Am J Transl Res 2018;10(9):2958-2966
www.ajtr.org /ISSN:1943-8141/AJTR0079183

Original Article

A high circulating FGF21 level as a prognostic marker in patients with acute myocardial infarction

Haifeng Chen*, Nan Lu*, Meifan Zheng

*Department of Cardiology, Fujian Provincial Clinical College, Fujian Medical University, Fuzhou 350001, Fujian, P. R. China. *Equal contributors and co-first authors.*

Received May 7, 2018; Accepted August 7, 2018; Epub September 15, 2018; Published September 30, 2018

Abstract: Objective: The purpose of this study was to examine the level of serum FGF21 in acute myocardial infarction (AMI) and to explore the association between serum FGF21 and major adverse cardiovascular events in AMI patients. Methods: A total of 238 Chinese patients were recruited for this study between January 2016 and June 2016, including 183 AMI patients and 55 patients without AMI were enrolled in this study. The level of serum FGF21 was measured by ELISA. Patients were followed-up after admission using a standardized protocol that included Outpatient follow-up and telephone contacts to record the Major Adverse Cardiovascular Events (MACEs). Finally, 165 patients were enrolled and followed up during the period of 24 months. Results: Circulating FGF21 level was elevated in the AMI patients compared to control ($P < 0.05$). Multivariate linear regression analysis showed that cTnI ($\beta = -0.001$, 95% CI = 0.021-0.001, $P = 0.002$), fibrinogen ($\beta = -0.055$, 95% CI = 0.098-0.013, $P = 0.011$) and hyperlipidemia ($\beta = 0.129$, 95% CI = 0.014-0.243, $P = 0.011$) were the independent risk factors for the serum of FGF21 in AMI patients. After follow-up, A Kaplan-Meier analysis showed that the all-cause mortality rate was not significantly different between the two groups ($P = 0.4146$). Meanwhile the rate of cardiovascular events was significantly higher in the high-FGF21 group than in the low-FGF21 group ($P = 0.0399$). In the multivariate Cox proportional hazards regression model suggested that the predictive independent risk factors for the occurrence of MACEs were FGF21 ≥ cut-off (HR: 1.637; 95% CI: 1.357-3.647, $P = 0.029$) and D-Dimer (HR: 1.420; 95% CI: 1.069-3.014, $P = 0.046$). Conclusion: Circulating FGF21 level is elevated in the AMI patients. In AMI patients, cTnI, fibrinogen and hyperlipidemia are the inde pendent risk factors for the serum of FGF21. Higher circulating FGF21 level is associated with increased MACEs rate. This study suggests that circulating FGF21 level may be a predictive marker of the clinical outcomes in AMI patients.

Keywords: FGF21, acute myocardial infarction, major adverse cardiovascular events

Introduction

In recent years, biomarkers have been widely studied in attempts to understand different cell functions and their role in cardiovascular disease (CVD). A number of biomarkers have been proved to be excellent predictors of outcome in patients with acute myocardial infarction (AMI). The family of fibroblast growth factors (FGFs) is a hormone-like factor that modulates a number of metabolic processes, including cell proliferation, development and hyperplasia in vitro and vivo. FGF21 plays a significant role in those processes including endothelial cell apoptosis, myocardial ischemia protection and so on [5, 11]. Under the oxidative stress, myocardial cells can secrete FGF21, which can protect from damage myocardial hypertrophy induced by isoproterenol [16]. Recent studies show that there were a large amount of FGFR1 receptors and β Klotho distributing in cardiac myocytes and FGF21 also plays an important role in the field of cardiovascular disease [3, 4].

Moreover, FGF21 was identified as an independent factor of acute myocardial infarction [22]. Although there are data to demonstrate that FGF21 might be a marker of coronary artery Disease, the role of FGF21 in the prognostication of AMI patients is still unclear. The aim of our study is to explore the relationship between FGF21 and clinical major adverse cardiovascular events in Chinese AMI patients.

