM (196 pg/mL [137–280]) were significantly lower than those in NGT subjects (289 pg/mL [224–393]) (both $P < 0.001$). However, no significant difference in fasting FGF19 levels was observed between IGT (246 pg/mL [138–379]) and NGT subjects. Fasting serum FGF19 levels were negatively associated with fasting plasma glucose and independently associated with the deterioration of glucometabolic status from NGT to IFG and T2DM.

CONCLUSIONS—Fasting serum FGF19 levels were decreased in Chinese subjects with IFG and inversely associated with fasting glucose levels.

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The fibroblast growth factor (FGF) family comprises >20 members with diverse functions, such as embryonic development, cell growth, and differentiation (1,2). Three members of

this family, including FGF15/19 (FGF15 and FGF19 are the mouse and human orthologs, respectively), FGF21, and FGF23, are endocrine factors involved in hormone-like metabolic effects

through activation of FGF receptors (3–8). FGF19 is mainly produced by the enterocytes in the distal part of the small intestine (9,10) and is implicated in regulating bile acid homeostasis. After consumption of a meal, FGF19 expression is induced by bile acid-mediated activation of the farnesoid X receptor (10,11). FGF19 is released into the portal circulation that supplies nutrient-rich blood to the liver and functions as an enterohepatic signal to regulate bile acid homeostasis (10).

The role of FGF19 in controlling energy homeostasis was first discovered in mice with transgenic overexpression of FGF19. FGF19 transgenic mice exhibited increased energy expenditure and a significant reduction in fat mass and were also resistant to diet-induced obesity (12). Administration of recombinant FGF19 protein recapitulated most of these metabolic effects, which prevented the development of glucose intolerance in both high fat diet-fed and *ob/ob* mice (13). FGF19 induces hepatic glycogen synthesis through an insulin-independent Ras-ERK-p90RSK pathway (14). In addition, it activates the components of the protein translation machinery and increases hepatic protein synthesis *in vivo* (14). Furthermore, FGF19 also represses gluconeogenesis by inhibiting the activity of the transcription factor cAMP regulatory element binding protein, a key regulator of proliferator-activated receptor γ coactivator-1 α and other gluconeogenic genes (15). Although these animal-based studies are certainly of interest, whether FGF19 is related to glucose metabolism in humans is unclear.

Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are two important categories of prediabetes that represent an intermediate stage between normal glucose tolerance (NGT) and diabetes (16). IFG and IGT have different pathophysiological characteristics of glucose metabolism (17–19). IFG is due to

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increased hepatic glucose production, whereas IGT mainly results from peripheral insulin resistance (17–19). Although FGF19 has an obvious effect on hepatic glucose production in animal-based studies, the change of FGF19 levels in subjects with IFG and IGT remains unknown. The objective of this study was to compare serum FGF19 levels in the different glucose tolerance categories and to explore their association with parameters of glucose metabolism in Chinese subjects.

RESEARCH DESIGN AND METHODS

Study subjects

The subjects with isolated impaired glucose tolerance (I-IGT) ($n = 93$), isolated impaired fasting glucose (I-IFG) ($n = 91$), newly diagnosed type 2 diabetes mellitus (T2DM) ($n = 104$), and NGT ($n = 81$) were recruited from the epidemiological survey of diabetes and metabolic syndrome in Shanghai communities in 2008. All subjects were of Han Chinese origin, including 189 men and 180 women. All subjects underwent comprehensive physical examinations, routine biochemical analyses of blood, hepatitis B surface antigen, and hepatitis C virus antibody, electrocardiogram, B ultrasonography, and a 75-g oral glucose tolerance test (OGTT). The participants completed a uniform questionnaire containing questions about the histories of present and past illness and medical therapy. Fasting serum FGF19 levels were measured in these 369 subjects. In the subgroup, the subjects with I-IGT ($n = 38$), I-IFG ($n = 34$), combined I-IFG/I-IGT ($n = 41$), T2DM ($n = 40$), and age- and sex-matched NGT ($n = 33$) were recruited. Serum FGF19 levels at 2 h after oral glucose load were measured in this subgroup. Subjects with the following conditions were excluded from this study: acute or chronic cholecystitis, biliary obstructive diseases, malabsorption syndrome, diarrhea, acute or chronic virus hepatitis, cirrhosis, alcoholic abuse, chronic renal insufficiency, known hyperthyroidism or hypothyroidism, presence of cancer, pregnancy, acute infectious disease, acute myocardial infarction, heart failure and stroke in acute phase, and current treatment with bile acid, bile acid sequestrant, and drugs that affect insulin secretion and sensitivity. The study was approved by the human research ethics committee of the hospital, and written informed consent was obtained from all subjects.

