Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

High serum level of fibroblast growth factor 21 is an independent predictor of non-alcoholic fatty liver disease: A 3-year prospective study in China

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Background & Aims: Fibroblast growth factor 21 (FGF21), a hormone predominantly secreted by the liver, has been shown to be positively associated with the severity of non-alcoholic fatty liver disease (NAFLD) in cross-sectional studies. We investigated the prospective association of FGF21 with NAFLD development in a 3-year prospective study involving a population-based cohort comprising 808 Chinese subjects.

Methods: Serum FGF21 levels at baseline and follow-up were measured using an enzyme-linked immunosorbent assay. Independent predictors of NAFLD development were identified using multiple logistic regressions. The predicting accuracy of the models was evaluated using area under the receiver-operating characteristic (ROC) curves (AUCs).

Results: In subjects who had progressed to NAFLD, the baseline FGF21 concentration (319.12 pg/ml [172.65, 518.78]) was significantly higher than that in subjects who did not develop NAFLD (199.10 pg/ml [123.56, 322.80]) (p <0.001). At follow-up, significant increase of FGF21 level was observed in those subjects who developed NAFLD (p <0.05). Baseline FGF21 was an independent predictor of NAFLD (OR: 7.102 [95% CI 2.488–20.270]; p <0.001), together with body mass index (BMI) (OR: 1.489 [95% CI 1.310–1.691]; p <0.001). The ROC-AUC was 0.816 (95% CI 0.766–0.867) for the FGF21 Model, which was calculated with FGF21 and BMI. FGF21 Model <0.13 can be used to rule out (sensitivity = 85.71%, negative likelihood ratio = 0.23) and ⩾0.30 can be rule in (specificity = 86.34%, positive likelihood ratio = 3.66) ultrasonography-diagnosed NAFLD after 3 years.

Conclusions: High serum FGF21 concentration was an independent predictor of NAFLD in humans. The FGF21 Model and its cut-offs may be useful for early diagnosis and intervention of NAFLD.

Keywords: FGF21; NAFLD; Predictor.

Received 1 June 2012; received in revised form 29 October 2012; accepted 31 October 2012; available online 7 November 2012

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Abbreviations: FGF, fibroblast growth factor; NAFLD, non-alcoholic fatty liver disease; ROC, receiver-operating characteristic; AUC, area under the curve; OR, odds ratio; BMI, body mass index; PPAR, peroxisome proliferator-activated receptor; TG, triglyceride; IGT, impaired glucose tolerance; GGT, γ-glutamyltransferase; HDL-C, high density lipoprotein cholesterol; FPG, fasting plasma glucose concentration; 2hPG, 2-h plasma glucose concentration; HbA_{1c}, hemoglobin A1c; HOMA, homeostasis model assessment; FINS, fasting insulin concentration; ELISA, enzyme-linked immunosorbent assay; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate transaminase; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; FLI, fatty liver index.

Introduction

Three members of the fibroblast growth factor (FGF) family, including FGF19, FGF21 and FGF23, act as endocrine factors involved in hormone-like metabolic effects by interacting with FGF receptors [1–4]. FGF21, a polypeptide with 210 amino acid residues, has been shown to be an important regulator of glucose and lipid metabolism in animal models [2]. The liver is the primary source of circulating FGF21, and hepatic synthesis is driven by peroxisome proliferator-activated receptor (PPAR) α activation [5]. In addition, adipocytes are a secondary source of FGF21. Unlike hepatocytes, adipocytes make FGF21 in response to PPARγ agonists or feeding [6]. Transgenic mice with overexpression of FGF21 were resistant to diet-induced obesity and metabolic disturbance [2]. The therapeutic intervention with recombinant FGF21 resulted in a reduction of triglycerides (TG) to near normal levels in both *ob/ob* and *db/db* mice [2]. Systemic administration of FGF21 resulted in a significant decrease in hepatic steatosis in diet-induced obese mice [7]. On the other hand, *FGF21* knockout mice exhibit deficiency in ketogenesis, loss response to ketogenic diet, gain weight and develop hepatic steatosis [8].

Despite the multiple benefits of FGF21 on lipid homeostasis and hepatic steatosis, circulating FGF21 levels are elevated in animals with dietary and genetic obesity, suggesting the presence of FGF21 resistance [9]. In clinical studies, elevated FGF21 levels