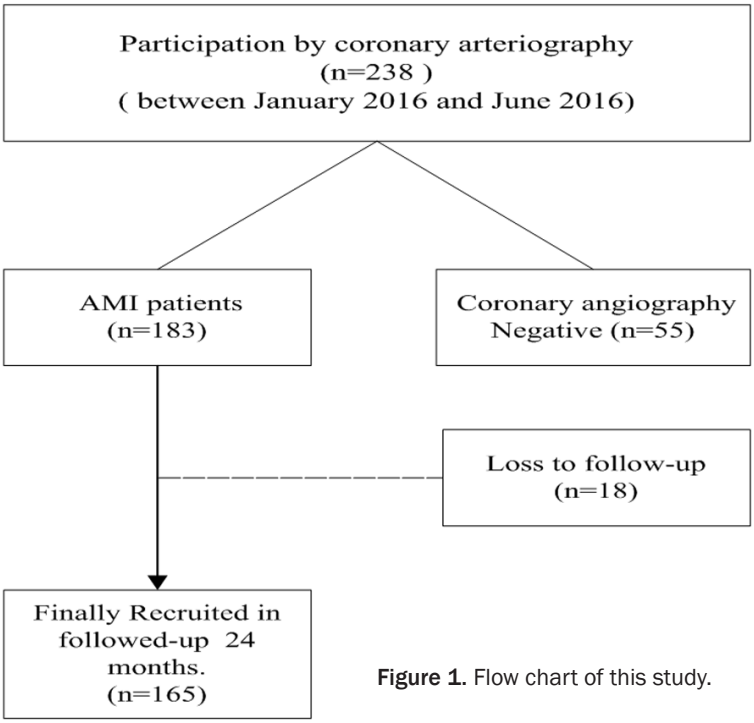

Figure 1. Flow chart of this study.

Materials and methods

Study population

Totally 238 Chinese patients visiting the Department of Cardiology in Fujian Provincial Hospital for examination by coronary arteriography were recruited for this study from January 2016 and June 2016. After the coronary angiography, a total of 183 AMI patients were enrolled in this study (including ST-segment and non-ST-segment elevation). The control group included 55 patients with chest pain, whose coronary angiography and Troponin I (cTn I) were negative.

The included patients were Chinese patients aged over 18 years old in whom AMI was diagnosed according to published criteria. Exclusion criteria was the presence of acute or chronic viral hepatitis, fatty liver, drug or alcoholic-induced liver disease, a history of valvular heart disease, cardiomyopathy, myocarditis, congenital heart disease, peripheral vascular disease, or infective endocarditis, or of a combination of these ailments, acute or chronic kidney diseases (CKD stage 3-5), total parenteral nutrition, alcoholism, hyper-or hypothyroidism, cancer, current treatment with systemic corticosteroid, fenofibrate, metformin or thiazolidane theatment [13, 14].

The local Ethics Committee of Fujian Provincial Hospital has approved this study, the Ethics research number (K2016-01-001) (Supplemental Materials) and all enrolled subjects provided informed consent.

Anthropometric and biochemical parameter

The base characteristics including height, weight and Blood pressure (BP) were measured. The body mass index (BMI) and mean arterial pressure (MAP) were calculated respectively. Smoking status was also recorded.

At hospital admission, Blood samples were measured and obtained 12 hours in the Department of Clinical Laboratory. The concentrations of glucose, total cholesterol, triglycerides, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, apolipoprotein (a), apolipoprotein (b), Serum creatinine, alkaline phosphatase (ALT), D-dimer two polymer and fibrinogen were measured using the Cobas 8000 biochemical autoanalyzer (Roche, Tokyo, Japan). Glycated hemoglobin A1c (HbA1c) was measured by high-performance liquid chromatography using HA-8180 automatic glycosylated hemoglobin analyzer (arkray, Tokyo, Japan).

Specific FGF21 ELISA

Plasma was collected with the patient in the fasting state on the next morning after hospitalization. Blood was collected and immediately processed. Peripheral blood was centrifuged at 2000 rpm for 10 minutes. Serum was collected and stored at -70°C until analysis. Serum concentrations of FGF21 were measured with a sandwich ELISA and a biotin-labelles antibody with the RD191108200R human FGF21 ELISA Kit (Biovendor Laboratory Medicine, Inc. Brno, Czech Republic). The intra-assay variation among the duplicates was < 4%. All of the coefficient of variation (CV) of inter-assay for quantitative detection were less than 5%.

