Int J Clin Exp Med 2017;10(10):14632-14638
www.ijcem.com /ISSN:1940-5901/IJCEM0033590

Original Article

Elevated serum levels of fibroblast growth factor 21 from patients with nephrolithiasis

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Received February 12, 2016; Accepted November 15, 2016; Epub October 15, 2017; Published October 30, 2017

Abstract: Objectives: It was aimed to detect serum fibroblast growth factor-21 (FGF-21) levels among patients with nephrolithiasis and healthy control, and to identify whether FGF-21 is disease-correlated. Methods: Serum concentrations of total FGF-21 were determined by enzyme-associated immunosorbent assay in 60 participants with nephrolithiasis from our unit and 50 non-nephrolithiasis normal control from the general health examination center. Renal failure, chronic urinary tract infection, renal tubular acidosis, cancer, chronic diarrhea, diabetes and gout were totally excluded. Results: It was shown that FGF-21 levels were obviously higher in the serum of the patients with nephrolithiasis, compared with that in the healthy individuals. Serum levels of FGF-21 were obviously inversely related to renal function parameter while it positively correlated with serum C-reactive protein (CRP) and interleukin-6. By univariate analysis, it was shown that FGF-21 was obviously and proportionally related to serum creatinine, age, triglycerides, CRP; and negatively correlated with blood pressure, HDL cholesterol and LDL cholesterol. Conclusions: Taken all factors into consideration, the consequence showed that circulating levels of FGF-21 elevated in patients with nephrolithiasis. The pathophysiological significance of the study required further investigation.

Keywords: Nephrolithiasis, fibroblast growth factor-21, ELISA, inflammation, renal function

Introduction

Nephrolithiasis is a condition which refers to the progress of stones in peoples' kidney; it is believed to be a popular disease in the world that almost 8% population is afflicted with it [1]. The exact cause and etiology of nephrolithiasis remained unclear. The risk factors for developing nephrolithiasis comprise of sex, genetics, geography, age, diet, seasonal factors and jobs [2]. There is no specific forecasted sign for the illness which come on the scene and many patients are diagnosed late after marked symptoms such as renal colic and hematuria appear. A trustworthy sign showing nephrolithiasis which may predict previous diagnosing, cure or effective supervision is greatly demanded.

One of the underlying mechanisms of metabolic disorders in the etiology of nephrolithiasis have been recently proposed however not clarified [3]. Fibroblast growth factor-21 (FGF-21) is considered as a part of FGF big group, consisting of FGF-19, FGF-21, and FGF-23. FGF-21 is a hormone mainly produced by white adipose tissue and the liver, where it is in part induced by peroxisome proliferator-activated receptor gamma (PPARg) and the peroxisome proliferator-activated receptor alpha (PPARa) respectively [4, 5]. Recently, literature reported that inflammation, infection, malignancy and trauma could to some degree lead to acute phase response (APR), which is believed to be caused by alterations in hepatic protein synthesis. This would lead to changes to the specific serum proteins. The common APR included C-reactive protein, serum amyloid A as well as apolipoprotein A1 [6].

Recently, FGF-21 is believed to be acted as an adipokine incentive which obtained from the rising insulin sensitivity and adipocytes in certain animals [7]. Nevertheless, the adipokine is contradictorily up-regulated among lots of metabolic illnesses among the human beings. For example, *Lin Z* once indicated that the upregulation phenomenon of FGF-21 was discovered among one hundred thirty five sick with coro-

nary heart disease while comparing with the healthy people [8]. In the latest meta-study demonstrated that there is an increasing danger of coronary heart disease in the sick that are diagnosed with kidney stones before [9]. In addition, *Chavez AO* revealed that there was rising FGF-21 serum levels among the sick who suffer from type 2 diabetes mellitus while comparing with healthy people [10]. Seen together, FGF-21 is likely to be a very important adipokine. Nevertheless, the precise mechanisms of FGF-21 upregulation among the human beings are still unsure. To date, there was no research which has specifically study the metabolite-related cytokines & adipokines among the sick of nephrolithiasis. So in terms of this research, it will compare the serum levels of FGF-21 among the sick with nephrolithiasis and controlled health people.