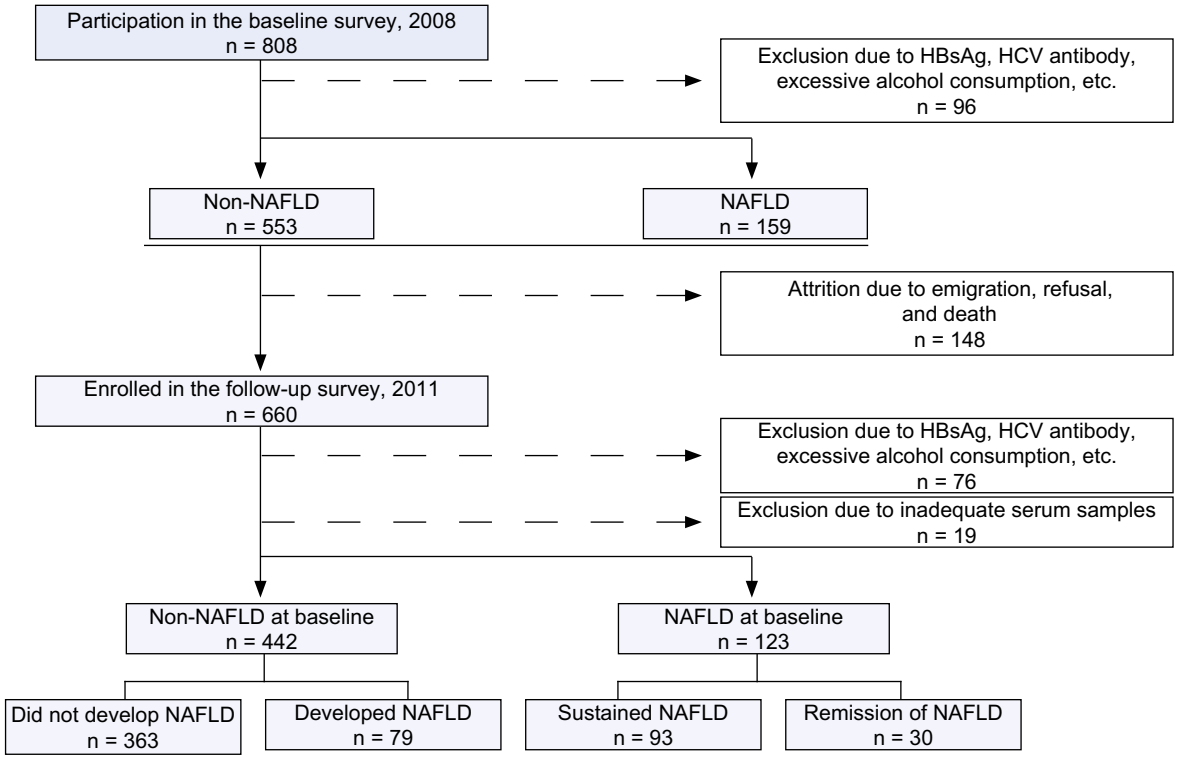

Fig. 1. Flow chart of the study population.

were observed in obese subjects and patients with hypertriglyceridemia, impaired glucose tolerance (IGT) and patients with type 2 diabetes [10–13]. In our previous study, γ-glutamyltransferase (GGT) was found to be independently associated with serum FGF21 in Chinese subjects, suggesting that the function of FGF21 is closely related to chronic liver injury [12]. Furthermore, several reports from us and others have demonstrated that serum FGF21 was elevated in patients with non-alcoholic fatty liver disease (NAFLD) [14–17]. In human liver tissues, FGF21 expression levels were also positively correlated with hepatic TG concentrations [14]. However, almost all these studies were of cross-sectional nature and cannot address the cause-effect relationship between FGF21 and NAFLD. In the present study, we investigated the prospective association between FGF21 and NAFLD in a 3-year follow-up study involving a population-based cohort comprising 808 Chinese subjects.

Patients and methods

Study subjects

This epidemiological survey was a multi-stage stratified study designed to assess the prevalence of related diseases in a community in Shanghai. From June to August 2008, a total of 808 subjects of Chinese origins (Han Chinese) aged from 20 to 79 years were enrolled in the study. From July to September 2011, the subjects were invited for follow-up assessments. Of the 808 subjects who initially participated in at baseline, 660 were enrolled in the follow-up study. The participants underwent comprehensive physical examinations, routine biochemical analyses of blood, 75-g oral glucose tolerance test, hepatitis B surface antigen, hepatitis C virus antibody and B ultrasonography. The participants completed a uniform questionnaire containing questions about the histories of present and past illness and medical therapy. Subjects with the following conditions were excluded from this study: acute or chronic virus hepatitis, drug-induced liver disease, current drinkers, ex-drinkers, biliary obstructive diseases, total parenteral nutrition, autoimmune hepatitis, Wilson's disease, known hyperthyroidism or hypothyroidism, presence of cancer, current treatment with systemic corticosteroids and pregnancy. Nineteen subjects with inadequate serum samples for the follow-up study were excluded. The study was approved by the human research ethics committee of the Shanghai Sixth People's hospital, following the principles of the declaration of Helsinki. Written informed consent was obtained from all subjects.

Clinical diagnosis of NAFLD and metabolic syndrome

Guidelines for the diagnosis of NAFLD proposed by the Asia–Pacific Working Party were used [18]. NAFLD was clinically defined as manifestations of B ultrasonography, ruling out the habit of drinking and the history of specific diseases that could result in fatty liver. Abdominal ultrasonography was performed by experienced radiologists who were blinded to clinical presentation and laboratory findings. Hepatic steatosis was defined as a diffuse increase of fine echoes in the liver parenchyma compared with that in the kidney or spleen parenchyma based on standard criteria.

Metabolic syndrome was defined according to the definition of Chinese Joint Committee for Developing Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults as having $\geqslant$3 of the following metabolic risk factors: (i) central obesity (waist circumference >90 cm for men and >85 cm for women), (ii) TG $\geqslant$1.70 mmol/L, (iii) fasting high-density lipoprotein cholesterol (HDL-C) <1.04 mmol/L, (iv) hypertension (sitting blood pressure $\geqslant$130/85 mmHg or on regular antihypertensive medications), (v) hyperglycemia defined as fasting glucose (FPG) $\geqslant$6.1 mmol/L and/or 2-h plasma glucose concentration (2hPG) $\geqslant$7.8 mmol/L or on hypoglycemic therapy for treatment of diabetes [19].

Anthropometric and biochemical measurements

Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Waist circumference was measured at the midpoint between the inferior costal margin and the superior border of the iliac crest on the midaxillary line. Body fat percentage was quantified with the TBF-410 Tanita Body Composition Analyzer (Tanita, Tokyo, Japan).