Table 1. Clinical and biochemistry characteristics of participants

Variables	Control (N = 55)	AMI (N = 183)	*P* valve
Age (years)	66.9 ± 9.5	63.6 ± 10.9	0.053
Gender (male) (%)	33 (60)	155 (84.7)**	**<0.001**
BMI (kg/m^2)	23.5 ± 2.3	23.9 ± 2.9	0.347
Diabetes [n (%)]	10 (18.2)	56 (30.6)	0.071
Hypertension [n (%)]	33 (60)	74 (40.4)*	**0.011**
Hyperlipidemia [n (%)]	21 (38.2)	34 (18.6)**	**0.002**
AMI history [n (%)]	0	25 (13.7)**	**0.004**
Smoker [n (%)]	17 (30.9)	115 (62.8)**	**<0.001**
Medication [n (%)]			
Anti-hypertensive drugs	15 (27.3)	47 (25.7)	0.814
Anti-diabetic drugs	2 (3.6)	14 (5.1)	0.297
Anti-hyperlipidemic drugs	2 (3.6)	7 (3.8)	0.949
Systolic blood pressure (mmHg)	129.0 ± 19.7	128.7 ± 19.8	0.400
Diastolic blood pressure (mmHg)	74.4 ± 10.5	75.9 ± 11.9	0.387
Mean arterial pressure (mmHg)	95.5 ± 11.9	93.5 ± 12.9	0.311
Fast plasma glucose (mmol/L)	5.6 ± 1.5	6.2 ± 2.1*	**0.026**
HbA1c (%)	6.2 (5.8, 6.7)	6.0 (5.4, 6.9)	0.870
TG (mmol/L)	1.4 ± 0.6	1.5 ± 0.9	0.244
TC (mmol/L)	4.2 ± 1.0	4.3 ± 1.0	0.768
HDL-C (mmol/L)	1.2 ± 0.3	1.0 ± 0.3**	**<0.001**
LDL-C (mmol/L)	2.6 ± 0.8	2.5 ± 0.9	0.199
Apolipoprotein A (g/L)	1.3 ± 0.2	1.2 ± 0.4	0.090
Apolipoprotein B (g/L)	0.8 ± 0.2	0.9 ± 0.3*	**0.014**
Albumin (g/L)	42.9 ± 4.3	39.5 ± 4.3**	**<0.001**
ALP (U/L)	76.4 ± 25.0	79.5 ± 38.5	0.572
Creatinine (μmol/L)	73.3 ± 18.8	81.6 ± 26.0*	**0.028**
D-Dimer (mg/L)	0.4 ± 0.2	0.7 ± 1.1*	**0.016**
Fibrinogen (g/L)	3.3 ± 0.8	4.2 ± 1.2**	**<0.001**
cTnI (ng/mL)	0.01 (0, 0.01)	5.6 (1.1, 28.3)**	**<0.001**
NT-proBNP (pg/mL)	124.0 (59.0, 200.9)	678.0 (278.0, 1862.0)**	**<0.001**
FGF21 (pg/mL)	121.0 (57.1, 179.6)	143.8 (75.2, 254.3)**	**<0.001**

Data were expressed as mean ± SD or median (25th and 75th percentile). *P* values in bold were statistically significant in the Student t-test or Chi-square test. AMI, acute myocardial infarction; ALP, alkaline phosphatase; BMI, body mass index; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; NT-proBNP, N-terminal pro-brain natriuretic peptide; cTnI, cardiac Troponin I; FGF21, fibroblast growth factor 21. (AMI group vs control group, *P < 0.05; **P < 0.01).

Coronary angiography

All participated patients were subjected to coronary angiography. The arteriography analysis was conducted by two experienced interventional cardiologists, who were blinded to the study's objective and design. A patient was considered to have CAD when a stenotic lesion resulting in a 50% or greater reduction in lumen diameter existed in at least one of the coronary arteries. According to the number of stenosis was detected in ≥ 50% of the lumen diameter of a coronary artery, we also divided it into single-vessel lesion, double vessel lesion and multi-vessel lesion.

Follow-up and endpoints definitions

Patients were followed-up after admission using a standardized protocol that included Outpatient follow-up and telephone contacts to record the Major Adverse Cardiovascular Events (MACEs). Endpoints were all-cause mortality and the occurrence of MACEs, including car-

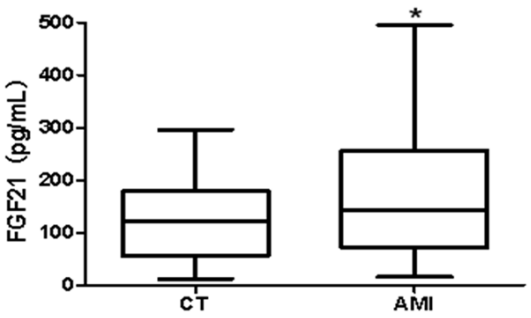

Figure 2. Serum FGF21 levels in patients with acute myocardial infarction (n = 183), compared with control patients (n = 55). Values are shown as medians with the interquartile range. Data were log-transformed before analysis, *P < 0.01.

diac death and nonfatal outcomes: recurrent myocardial infarction (re-MI), target vessel revascularization (TVR) or re-admission due to advanced heart failure.

Death was defined as all causes of death. Re-MI was defined by the presence of recurrent ischemic symptoms or EKG changes accompanied with t least one cardiac serum biomarker e.g. troponin I rises above the upper limit of 99% normal reference values measured during hospitalization. We defined TVR as the repeat PCI performed in the revascularization vessel during the index admission. Advanced heart failure requiring re-admission was diagnosed on the basis of clinical symptoms, NT-proBNP and echocardiography.

Statistical analysis

The version 19.0 SPSS software suite was used for all statistical analyses. All distributed data was expressed as mean ± standard deviation, and skewed data was expressed as median (inter-quartile range). Inter-group comparisons of clinical values were performed with student's t test (normally distributed data) or the Mann-Whitney U test. Inter-group comparisons of categorical variables were analyzed using by the chi-square test. Multivariate linear regression analysis was performed to the correlation analysis. The correlation of two factors was assessed by Spearman or Kendall correlation test. The cut-off valve for FGF21 as a predictor for occurrence of MACEs was calculated by receiving operating characteristics (ROC) analysis. We then assessed the impact of the serum FGF21 levels on the cumulative patient and cardiovascular event-free survival rates according to the Kaplan-Meier method. Cox regression models were used to analyze the relationships between MACEs and the serum FGF21 levels. All reported values were two-tailed and considered statistically significant for P < 0.05.