Methods

Patients

This study is carried out from July 2011 to September 2012 in the 1st affiliated hospital to Wenzhou Medical University. We selected the patients who were diagnosed with nephrolithiasis in radiography and ultrasonography during the period. It was shown that so special case was discovered with radiolucent stones through the ways of X-ray or cystine, or uric acid stones by the means of medical examination. If through the approaches of surgery, the stone specimens could be moved or gained through shockwave lithotripsy or medical treatment, and the stones components could be testified through the means of infrared spectroscopy [11]. All patients had been followed every two months for at least 12 months. And renal function was assessed at every visit. Clinical data included serum creatinine and urine routine were determined by the responsible physicians and not affected by the study. All physicians were blinded from the results of measurements.

In the process, it randomly chose normal controls among the patients who had received health examination in this hospital almost in the same time. There was premise that the controlled patients were deprived of nephrolithiasis before and had no history of stones which were detected by X-ray or other methods such as abdominal ultrasound. It made sure that all subjects would be excluded if they once were diagnosed with renal failure, gout, chronic urinary tract infection, autoimmune diseases, renal tubular acidosis, chronic diarrhea, first and secondary hyperparathyroidism, diabetes as well cancer. And they were excluded the history of inflammatory disorders and recent inflammations. In addition, all participants lived in Zhejiang Province. The Institutional Review Board in the 1st affiliated hospital to Wenzhou Medicine University also authorized this research, and researchers collected the information with the permission of patients.

Samples collection and detection

The researched collected blood samples from the participants with their permission in advance. Through the means of venous puncture in healthy volunteers or arterial catheter, 20 milliliters of heparinized blood were abstracted from each participant. Serum FGF-21 concentrations could be gauged through a merchant ELISA Kit, under the guidance of instructions. C-reactive protein (CRP), interleukin 6, as well as glucose had been gauged by using normative approached by the central laboratory of Wenzhou medical university 1st affiliated hospital.

C-reactive protein (CRP), Serum standards from the fasting blood glucose, low-density lipoprotein cholesterol (LDL-c), triglycerides (TG) as well as high-density lipoprotein cholesterol (HDL-c) were gauged through standard laboratory approaches in a qualified laboratory. When the overnight fasting was done, researched collected blood samples from the participants. TC and TG proportions were confirmed by the means of CHOP-PAP and GPO-PAP approaches. The selective solubilization approach (LDL-c test kit, Kyowa Medex, Tokyo) was used to analyze the concentration of LDL-c, and a similar approach was employed to determine the concentration of HDL-c (Determiner L HDL, Kyowa Medex).

Since literature reported that staghorn nephrolithiasis was usually related to the drop of estimated glomerular filtration (eGFR), the researchers conduct measurement over fasting serum levels of creatinine (Cr) in each patients (Wako Pure Chemical Industries, Osako, Japan); and the eGFR was obtained through the following equation [12]: eGFR (mL/min/1.73 m^2) $=194 \times Cr^{-1.094} \times age^{-0.287}$ (1) in males and eGFR

Table 1. Clinical characteristics of patients with nephrolithiasis and healthy volunteers, Data are shown as means ± SD

Characteristics	Nephrolithiasis group	Control group	P
Number of cases (n)	60	50	
Male, n (%)	48 (80.0)	39 (78.0)	>0.05
Mean age (years) (mean ± SD)	46.6±9.5	44.4±7.3	0.236
Fasting glucose (mmol/L)	6.0±1.3	5.8±1.4	0.229
Hypertension, n (%)	39 (65.0)	31 (62.0)	1.000
Hyperlipidemia, n (%)	38 (63.3)	31 (62.0)	0.838
Ca^{2+}	3.2±0.9	2.4±0.2	<0.001
TC (mmol/L)	4.3±1.4	4.1±1.2	0.201
LDL-c (mmol/L)	2.8±0.9	2.6±1.0	0.465
HDL-c (mmol/L)	1.0±0.2	1.0±0.2	0.486
TG (mmol/L)	1.7±1.0	1.5±0.9	0.222
FGF21 (ng/ml)	0.25 (0.16-0.34)	0.14 (0.11-0.20)*	<0.001

TC: total cholesterol; TG: triglycerides; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol. *P<0.05, Nephrolithiasis group vs. control group. Standard BUN 1.8-7.1 mmol/L, standard SCr 59-104 mmol/L.