Definition for glucose tolerance status

The glucose tolerance status of the study subjects was defined by the 1997 American Diabetes Association diagnostic criteria (16). Fasting plasma glucose concentration (FPG) < 6.1 mmol/L and 2-h plasma glucose concentration (2hPG) < 7.8 mmol/L was defined as normal. IFG was defined as an FPG of 6.1–7.0 mmol/L. IGT was defined as a 2hPG of 7.8–11.1 mmol/L. This stratification resulted in three groups of prediabetes: I-IFG (an FPG of 6.1–7.0 mmol/L and normal 2hPG), I-IGT (a 2hPG of 7.8–11.1 mmol/L and normal FPG), and combined I-IFG/I-IGT (an FPG of 6.1–7.0 mmol/L and 2hPG of 7.8–11.1 mmol/L) (18,19).

Anthropometric and biochemical measurements

Waist circumference was measured at the midpoint between the inferior costal margin and the superior border of the iliac crest on the midaxillary line. Systolic pressure and diastolic pressures were measured when people were at rest for at least 5 min, defined as the mean of the second and third reading of three consecutive blood pressure measurements.

FPG and 2hPG were measured by the hexokinase method, and serum levels of total cholesterol (TC), triglycerides (TG), HDL cholesterol (HDL-C), and LDL cholesterol (LDL-C) were determined enzymatically on a Hitachi 7600 analyzer. Glycated hemoglobin A_{1c} (HbA_{1c}) was measured by high-performance liquid chromatography (HLC-73G7; Tosoh, Tokyo, Japan). Serum insulin was assayed via radioimmunoassay (Linco Research, St. Charles, MO).

Homeostasis model assessment

Basal insulin secretion and insulin sensitivity were estimated by the homeostasis model assessment (HOMA) of insulin secretion: $\text{HOMA-}\%B = [\text{fasting serum insulin concentration (FINS) (mU/L)} \times 6 \times 3.33] / [\text{FPG (mmol/L)} - 3.5]$, and homeostasis model assessment of insulin resistance: $\text{HOMA-IR} = \text{FINS (mU/L)} \times \text{FPG (mmol/L)} / 22.5$ (20).

Measurement of FGF19 in human serum

Serum FGF19 levels were determined using ELISA (Antibody and Immunoassay Services, University of Hong Kong). The assay was proven to be highly specific to human FGF19 and did not cross-react with other members of the FGF family.

The intra- and interassay variations were 4.5 and 5.6%, respectively.

Statistical analysis

All analyses were performed with Statistical Package for the Social Sciences version 16.0 (SPSS, Inc., Chicago, IL). Normally distributed data were expressed as mean \pm SD. Data that were not normally distributed, as determined using the Shapiro-Wilk test, were logarithmically or double logarithmically transformed before analysis and expressed as the median with interquartile range (IQR). Unpaired Student *t* test was used for comparison between two groups. Pearson correlations, one-way ANOVA, or ANCOVA were used as appropriate for comparisons between groups, and multiple testing was corrected using Bonferroni correction. Multiple stepwise regression analysis was used to examine the association of serum FGF19 and other parameters. The variables that correlated significantly with serum FGF19 (after Bonferroni correction for multiple testing) were selected to enter into stepwise regression. Ordinal logistic regression analysis was performed to explore the factors independently associated with the deterioration of glucometabolic status from I-IFG to T2DM. In all statistical tests, *P* values < 0.05 were considered significant.

RESULTS

Characteristics of subjects

Clinical characteristics of the study subjects were shown in Table 1. Compared with NGT subjects, I-IGT, I-IFG, and T2DM subjects were older (all $P < 0.05$). No significant differences in the male-to-female ratio were observed in I-IGT, I-IFG, and T2DM subjects in comparison with NGT. After adjustment for age and sex, I-IGT, I-IFG, and T2DM subjects had a higher BMI and waist circumference than NGT subjects (all $P < 0.001$). Waist circumferences in I-IGT individuals were higher than in I-IFG ($P < 0.01$). FINS levels in I-IGT, I-IFG, and T2DM subjects were higher than in NGT subjects (all $P < 0.05$). Compared with I-IGT subjects, the I-IFG subjects had a significant reduction in HOMA-%B ($P < 0.001$) and a trend of elevation in HOMA-IR. Patients with T2DM had greater changes in HOMA-IR and HOMA-%B than I-IFG subjects ($P < 0.05$).

