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Factors associated with fibroblast growth factor 19 increment after oral glucose loading in patients who were previously admitted for coronary angiography

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ABSTRACT

Background: We investigated factors associated with fibroblast growth factor 19 (FGF-19) increment after oral glucose loading (OGL) in human subjects.
Methods: A total of 240 outpatients without known diabetes who were previously admitted for coronary angiography underwent an oral glucose tolerance test. FGF-19 increment (pg/ml) was calculated as FGF-19 2 h after OGL minus fasting FGF-19.
Results: Overall, FGF-19 significantly increased after OGL (from 123 [78–201] to 141 [80–237], $p = 0.001$). By age tertiles (≦54, 55–64, ≧65), FGF-19 significantly increased only in patients aged ≧65 (from 143 [98–209] to 189 [124–332], $p < 0.001$). By glucose regulation status, FGF-19 significantly increased in patients with normal glucose tolerance (from 117 [78–211] to 153 [106–325], $p = 0.014$) and in patients with prediabetes (from 117 [73–179] to 123 [70–204], $p = 0.043$), but not in patients with diabetes (from 181 [102–243] to 178 [111–275], $p = 0.139$). FGF-19 significantly increased in patients on statin treatment (from 120 [78–207] to 145 [86–264], $p < 0.001$), but not in patients not on statin therapy (from 125 [86–196] to 128 [68–230] pg/ml, $p = 0.676$). These findings remained significant after adjustment for confounders.
Conclusions: FGF-19 increment after OGL was positively associated with age, and negatively associated with abnormal glucose regulation and statin treatment.

1. Introduction

Fibroblast growth factor 19 (FGF-19) and its mouse ortholog, FGF-15, have been recently identified as endocrine factors which exert hormone-like metabolic effects through activation of FGF receptors [1–4]. FGF-19 is a postprandial hormone which is mainly produced in the distal part of the small intestine in response to bile acid secretion after meals [5,6]. FGF-19 is released into the portal circulation with a peak plasma concentration 2–3 h after meals [7,8] to regulate bile acid and lipid metabolism through repressing liver cholesterol 7α-hydroxylase (CYP7A1) gene, which encodes the rate-limiting enzyme of bile acid synthesis [9,10].

In addition to regulating bile acid metabolism, FGF-19 has been reported to regulate energy homeostasis [1–4]. Transgenic mice expressing human FGF-19 exhibit increased energy expenditure and decreased adiposity, and are also resistant to high-fat-diet-induced weight gain and glucose intolerance [1]. Administration of FGF-19 decreased body weight and improved glucose homeostasis in both high-fat-diet-fed and leptin-deficient obese mice [2]. It has been reported recently that FGF-19 induces postprandial hepatic glycogen and protein synthesis through an insulin-independent pathway in vivo [3]. Furthermore, FGF-19 inhibits hepatic gluconeogenesis through inactivation of the transcription factor cAMP regulatory element binding protein (CREB) and peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) [4]. These findings suggest that FGF-19 may have a role in regulating postprandial glucose homeostasis.

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It has been reported that serum FGF-19 significantly increased 2 h after oral glucose loading (OGL) in patients with normal glucose tolerance [11]. However, whether FGF-19 increment after OGL is related to abnormal glucose regulation (AGR) is unclear. Hao et al. [12] recently reported that fasting FGF-19 levels were inversely associated with coronary artery disease (CAD). Undiagnosed AGR, especially hyperglycemia after OGL, is common in patients with CAD [13–16], but the association between FGF-19 increment after OGL and AGR has not been addressed in patients with CAD.

2. Methods

2.1. Study design and patients

This study was approved by the Institutional Review Board of Taichung Veterans General Hospital, Taichung, Taiwan, and was conducted in accordance with the Declaration of Helsinki. All study subjects provided written informed consent prior to any study-related procedures. We enrolled patients without history of diabetes who were referred from our cardiovascular center for screening for AGR. Patients were previously admitted to our cardiovascular center for coronary angiography due to suspected or known CAD. All study procedures were carried out after hospital discharge when patients' heart disease was deemed to be stable.

2.2. Study procedures

Overnight-fasting patients were interviewed by a trained nurse at our outpatient clinic. Height and weight were measured with the patients wearing light clothes but no shoes. Waist circumference was measured at the midpoint between the lowest rib and the top of the iliac crest. Two consecutive readings of blood pressure from the upper arm of seated patients were recorded with a 30-s interval. The average of blood pressure readings was used for analysis. A small polyethylene catheter was placed into an antecubital vein and a blood sample was obtained for fasting plasma glucose (FPG), insulin, glycated hemoglobin (HbA_{1c}), FGF-19, and lipids measurements. A standard 75-g oral glucose tolerance test (OGTT) [17] was then performed and a blood sample was collected at 120 min for the measurements of 2-h plasma glucose (2-h PG) and FGF-19.