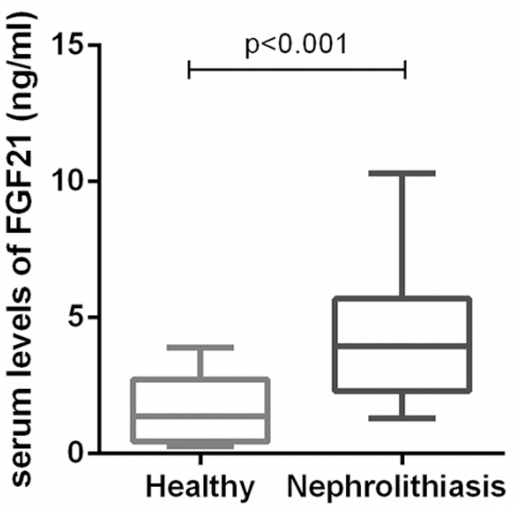

Figure 1. Serum levels of FGF21 in patients with nephrolithiasis (n=60) and in normal controls (n=50).

(mL/min/1.73 m^2)=194 × $Cr^{1.094}$ × $age^{-0.287}$ × 0.739 (2) in females.

Statistical analysis

Enumeration data were given as mean ± standard deviation. Statistical Package for Social Science version 19.0 (SPSS, Inc., Chicago, IL, USA) was adopted to make analysis of all data. Intergroup comparisons for medical values had been evaluated by the means of unpaired Student's *t*-test, while intergroup comparisons in different categorical variables had been calculated by Chi-square test. In addition, it still adopted the multivariate linear regression analysis which was introduced in advance. Among the analysis, parameters that were related obviously to FGF-21 during the analyzing process would be composed. For instance, gender and age were both contained in these multivariate analyses. *P*-value of <0.05 was regarded as significant.

Results

Patients' characteristics

This research included 60 nephrolithiasis patients and 50 normal healthy people in the control group. The demographic parameters were listed in **Table 1**. It showed no obvious difference on mean age between patients in nephrolithiasis group or controlled group (P>0.05) (See **Table 1**). In order to exclude the possible consequence caused by diabetes, in both groups we have excluded diabetes patients. So there is no diabetes in nephrolithiasis group or healthy control. Urine detection were performed in all patients, and pre-existed urinary infection candidates were excluded either.

To date, no reliable study has validated the FGF-21 expression in the cohort of nephrolithiasis patients, so we used median and interquartile range (IQR) for the others to quantify the expression profile of FGF-21. As compared to healthy control, the serum FGF-21 levels were significantly higher in nephrolithiasis patients (3.83, IQR 2.55 to 8.29) versus 1.67, IQR 0.43 to 3.24, P<0.01 (**Figure 1**).

Correlations between serum FGF21 levels and some laboratory parameters

50 healthy volunteers provided us the plasma samples for detection of FGF21; we analyzed the correlations between serum FGF21 levels and renal function parameter, estimated glomerular filtration (eGFR) and inflammatory

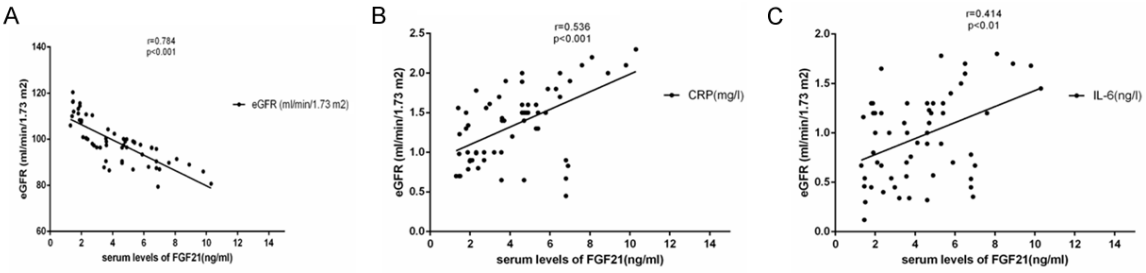

Figure 2. Relation between serum levels of FGF21 and (A) estimated glomerular filtration (eGFR), (B) CRP and (C) IL-6. Data are compared by Spearman's rank correlation coefficient.