Table 1—Anthropometric parameters and biochemical indexes among subjects with NGT, I-IGT, I-IFG, and T2DM

Variables	NGT (n = 81)	I-IGT (n = 93)	I-IFG (n = 91)	T2DM (n = 104)
Male/female	46/35	43/50	43/48	57/47
Age (years)	40.8 ± 8.8	48.3 ± 10.7	49.9 ± 12.2	50.3 ± 11.1
BMI (kg/m ²)	22.2 ± 2.2	25.2 ± 3.7***	24.5 ± 2.6***	25.4 ± 3.6***
Waist circumference (cm)	74.9 ± 7.8	84.2 ± 9.9***	80.9 ± 9.3***†	85.0 ± 10.1***
SBP (mmHg)	119 ± 13	126 ± 17	125 ± 16	129 ± 19*
DBP (mmHg)	79 ± 10	81 ± 11	77 ± 10*†	84 ± 11
TC (mmol/L)	4.30 ± 0.85	4.89 ± 0.85**	4.78 ± 0.90	4.76 ± 1.03
TG (mmol/L)§	1.04 (0.76–1.62)	1.54 (1.01–2.33)*	1.23 (0.85–1.95)	1.78 (1.14–3.18)***
HDL-C (mmol/L)	1.30 ± 0.30	1.28 ± 0.31	1.29 ± 0.32	1.18 ± 0.26**
LDL-C (mmol/L)	2.75 ± 0.66	3.11 ± 0.76*	3.00 ± 0.84	2.99 ± 0.84
HbA _{1c} (%))§§	5.5 (5.3–5.7) (37 [34–39])	5.8 (5.5–5.9)** (40 [37–41])	5.7 (5.5–6.0)** (39 [37–42])	6.7 (6.0–7.8)*** (50 [42–62])
FPG (mmol/L)§§§	5.12 (4.72–5.42)	5.39 (4.92–5.67)	6.33 (6.17–6.50)***†	7.62 (6.60–9.17)***
2hPG (mmol/L)§§§	5.32 (4.63–6.47)	8.70 (8.12–9.09)***	6.21 (5.38–6.85)*†	13.38 (11.32–16.76)***
FINS (μU/mL)§	5.60 (4.06–7.08)	6.99 (5.04–11.19)**	7.39 (4.46–11.68)*	7.35 (5.86–10.70)*
HOMA-IR§	1.24 (0.89–1.61)	1.65 (1.19–2.70)***	2.04 (1.24–3.27)***	2.81 (1.77–4.04)***
HOMA-%B§	79.19 (49.74–105.61)	83.32 (54.68–130.97)	56.85 (32.93–84.31)*†	39.73 (19.55–61.59)***
FGF19§	289 (224–393)	246 (138–379)	210 (142–327)***	196 (137–280)***

Data are means ± SD or median (IQR). P values of FGF19 are calculated after adjustment for age, sex, and BMI, and those of others are calculated after adjustment for age and sex. Sample size of FINS measurement: NGT, n = 76; I-IGT, n = 47; I-IFG, n = 35; T2DM, n = 66. DBP, diastolic blood pressure; SBP, systolic blood pressure. §Log transformed before analysis. §§Log transformed before analysis. §§§Log transformed before analysis. *P < 0.05 vs. NGT. **P < 0.01 vs. NGT. ***P < 0.001 vs. NGT. †P < 0.01, I-IGT vs. I-IFG. ‡P < 0.001, I-IGT vs. I-IFG.