Results

Clinical characteristics

A total of 238 patients were enrolled in this study and represented by 183 patients with AMI and 55 patients as control group. The flow chart of group in this follow-up study is **Figure 1**. The mean age of participates was 64.4 ± 10.7 years old. For the established cardiovascular risk factors, the proportions of males (84.7%), smokers (62.8%) and diabetics (30.6%) were much larger in AMI group than in control group. In AMI group, lower proportion of patients were taking medication. The proportions of taking anti-hypertensive drugs, Anti-hyperlipidemic drugs and Anti-diabetic drugs were respectively 25.7%, 3.8% and 5.1%. The clinical characteristics analysis showed the AMI group had significantly higher fasting blood glucose, serum creatinine, Apo B, fibrinogen, NT-proBNP, cTnI, D-dimer (all P < 0.05) and lower HbA1c, HDL-C, albumin compared with control group. Meanwhile, age, BMI, medication, systolic blood pressure and diastolic blood pressure, HbA1c, TC, TG, LDL-C, Apo A, ALP and other clinical parameters were not different between this two groups (**Table 1**). As seen in **Figure 2**, serum FGF21 level was elevated in the AMI group compared to control group [143.8 (75.2-254.3) vs 121.0 (57.1-179.6), P < 0.05].

Multivariate linear regression model for FGF21

In the spearman correlation analysis, serum FGF21 levels correlated negatively with Fibrinogen and HDL-C (r = -0.192, P = 0.009; r = -0.149, P = 0.044), positively correlated with HbA1C and triacylglycerol (r = 0.169, P = 0.014; r = 0.181, P = 0.024). The stepwise selection method was used to create a multivariate linear regression model for FGF21 (**Table 2**). Multivariate linear regression analysis show that cTnI (β = -0.001, 95% CI = 0.021-0.001, P = 0.002), fibrinogen (β = -0.055, 95% CI = 0.098-0.013, P = 0.011) and hyperlipidemia (β = 0.129, 95% CI = 0.014-0.243, P = 0.011) are the independent risk factors for the serum of FGF21 in AMI patients.

Table 2. Independent factors of FGF21 were analyzed by multivariate linear regression analysis

	β	S.E	95% CI	*P* value
cTnI	-0.001	0.001	1.021-1.058	0.002
Fibrinogen	-0.055	0.022	0.098-0.013	0.011
Hyperlipidemia	0.129	0.058	0.014-0.243	0.028

β: standardized regression coefficient; S.E: standard errors; OR: odds ratio; 95% CI, 95% confidence interval.

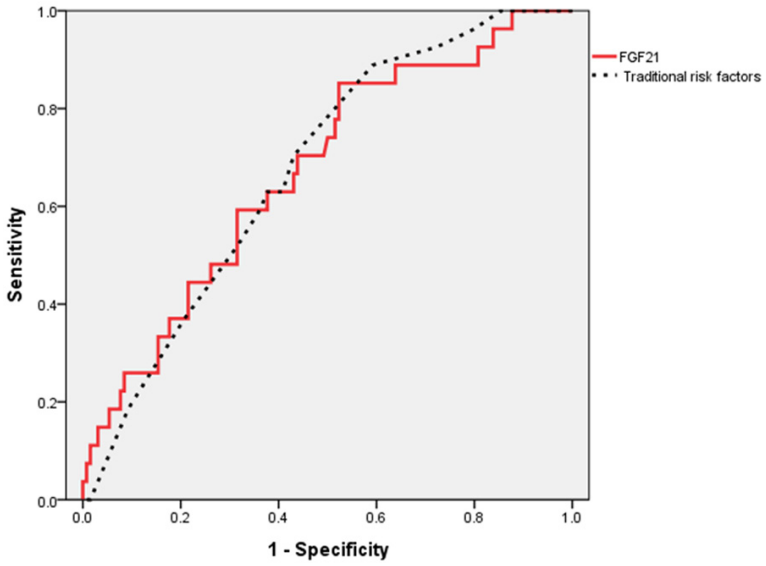

Figure 3. The ROC curve between FGF21 and traditional cardiovascular risk factors in predicting occurrence of MACEs.

Predictive value and prognostic value of FGF21

Incidence of follow-up in AMI patients: A total of 183 patients were hospitalized during the study period. Among them, 18 patients refused to participate. Only 165 patients were enrolled and followed up during the period of 24 months. The total incidence of all-cause mortality was 9.1% (15 of 165 patients), including seven patients cardiac death and eight patients non-cardiac death. Additionally, the incidence of Major Adverse Cardiovascular Events (MACEs) was 18.2% (30 of 165 patients). There were 2 patients recurrent myocardial infarction, 13 patients re-admission due to advanced heart failure, 8 patients suffered the TVR and 7 patients had cardiac death.

