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Contribution of fibroblast growth factor 23 to Framingham risk score for identifying subclinical atherosclerosis in Chinese men

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KEYWORDS
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Abstract *Background and aims:* Fibroblast growth factor 23 (FGF23) was demonstrated to be involved in the occurrence and development of cardiovascular disease (CVD). The goal of the present study was to investigate the relationship between serum FGF23 levels and carotid intima-media thickness (C-IMT) in men with a low-to-moderate CVD risk.
Methods and Results: Subjects with normal kidney function were selected from the Shanghai Obesity Study. Serum FGF23 levels were determined by sandwich enzyme-linked immunosorbent assay. C-IMT was measured by ultrasonography. The Framingham risk score (FRS) was used to assess CVD risk. A total of 392 men with low CVD risk and 372 men with moderate CVD risk were enrolled. The recognition rate of an elevated C-IMT was 85.66% with the combination of a moderate CVD risk and high serum FGF23 levels, which was greater than that with either parameter alone (65.44% and 61.03%, respectively). Subjects with high serum FGF23 levels, and either low or moderate CVD risk, were more likely to have elevated C-IMT than those with low serum FGF23 levels and low CVD risk ($P = 0.014$ and 0.001, respectively). The serum FGF23 levels were independently and positively associated with C-IMT in subjects with low or moderate CVD risk (both $P = 0.007$).
Conclusion: In men with low-to-moderate CVD risk, serum FGF23 levels were associated independently and positively with C-IMT. As a complementary index, serum FGF23 levels strengthen the capacity of the FRS to identify subclinical atherosclerosis.

Abbreviations: AS, atherosclerosis score; BMI, body mass index; Ca, serum calcium; CHD, coronary heart disease; C-IMT, carotid intima-media thickness; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FGF23, fibroblast growth factor 23; FINS, fasting serum insulin; FPG, fasting plasma glucose; FRS, Framingham risk score; HbA1c, glycated hemoglobin A1c; HDL-c, high density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; LDL-c, low density lipoprotein cholesterol; Scr, serum creatinine; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; T2DM, type 2 diabetes mellitus; W, waist circumference; 2hPG, 2-hour plasma glucose.

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Introduction

In China, the prevalence of cardiovascular disease (CVD) is continuously increasing with current trends in socioeconomic prosperity, changes in lifestyle, the ageing population, and rapid urbanization, and will remain on an upward trend during the next 10 years. Early screening and intervention for individuals with increased CVD risk should be enforced urgently as an effective strategy for the prevention of CVD [1]. The onset and development of CVD are characterized by atherosclerosis and atherothrombosis, of which the most important physiopathological change is the presence of endothelial dysfunction in the early stage [2]. In the pathogenesis and progression of atherosclerosis, complicated interactions of genetic and environmental factors result in vascular intimal thickening, which is especially manifested in the carotid artery. Therefore, carotid intima-media thickness (C-IMT) is one of the most appropriate screening parameters for identifying subclinical atherosclerosis.

Fibroblast growth factor (FGF) 23, categorized as a bone-derived hormone, is generally believed to be a primary regulator of mineral homeostasis in vivo [4]. Theoretically, the target organ of FGF23 requires the coexpression of FGF receptors and αklotho. Given the established klotho expression in cardiovascular system, the role that FGF23 plays in the development of CVD has attracted increasing interest [4]. Recent evidence from basic research indicates that FGF23 is involved in endothelial dysfunction and vascular calcification [5,6]. A study in Sweden suggested FGF23 as independent predictor of cardiovascular events, including myocardial infarction, stroke, and all-cause mortality [7]. Additionally, the Ludwigshafen Risk and Cardiovascular Health Study, a prospective study with a median follow-up of 9.9 years, demonstrated that serum FGF23 levels could predict all-cause and cardiovascular mortality, independent of the established cardiovascular risk factors [8]. These finding from observational studies suggest that FGF23 plays a critical role in the occurrence and development of CVD. The positive relationship between circulating FGF23 levels and C-IMT, as well as the presence and severity of carotid plaque, has been confirmed in several clinical studies [9–12]. However, Reyes-Garcia et al. [13] reported a decrease in circulating FGF23 levels among diabetes patients with an abnormal C-IMT. Due to the inconsistencies in these findings, the association between serum FGF23 levels and subclinical atherosclerosis remains to be determined.

The Framingham risk score (FRS) is used to assess individuals' 10-year CVD risk. Individuals with a 10-year CVD risk >20%, clinical carotid artery disease, and diabetes are defined as having coronary heart disease (CHD) risk equivalents [14]. With a focus on the identification of atherosclerosis in the early stage, the present study excluded individuals with established cardiovascular and cerebrovascular diseases as well as those with CHD risk equivalents. The goal of the present study was to investigate the relationship between serum FGF23 levels and subclinical atherosclerosis in individuals with low-to-moderate CVD risk. In order to eliminate the influence of gender differences, the study population was limited to men, who were believed to bear a higher CVD risk than women.

Methods

Subjects

Between December 2009 and December 2011, a total of 764 men with normal kidney function (estimated glomerular filtration rate [eGFR] ≥60 mL/min/1.73 m^2) were selected from the Shanghai Obesity Study [15]. Subjects with established cardiovascular or cerebrovascular diseases (myocardial infarction, cardiomyopathy, valvular heart disease, congenital heart disease, or stroke), diabetes mellitus (based on the 1999 World Health Organization classification criteria [16]), carotid plaque (C-IMT >1.5 mm or focal structure penetrating the arterial lumen by at least 0.5 mm or 50% of the C-IMT [17]), hepatic dysfunction (acute vital hepatitis and advanced fibrosis or cirrhosis), hyperthyroidism or hypothyroidism, hypercalcemia, acute infection, tumors, or psychiatric disease as well as those currently on lipid-lowering therapy or replacement therapy with systemic corticosteroids or thyroxine were excluded. All participants provided complete clinical data and finished a standardized questionnaire to provide information on their disease history, medication usage, family history, and smoking status.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital. All subjects provided written informed consent before participation in the study.

Anthropometric and biochemical assessments

Anthropometric parameters (weight, height, waist circumference [W], and resting blood pressure) were determined as previously described [15]. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m).

Blood samples were collected after a 10-h overnight fast to measure serum FGF23 levels and other biochemical indices including fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), fasting serum insulin (FINS), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), C-reactive protein (CRP), serum creatinine (Scr), and serum calcium (Ca) levels. The 2-h plasma glucose (2hPG) was determined at 2 h after a 75-g oral glucose tolerance test. All laboratory measurements were performed using standard methods [15]. Serum FGF23 levels were determined using the Kainos sandwich enzyme-linked immunosorbent assay kit (Kainos Laboratories Inc., Tokyo, Japan), for which the intra- and inter-assay coefficients of variations are 5.6% and 8.2%, respectively. The Chronic Kidney Disease Epidemiology Collaboration equation was recommended for calculation of eGFR [18].

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