2.3. Biochemical analyses

Serum FGF-19 levels were determined using ELISA kit (FGF19 Quantikine ELISA kit, R&D Systems) following the manufacturer's instructions. The range of detection of serum FGF-19 is 31–554 pg/ml, and the intra- and inter-assay coefficients of variation were both <6.4%. HbA_{1c} was measured by boronate affinity high performance liquid chromatography (CLC385TM, Primus Corp.). The intra- and inter-assay CVs for HbA_{1c} (range 4.2% [22 mmol/mol] to 19.6% [191 mmol/mol]) were <0.9% and <2.9%, respectively. Plasma glucose was measured by the glucose oxidase–peroxidase method (Wako Diagnostics). The intra- and inter-assay CVs for glucose (range 0 to 800 mg/dl) were both <1.5%. Plasma insulin was determined by using electrochemiluminescence immunoassay (Elecsys 2010; Roche Diagnostics). The intra- and inter-assay CVs for insulin were 1.8% and 2.5%, respectively. Serum lipids were determined using UniCel DxC Systems (Beckman Coulter, Inc.). The intra- and inter-CVs for serum lipids were <3.0% and <4.5%, respectively.

2.4. Definition of study objectives

Patients' glucose regulation status was defined by their FPG, 2-h PG, and HbA_{1c} values, as recommended by the American Diabetes Association [18]. Insulin resistance and β-cell function were assessed with the homeostasis model assessment of insulin resistance (HOMA-IR) and β-cell function (HOMA-β), respectively [19]. CAD was defined as ≧50% stenosis of the lumen diameter in any coronary artery demonstrated by coronary angiography. FGF-19 increment was calculated as FGF-19 2 h after OGL minus fasting FGF-19.

2.5. Statistical analysis

All of the statistical analyses were performed using the Statistical Package for the Social Science (IBM SPSS ver. 22.0). Continuous variables are reported as mean ± SD or median (interquartile range), and categorical data are given as numbers (percentages). Differences in clinical variables between groups were tested for statistical significance with the Mann–Whitney *U* test for continuous variables, and with the χ^2 test for categorical variables. Wilcoxon signed-rank test was used to test the statistical difference of serum FGF-19 levels before and after OGL. Univariate and multivariate regression analyses were used to examine the association of serum FGF-19 increment after OGL with other parameters. Generalized linear model with logit link function was used to analyze the odds ratio of FGF-19 increase after OGL (vs. decrease) with adjustment for associated factors. In all statistical analyses, a 2-sided *P* value <0.05 was considered statistically significant.

3. Results

From May 2011 to June 2013, a total of 240 patients (mean age 61.1 ± 12.3 years, male 82.1%) were recruited and underwent an OGTT. Characteristics of study subjects according to FGF-19 change 2 h after OGL are given in Table 1. Fasting FGF-19 was higher (141 [97–215] vs. 111 [67–181] pg/ml, $p = 0.002$), while FGF-19 2 h after OGL was lower (86 [55–128] vs. 192 [132–334] pg/ml, $p < 0.001$) in patients who had a decrease of FGF-19 2 h after OGL, as compared with patients who had an increase of FGF-19 2 h after OGL. The change of FGF-19 2 h after OGL (−50 [−98 to −21] vs. 77 [30–148] pg/ml, $p < 0.001$), as well as FGF-19 relative change from baseline after OGL (−40.7 [−53.8 to −21.1] vs. 60.0 [29.5–141.8] %, $p < 0.001$), was significantly different between groups. Patients with an increase of FGF-19 after OGL were older (63.3 ± 12.5 vs. 58.1 ± 11.4 years, $p = 0.001$), and had fewer patients on statin therapy (34.3% vs. 52.4%, $p = 0.005$). Regarding glucose regulation status, more patients in the group with an increase of FGF-19 after OGL had normal glucose regulation (15.3% vs. 6.8%), but the difference did not reach statistical significance ($p = 0.104$). There was no significant difference in HbA_{1c}, FPG, and 2-h PG levels. However, fasting insulin, as well as HOMA-IR and HOMA-β, was lower in patients with an increase of FGF-19 after OGL.

Table 2 shows serum FGF-19 levels before and 2 h after OGL by age tertile, and status of glucose regulation, CAD, and statin treatment. Overall, there was a significant increase in serum FGF-19 after OGL (from 123 [78–201] to 141 [80–237] pg/ml, $p = 0.001$). However, FGF-19 significantly increased after OGL only in patients in the old age tertile (from 143 [98–209] to 189 [124–332] pg/ml, $p < 0.001$). We divided patients into different glucose regulation status, and revealed that FGF-19 significantly increased after OGL in patients with normal glucose regulation (from 117 [78–211] to 153 [106–325] pg/ml, $p = 0.014$), and, to a lesser extent, in patients with prediabetes (from 117 [73–179] to 123 [70–204] pg/ml, $p = 0.043$). However, FGF-19 did not change significantly after OGL in patients with newly diagnosed diabetes (from 181 [102–243] to 178 [111–275] pg/ml, $p = 0.139$). FGF-19 significantly increased after OGL irrespective of patients' CAD status. In patients treated with statin, FGF-19 did not change significantly after OGL (from 125 [86–196] to 128 [68–230] pg/ml, $p = 0.676$). In contrast, FGF-19 significantly increased after OGL (from 120 [78–207] to 145 [86–264] pg/ml, $p < 0.001$) in patients who were not on statin therapy.

Table 3 shows the results of linear regression analysis with serum FGF-19 increment after OGL as the dependent variable. Among the variables included in the univariate analysis, age was positively (β coefficient 2.97, 95% CI 1.45 to 4.49, $p < 0.001$) associated with