ROC analysis: The receiver operating characteristic (ROC) curves of FGF21 and traditional cardiovascular risk factors in predicting MACEs were presented in **Figure 3**, and pairwise comparison between areas under ROC curves (AUCs) were performed. the model consisting of traditional cardiovascular risk factors such as age, BMI smoking status, hypertension, diabetes and hyperlipidemia showed a 0.676 AUC (95% CI, 0.577-0.775, P = 0.04) with a 88.9% sensitivity and 59.2% specificity.

Contribution of Serum FGF21 Levels in discriminating MACEs was assessed by receiver-operating characteristic analysis which showed that the serum FGF21 levels had a 0.672 area under curve (AUC) (95% CI, 0.564-0.780, P = 0.005) with a 80.0% sensitivity and 50.4% specificity for predicting MACEs. After calculation of the Youden index, the cut-off value of a FGF21 for predicting the occurrence of MACEs produced was 123.0 pg/mL.

Overall survival and MACE-free survival analysis

In 183 AMI patients, the serum FGF21 concentrations ranged from 16.24 to 925.11 pg/mL (median: 143.78, [IQR]: 75.2-254.3 pg/mL). The subjects were categorized as follows: low-FGF21 group: (subjects with circulating FGF21 level < cut-off value) and high-FGF21 group: subjects with circulating FGF21 level ≥ cut-off value).

According to the serum FGF21 concentrations, the subjects were categorized as low-FGF21 group (n = 73) and high-FGF21 group (n = 92). After the follow-up, four patients (two congestive heart failure, one re-myocardial infarction, one sudden cardiac death) in the low-FGF21 group and six patients (four heart failure, two sudden cardiac death) in the high-FGF21 died of cardiac events. Meanwhile there were two patients (one pneumonia, one esophageal cancer) in the low-FGF21 group and three patients (one leukemia, one stroke, one pulmonary embolism) in the high-FGF21 group died of non-

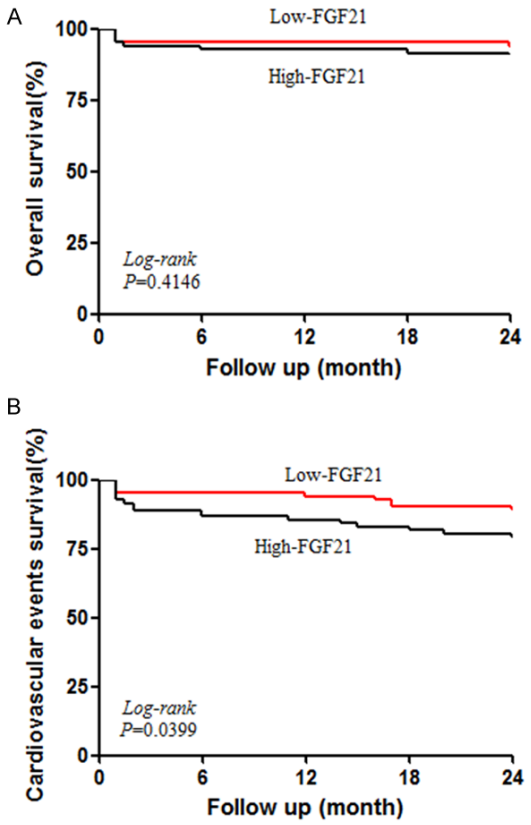

Figure 4. Kaplan-Meier curve for cumulative probability of different clinical outcomes.

cardiovascular events. A Kaplan-Meier analysis showed that the all-cause mortality rate was not significantly different between the two groups [9.8% (n = 9) vs 8.3% (n = 6), log-rank, P = 0.4146] (**Figure 4A**). Furthermore, the cardiac death rate was similar between the two groups [6.5% (n = 6) vs 5.4% (n = 4), log-rank, P = 0.826].

Meanwhile, we also found that nine patients (congestive heart failure, n = 3; re-infarction, n = 1; TVR, n = 1; cardiac death, n = 4) in the low-FGF21 group and twenty-one patients (congestive heart failure, n = 10; re-infarction, n = 2; TVR, n = 3; cardiac death, n = 6) in the high-FGF21 group experienced MACEs. A Kaplan-Meier analysis showed the rate of cardiovascular events was significantly higher in the high-FGF21 group than in the low-FGF21 group [24.4% (n = 20) vs 12.1% (n = 10), log-rank, P = 0.0399] (**Figure 4B**).

The Kaplan-Meier analysis showed that the mortality rate was not different between the two groups (Log-rank, *P* = 0.4146) (**Figure 4A**). while the MACE-free survival rate was significantly higher in the low-FGF21 group than in the high-FGF21 group (Log-rank, *P* = 0.0399) (**Figure 4B**).