Fasting serum FGF19 levels in NGT, I-IGT, I-IFG, and T2DM groups

In this study cohort, fasting serum concentrations of FGF19 ranged from 27 to 1,314 pg/mL. There were no sex differences in serum FGF19 levels: men (n = 189), median 224 pg/mL (IQR 142–342), vs. women (n = 180), 262 pg/mL (167–358) (P = 0.110). After adjustment for age, sex, and BMI, fasting serum FGF19 levels in subjects with I-IFG (210 pg/mL [142–327]) were significantly lower than NGT subjects (289 pg/mL [224–393]) (P < 0.001), and fasting serum FGF19 in patients with T2DM (196 pg/mL [137–280]) were even lower (P < 0.001 vs. NGT). However, no significant difference in fasting serum FGF19 levels was observed between I-IGT (246 pg/mL [138–379]) and NGT subjects (Table 1).

Relationship between fasting serum FGF19 and glucose levels

We next analyzed the relationship between fasting serum FGF19 levels and a cluster of anthropometric parameters, biochemical indexes, and insulin secretion and sensitivity. The analysis demonstrated a negative association of serum FGF19 with age (r = -0.183, P < 0.01) and FPG (r = -0.185, P < 0.01). After adjustment for age, we still found a significant negative association of serum FGF19 levels with FPG (r = -0.147, P < 0.05). No significant associations were found between serum FGF19 and FINS levels or HOMA-%B. However, the significant association of FGF19 with BMI, waist circumference, HbA_{1c}, 2hPG, and HOMA-IR no longer existed after age adjustment.

To determine which parameters were independently associated with serum FGF19, multiple stepwise regression analysis was performed. In model A, the analysis involved the above parameters with significant correlations with serum FGF19, including age, BMI, waist circumference, FPG, 2hPG, and HOMA-IR. As a result, FPG (standard β = -0.157, t = -2.244, P < 0.05) was found to be independently associated with serum FGF19 in addition to age (standard β = -0.140, t = -1.990, P < 0.05). In model B, when FPG and 2hPG were replaced with HbA_{1c} level, HbA_{1c} was found to be independently associated with serum FGF19 (standard β = -0.181, t = -2.623, P < 0.01).

Ordinal logistic regression analysis showing FGF19 independently associated with deterioration of glucometabolic status from NGT to I-IFG and T2DM

As FPG was found to be independently associated with serum FGF19, an ordinal logistic regression analysis was performed in subjects with three glucometabolic statuses (NGT, I-IFG, and T2DM). The analysis involved age, BMI, waist circumference, systolic blood pressure, diastolic blood pressure, TG, TC, HDL-C, LDL-C, and FGF19. As a result, FGF19 (odds ratio 0.159 [95% CI 0.059–0.432], $P < 0.001$, log transformed), age (1.041 [1.017–1.066], $P = 0.001$), and TG (7.128 [1.409–36.050], $P = 0.018$, log transformed) were found to be independent factors for deterioration of glucometabolic status from NGT to I-IFG and T2DM. However, other variables were all excluded in the final model.

Serum FGF19 after oral glucose challenge in subjects with different degrees of glucose intolerance

To investigate the serum FGF19 after oral glucose challenge in the different glucose tolerance categories, we measured serum FGF19 levels at 2 h after OGTT in the subgroup, including I-IGT ($n = 38$), I-IFG ($n = 34$), combined I-IFG/I-IGT ($n = 41$), T2DM ($n = 40$), and age- and sex-matched NGT subjects ($n = 33$). No significant differences in BMI were observed among the five groups. The comparison results of fasting serum FGF19 levels among NGT, I-IFG, I-IGT, and T2DM subjects were similar to the above result. Fasting serum FGF19 levels in combined I-IFG/I-IGT subjects were significantly lower than NGT ($P < 0.01$) and I-IGT subjects ($P < 0.01$), but no significant difference between combined I-IFG/I-IGT and I-IFG was found. Compared with fasting levels, serum levels of FGF19 increased at 2 h after oral glucose administration in all five groups (NGT 246 pg/mL [190–371] vs. 270 pg/mL [201–594], I-IFG 231 pg/mL [135–324] vs. 286 pg/mL [186–341], I-IGT 250 pg/mL [128–345] vs. 263 pg/mL [182–428], combined I-IFG/I-IGT 193 pg/mL [125–286] vs. 230 pg/mL [168–329], and T2DM 175 pg/mL [147–271] vs. 216 pg/mL [149–338], all $P < 0.05$). However, there were no significant differences in FGF19 levels at 2 h after OGTT among the five groups. Moreover, serum levels of FGF19 at 2 h after OGTT did not correlate with the 2hPG and the corresponding insulin levels.