Table 2. Univariate correlations and multivariate regression analysis with serum FGF-21 in patients with nephrolithiasis

	Univariate correlations		Multivariate regression analysis		
	R	P	β	95% CI	P
Age (years)	0.115	0.010*	1.5 × 10-4	-0.001,0.001	0.062
Gender	/	/	-0.005	-0.032,0.022	0.698
BMI (kg/m^2)	0.028	0.515	/		/
SBP (mmHg)	-0.003	0.95	/		/
DBP (mmHg)	-0.169	<0.001*	0.001	-0.001,0.002	0.337
Creatinine (μmol/l)	0.717	<0.001*	/		/
eGFR (ml/min/1.73 m^2)	-0.722	<0.001*	-0.003	0.000,0.001	<0.025#
TC (mmol/L)	-0.243	<0.001*	/		/
LDL-c (mmol/L)	-0.297	<0.001*	-0.024	-0.039,-0.009	0.002#
HDL-c (mmol/L)	-0.339	<0.001*	0.022	-0.038,0.083	0.466
TG (mmol/L)	0.289	<0.001*	0.192	-0.20-0.002	<0.001#
CRP (mg/l)	0.323	<0.001*	/		/
IL-6 (ng/l)	0.565	<0.001*	0.60	0.029-0.090	<0.001#

Multivariate regression analysis of FGF-21 (dependent variable). adjusted for age and gender, as well as DBP, eGFR, TG, HDL cholesterol, LDL cholesterol, and IL-6. Non-normally distributed variables were logarithmically transformed prior to multivariate testing. r- and *P*-values, as well as standardized ß-coefficients and *P*-values, are given. Abbreviations are indicated in **Table 1**. *indicates significant correlation as assessed by Spearman's rank correlation method. #indicates significant correlation in multivariate analysis. P<0.05.

parameter, Interleukin 6 (IL-6), as well as C-reactive protein (CRP). Serum levels of FGF21 significantly inverses correlates with the eGFR (r=--0.495, P<0.01), whilst serum levels of FGF21 positively correlates with serum CRP (r=0.323, P<0.01) and IL-6 (r=0.209, P<0.001), the details were shown in **Figure 2**.

Univariate correlations and multivariate regression analysis

By univariate analysis, it showed that FGF-21 was obviously and actively correlated with serum creatinine, age, CRP, TG, and IL-6 (See **Table 2**). On the contrary, FGF-21 serum concentrations from the total quantity were shown as obviously associating with eGFR, DBP, HDL cholesterol, cholesterol as well as LDL cholesterol (See **Table 2**).

When making adjustment on gender and age, multivariate regression analysis for the research group 1 indicated that serum FGF-21 proportions stayed obviously but negatively related to HDL cholesterol, TG, eGFR independent of DBP, IL-6 and LDL cholesterol (See **Table 2**). In addition, it showed that circulating FGF-21 was independently and negatively related to LDL cholesterol (See **Table 2**). Furthermore, it could observe a positive and positive link between FGF-21 and TG and IL-6 (See **Table 2**).

Discussion

From the present research, it proved at the first time that FGF-21 levels increase among the nephrolithiasis participants while comparing with that of in non-nephrolithiasis control. In addition, it showed that renal responsibility is considered as the best reliable forecaster for FGF-21 among these diseases. Noteworthy, related alterations in FGF-21 are negatively and independently related to the lipid parameters (LDL cholesterol, HDL cholesterol) among the group. It was believed that these findings partially proved assumptions that renal excretion is a primary factor which could prevent FGF-21

from circulation, which is accordant with previous literature [13].