A univariate Cox regression analysis showed that age, history of hyperlipideia, high total cholesterol, low LDL-cholesterol, higher D-Dimer and FGF21 were predictive for the Cardiovascular events cardiovascular events. In the multivariate Cox proportional hazards regression model including age, gender, BMI, diabetes history, hypertension history, history of hyperlipideia, LDL-c, HDL-c D-Dimer, TG, TC, Fibrinogen, FGF21 ≥ 123 (pg/mL)) suggested that the predictive independent risk factors for the occurrence of MACEs were FGF21 ≥ 123 (pg/mL) (HR: 1.637; 95% CI: 1.357-3.647, P = 0.029) and D-Dimer (HR: 1.420; 95% CI: 1.069-3.014, P = 0.046). Higher circulating FGF21 level and D-Dimer level were associated with a higher MACEs rate (**Tables 3**, **4**).

Discussion

FGF21 is a novel polypeptide ligand that has been shown to play a pivotal role in the regulation of glucose homeostasis and lipid metabolism [15, 17]. After binding to the FGF receptor and β-Klotho, FGF21 activates the Mitogen-Activated Protein Kinase (MAPK) signaling pathway and enhances glucose uptake and ketogenesis. The heart was traditionally not regarded as a target or source of FGF21 because of modest expression of FGF21 and β-Klotho. However, emerging evidence suggests that the cardiomyocyte secreted FGF21 as an autocrine factor to protect the heart from adverse cardiac remodeling. Additionally, FGF21 was found to enhance cholesterol efflux mediated by LXRα-dependent ATP binding cassette (ABC) A1 and G1, which may have a protective effect against atherosclerosis [10]. Therefore, the anti-atherosclerosis function of FGF21 may provide both direct and indirect effects through the direct inhibition of apoptosis of the endotheliocyte and the indirect improvement of metabolism of glucose and serum lipid.

Many studies had shown that FGF21, as a potential biomarker, played an important role in cardiovascular diseases. FGF21 was elevated in heart failure with preserved LV ejection fraction (HFpEF) and associated with left ventricular diastolic dysfunction [1]. Researchers found

Table 3. Univariate Cox regression of cardiovascular events

Variable	Major Adverse Cardiovascular events	
	HR (95% CI)	*P* value
Age (years)	1.042 (1.005-1.080)	0.025
Gender (male)	0.488 (0.217-1.0970	0.082
BMI (kg/m^2)	0.985 (0.871-1.114)	0.811
Diabetes history	1.734 (0.825-3.643)	1.734
Hypertension history	1.925 (0.901-4.113)	0.091
History of Hyperlipideia	0.379 (0.131-1.095)	0.044
Smoking	0.677 (0.329-1.394)	0.29
HDL-c (mmol/L)	0.237 (0.053-1.064)	0.06
LDL-c (mmol/L)	0.547 (0.35-0.856)	0.008
TG (mmol/L)	0.569 (0.294-1.102)	0.094
TC (mmol/L)	1.528 (0.356-0.782)	0.001
D-Dimer (mg/L)	1.526 (1.174-1.983)	0.002
Fibrinogen (g/L)	0.981 (0.737-1.305)	0.893
FGF21 ≥ 123 (pg/mL)	1.914 (1.142-3.207)	0.014

HR, hazard ratio; 95% CI, 95% confidence interval.

Table 4. Multivariate Cox regression of cardiovascular events

Variable	Major Adverse Cardiovascular events	
	HR (95% CI)	*P* value
Age (years)	1.013 (0.976-1.051)	0.500
Gender (male)	0.520 (0.213-1.267)	0.150
LDL-c (mmol/L)	0.756 (0.449-1.274)	0.294
D-Dimer (mg/L)	1.420 (1.069-3.014)	0.046
FGF21 ≥ 123 (pg/mL)	1.637 (1.357-3.647)	0.028

HR, hazard ratio; 95% CI, 95% confidence interval.

circulating FGF21 was significantly elevated in atrial fibrillation patients which may be associated with atrial remodeling [19]. Several studies had demonstrated that FGF21 may play a physiological role in improving endothelial cell apoptosis and in regulating atherosclerosis [7]. Chow found that there was a positive correlation between FGF21 and carotid atherosclerosis and FGF21 was an independent risk factors for carotid atherosclerosis [2]. Lin et al found that serum FGF21 was significantly elevated in the coronary artery disease (CAD) patient. Multivariate linear regression analysis found that FGF21 correlated independently with CAD occurrence [12]. Shen [18] found that elevated serum FGF21 was an independent risk factor for CAD in 233 patients. However, only a few study analyzed the correlation between FGF21 and AMI. In our study, FGF21 level was elevated in the AMI group compared with control group [143.8 (75.2-254.3) vs 121.0 (57.1-179.6) ($P < 0.05$)]. In the spearman correlation analysis, serum FGF21 levels correlated negatively with Fibrinogen and HDL-C ($r = -0.192$, $P = 0.009$; $r = -0.149$, $P = 0.044$), positively correlated with HbA1C and triacylglycerol ($r = 0.169$, $P = 0.014$; $r = 0.181$, $P = 0.024$). Multivariate linear regression analysis showed that cTnI ($\beta = -0.001$, 95% CI = 0.021-0.001, $P = 0.002$), fibrinogen ($\beta = -0.055$, 95% CI = 0.098-0.013, $P = 0.011$) and hyperlipidemia ($\beta = 0.129$, 95% CI = 0.014-0.243, $P = 0.011$) were the independent risk factors for the serum of FGF21 in AMI patients. More and more research results found FGF21 showed a close relationship with cardiovascular diseases.