CONCLUSIONS—Although the recent animal-based studies suggested that FGF19 is a metabolic regulator with beneficial effects on glucose homeostasis (21,22), the clinical relevance of FGF19 remains poorly characterized. It was reported that fasting FGF19 levels were significantly lower in obese subjects with BMI ≥ 30 kg/m² than in the control group, whereas fasting and postprandial FGF19 levels did not differ between control and diabetic subjects (23,24). However, two other studies found that fasting FGF19 levels were lower in patients with the metabolic syndrome together with T2DM (25,26). The change of FGF19 levels in prediabetic subjects remains unknown. In this study, we first demonstrated that fasting serum FGF19 levels in subjects with I-IFG were significantly lower than in NGT subjects and such levels were further reduced in patients with T2DM. However, no significant differences in FGF19 levels were observed between I-IGT and NGT subjects. I-IFG and I-IGT have different pathophysiological characteristics of glucose metabolism. I-IFG is due to increased hepatic glucose production and impaired basal insulin secretion, whereas I-IGT mainly results from reduced second-phase insulin release and peripheral insulin resistance (17–19). Increased hepatic glucose production could result from enhanced glycogenolysis, gluconeogenesis, or a combination of both (27). Our finding that serum FGF19 levels were significantly decreased in I-IFG but not in I-IGT further demonstrated the plausible physiological roles for FGF19 in regulating hepatic glucose production.

Our study found that fasting serum FGF19 was independently associated with FPG in addition to age. However, no significant associations of FGF19 with 2hPG, HbA_{1c}, and insulin secretion and sensitivity assessed by HOMA were found after age adjustment. Moreover, there was no significant difference in FGF19 levels at 2 h after oral glucose challenge among the different glucose tolerance categories. Serum levels of FGF19 at 2 h after OGTT did not correlate with the 2hPG and insulin levels. Recently, it was demonstrated that mice lacking FGF15 have impaired glucose tolerance but retain normal insulin sensitivity. The impaired glucose tolerance of FGF15 knockout mice can be corrected by FGF19 treatment (14,15). These novel findings provide compelling evidence for a physiological role of FGF19 in the control of glucose

homeostasis. FGF19 shares some of the metabolic actions of insulin, including the stimulation of hepatic glycogen synthesis and inhibition of gluconeogenesis (14,15). In the overnight fasting state, ~75% of the glucose output of the liver is from glycogenolysis and 25% is from gluconeogenesis (28). Therefore, the negative relationship between the serum FGF19 level and FPG but not 2hPG in humans supports the concept that FGF19 plays an important role in stimulating hepatic glycogen synthesis and inhibiting gluconeogenesis.

FGF19 and FGF21 can be considered late-acting fed- and fasted-state hormones, respectively, acting on the heels of insulin and glucagon to regulate metabolism in response to nutritional stress (21). The pharmacological actions of FGF19 and FGF21 make them attractive as potential therapeutic agents for treating metabolic diseases (21). Interestingly, circulating FGF21 concentrations are increased in obese individuals and patients with T2DM, I-IGT, or nonalcoholic fatty liver disease (29–32), suggesting the possible existence of FGF21 resistance in humans (33,34). On the other hand, our finding that FGF19 decreased in I-IFG and T2DM subjects demonstrated that such a phenomenon may not exist in the action of FGF19.

There are several limitations of this study. The study did not address the cause-effect relationship between FGF19 and I-IFG as well as T2DM. Further prospective studies are warranted to determine whether decreased serum FGF19 is causally related to the exceeded hepatic glucose output.

In summary, this study demonstrates that fasting serum concentrations of FGF19, which has been regarded as a potential candidate for the treatment of diabetes, are decreased in I-IFG and T2DM subjects. However, no significant differences in fasting FGF19 levels were observed between I-IGT and NGT subjects. Fasting serum FGF19 is found to be independently associated with the deterioration of the glucometabolic status from NGT to I-IFG and T2DM by ordinal logistic regression analysis. Our data demonstrate that serum concentrations of fasting serum FGF19 are independently associated with FPG in addition to age.

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Q.F. and H.L. contributed to the study design, data analysis, and manuscript writing. Q.S. conducted the experiments. W.Y., X.H., X.M., and J.L. conducted the sample and clinical data collection. A.X. was involved in study design and revised the manuscript. W.J. designed the study and interpreted data. W.J. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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