Several studies also indicated that FGF-21 might function as a critical metabolic hormone in metabolic related diseases [6, 8, 9, 21]. FGF-21 was a hormone-like factors which was identified as a potent metabolic regulator in the recent years. The researchers found that circulating FGF21 was significantly elevated in metabolic related diseases [20]. Although it had been reported that FGF21 can improve insulin-sensitivity and exert beneficial effects on lipid metabolism, its role as a prognostic factor in cardiovascular disease had not been analyzed so far. Recent clinical studies had reported that the correlation between serum FGF21 and cardiovascular disease, but very few reports had investigated FGF21 as a predictive marker of the clinical outcomes. Our study showed that the rate of 24-months cardiovascular events was significantly higher in the high-FGF21 group than in the low-FGF21 group ($P = 0.0399$). In the multivariate Cox proportional hazards regression model, including age, gender, History of Hyperlipideia, LDL-c, D-Dimer, TC and FGF21 ≥ 123 pg/mL, the predictive independent risk factors for the occurrence of MACEs were FGF21 ≥ 123 pg/mL (HR: 1.637; 95% CI: 1.357-3.647, $P = 0.028$) and D-Dimer (HR: 1.420; 95% CI: 1.069-3.014, $P = 0.046$). Higher circulating FGF21 level is associated with increased MACEs rate. Although our results did not support FGF21 to replace the role of cTnI, the

strong association between FGF21 and acute myocardial infarction supported the findings of previous animal studies and provided us novel insight of how metabolic regulators affect the progression of cardiovascular disease and its clinical outcomes.

There were some limitations in our study. Firstly, our study population was composed of Chinese middle-and elderly patients presenting at a single hospital. The sample size was relatively inadequate and came from a single center. As a novel member of the endocrine FGF subfamily, the mechanisms of FGF21 in the cardiovascular system are still unclear, more multi-centers studies should be considered to resolve the controversy problem. In addition, correlation analysis is likely to be affected by a variety of uncorrected confounding factors present in daily life. Furthermore, our finding of the association between serum FGF21 and AMI patients' prognosis remains to be confirmed in other population-based studies involving even larger sample sizes and a wider multi-centers study.

Conclusions

We conclude circulating FGF21 level was elevated in the AMI patients compared to control. In AMI patients, cTnI, fibrinogen and hyperlipidemia were the independent risk factors for the serum of FGF21. Higher circulating FGF21 level is associated with increased MACEs rate. This study suggests that circulating FGF21 levels may be a predictive marker of the clinical outcomes.

Acknowledgements

This work was supported by National Natural Science Foundation of China (81470021). It was also supported by the Key Project of Cultivating Young Talent in Fujian provincial health and family planning commission (2016-ZQN-8).

Disclosure of conflict of interest

None.

Address correspondence to: Haifeng Chen, Department of Cardiology, Fujian Provincial Clinical College, Fujian Medical University, 134 Dongjie, Fuzhou 350001, Fujian, P. R. China. Tel: +8613705930769; E-mail: drchf1975@126.com

References

[1] Chou RH, Huang PH, Hsu CY, Chang CC, Leu HB, Huang CC, Chen JW, Lin SJ. Circulating fibroblast growth factor 21 is associated with diastolic dysfunction in heart failure patients with preserved ejection fraction. Sci Rep 2016; 6: 33953.

[2] Chow WS, Xu A, Woo YC, Tso AW, Cheung SC, Fong CH, Tse HF, Chau MT, Cheung BM, Lam KS. Serum fibroblast growth factor-21 levels are associated with carotid atherosclerosis independent of established cardiovascular risk factors. Arterioscler Thromb Vasc Biol 2013; 33: 2454-9.

[3] Domouzoglou EM, Naka KK, Vlahos AP, Papafaklis MI, Michalis LK, Tsatsoulis A, Maratos-Flier E. Fibroblast growth factors in cardiovascular disease: the emerging role of FGF21. Am J Physiol Heart Circ Physiol 2015; 309: H1029-38.

[4] He B, Ge H, Yang F, Sun Y, Li Z, Jiang M, Fan Y, Pu J, Shen X. A novel method in the stratification of post-myocardial-infarction patients based on pathophysiology. PLoS One 2015; 10: e0130158.

[5] Holland WL, Adams AC, Brozinick JT, Bui HH, Miyauchi Y, Kusminski CM, Bauer SM, Wade M, Singhal E, Cheng CC, Volk K, Kuo MS, Gordillo R, Kharitonenkov A, Scherer PE. An FGF21-adiponectin-ceramide axis controls energy expenditure and insulin action in mice. Cell Metab 2013; 17: 790-7.

[6] Hu Y, Liu J, Zhang H, Xu Y, Hong T, Wang G. Exenatide treatment decreases fasting fibroblast growth factor 21 levels in patients with newly diagnosed type 2 diabetes mellitus. Diabetes Metab 2016; 42: 358-363.

[7] Jin L, Lin Z, Xu A. Fibroblast growth factor 21 protects against atherosclerosis via fine-tuning the multiorgan crosstalk. Diabetes Metab J 2016; 40: 22-31.

[8] Jin QR, Bando Y, Miyawaki K, Shikama Y, Kosugi C, Aki N, Funaki M, Noji S. Correlation of fibroblast growth factor 21 serum levels with metabolic parameters in Japanese subjects. J Med Invest 2014; 61: 28-34.

[9] Kohara M, Masuda T, Shiizaki K, Akimoto T, Watanabe Y, Honma S, Sekiguchi C, Miyazawa Y, Kusano E, Kanda Y, Asano Y, Kuro-O M, Nagata D. Association between circulating fibroblast growth factor 21 and mortality in end-stage renal disease. PLoS One 2017; 12: e0178971.

[10] Lin Z, Pan X, Wu F, Ye D, Zhang Y, Wang Y, Jin L, Lian Q, Huang Y, Ding H, Triggle C, Wang K, Li X, Xu A. Fibroblast growth factor 21 prevents atherosclerosis by suppression of hepatic sterol regulatory element-binding protein-2 and in-

duction of adiponectin in mice. Circulation 2015; 131: 1861-71.
[11] Lin Z, Tian H, Lam KS, Lin S, Hoo RC, Konishi M, Itoh N, Wang Y, Bornstein SR, Xu A, Li X. Adiponectin mediates the metabolic effects of FGF21 on glucose homeostasis and insulin sensitivity in mice. Cell Metab 2013; 17: 779-89.
[12] Lin Z, Wu Z, Yin X, Liu Y, Yan X, Lin S, Xiao J, Wang X, Feng W, Li X. Serum levels of FGF-21 are increased in coronary heart disease patients and are independently associated with adverse lipid profile. PLoS One 2010; 5: e15534.
[13] Nygaard EB, Vienberg SG, Orskov C, Hansen HS, Andersen B. Metformin stimulates FGF21 expression in primary hepatocytes. Exp Diabetes Res 2012; 2012: 465282.
[14] Ong KL, Rye KA, O'Connell R, Jenkins AJ, Brown C, Xu A, Sullivan DR, Barter PJ, Keech AC. Long-term fenofibrate therapy increases fibroblast growth factor 21 and retinol-binding protein 4 in subjects with type 2 diabetes. J Clin Endocrinol Metab 2012; 97: 4701-8.
[15] Planavila A, Redondo I, Hondares E, Vinciguerra M, Munts C, Iglesias R, Gabrielli LA, Sitges M, Giralt M, van Bilsen M, Villarroya F. Fibroblast growth factor 21 protects against cardiac hypertrophy in mice. Nat Commun 2013; 4: 2019.
[16] Planavila A, Redondo-Angulo I, Ribas F, Garrabou G, Casademont J, Giralt M, Villarroya F. Fibroblast growth factor 21 protects the heart from oxidative stress. Cardiovasc Res 2015; 106: 19-31.
[17] Planavila A, Redondo-Angulo I, Ribas F, Garrabou G, Casademont J, Giralt M, Villarroya F. Fibroblast growth factor 21 protects the heart from oxidative stress. Cardiovasc Res 2015; 106: 19-31.
[18] Shen Y, Ma X, Zhou J, Pan X, Hao Y, Zhou M, Lu Z, Gao M, Bao Y, Jia W. Additive relationship between serum fibroblast growth factor 21 level and coronary artery disease. Cardiovascular Diabetology 2013; 12: 124.
[19] Wang R, Yi X, Li X, Jiang X. Fibroblast growth factor-21 is positively associated with atrial fibrosis in atrial fibrillation patients with rheumatic heart disease. Int J Clin Exp Pathol 2015; 8: 14901-8.
[20] Woo YC, Lee CH, Fong CH, Xu A, Tso AW, Cheung BM, Lam KS. Serum fibroblast growth factor 21 is a superior biomarker to other adipokines in predicting incident diabetes. Clin Endocrinol (Oxf) 2017; 86: 37-43.
[21] Xiao Y, Liu L, Xu A, Zhou P, Long Z, Tu Y, Chen X, Tang W, Huang G, Zhou Z. Serum fibroblast growth factor 21 levels are related to subclinical atherosclerosis in patients with type 2 diabetes. Cardiovasc Diabetol 2015; 14: 72.
[22] Zhang W, Chu S, Ding W, Wang F. Serum level of fibroblast growth factor 21 is independently associated with acute myocardial infarction. PLoS One 2015; 10: e0129791.