It is noteworthy that the parameters of renal function, such as creatinine or eGFR, should be taken into account for all FGF21 related studies. As we reported previously, the etiology of nephrolithiasis is usually accompanied with the deterioration of renal function, since calcium oxalate could induce renal tubular epithelial cells damage, oxidative stress injury, chronic inflammation and eventually, the progressing epithelial-mesenchymal transition, which will contribute to the loss of renal function [14-16]. Lin M demonstrated that significantly elevated FGF-21 levels were found among the sick with severe chronic kidney disease (CKD) when comparing with mild CKD and healthy groups [8]. However, there were no animal studies to elucidate the exact factors cause renal removing of FGF-21 or to calculate the physiological pertinence about growing FGF-21 proportions in chronic or acute renal dysfunction. According to our study, this could be considered as the first report relating FGF21 levels among the nephrolithiasis sufferers.

FGF-21 is believed to be a kind of endocrine factor, hided primarily by the liver, and have positive influence on the lipid homeostasis and glucose [17]. It is indicated to be elevated among participations who suffer from adverse lipid profiles, damaged glucose tolerance, obesity, type 2 diabetes mellitus (DM), hypertension, coronary disease and metabolic syndrome [18, 19]. It was believed that increased serum FGF-21 proportions were related to carotid atherosclerosis among human beings, and independent from the previous danger elements such as adverse lipid profiles and CRP. In our study, FGF-21 indicates a negative link with HDL cholesterol, cholesterol and LDL cholesterol, and sustain the assumption that upregulation of FGF-21 is correlated with lipid metabolism disorder in nephrolithiasis patients. As literature reported, management of FGF-21 in diabetic primates gave rise to declining LDL and TG cholesterol levels; and *Emanuelli B* found that FGF-21-cured fat mice exhibit growing spending on energy, fat use and lipid excretion [20, 21]. From the above, we may assume that the rising circulation FGF-21 in nephrolithiasis patients might function as a compensatory response to adverse metabolic status in the disease. Recently, it is demonstrated that stimulation for FGF-21 signaling pathways and FGF-2 intercede previous gene record is damaged among the fat mice model [22]; and interestingly, the mean Body Mass Index (BMI) in nephrolithiasis patients is higher than healthy control, regardless of no statistical significance. However, latest literature reported by *Sancak EB*, diabetes mellitus, hypertension and increased BMI may add to the possibility of stone formation, which is in accordant with our data [23].

In nephrolithiasis patients, FGF-21 correlates actively and separately with TG and CRP; it is similar to some other reports [24]. A previous study showed that FGF-21 improves LDL-receptor performance among cultivated human beings hepatocytes, which may lead to the increasing of lipoprotein obtained during the process [25]. Nevertheless, we need to pay attention to that some statistics in other patient cohort show a positive association between LDL cholesterol and FGF-21 standards which is in the contrary with our findings in the study [26]. Differences in participant features such as renal obligation, age, ethnicity, gender, as well as phenotyping might give an explanation to these differences.

It has to admit that there exist restrictions of our study that required to be issued. First of all, the researched adopted a cross-sectional design to ensure the nephrolithiasis patients, so causality cannot be established. In fact, the nephrolithiasis patients include calcium oxalate nephrolithiasis, phosphate nephrolithiasis, cysteine nephrolithiasis, and uric acid nephrolithiasis, etc, so we should enroll as more patients in the future study as possible. Secondly, more inflammatory elements were not detected and creatinine alteration before and after nephrolithiasis clearing operation could be written down. Therefore, gaining these statistics might greatly contribute to identify the factors which are hidden among the rising FGF-21 in kidney stone disease.

Taken all factors and studies into account, the study is the first time to prove that circle FGF-21 is raised among nephrolithiasis patients; and our findings sustain the assumption that renal excretion could be a primary factor to prevent FGF-21 from circulating. FGF-21 was considered to be included in renal protective impacts and may also act as a new sign for nephrolithia-

sis, however, novel potential therapeutic target and its potential role in modulating inflammation and lipid metabolic dysfunction warrants further investigation.

Acknowledgements

This study was supported by Zhejiang Provincial Natural Science Foundation of China (LY12H10004, LY13H030006), Wenzhou Municipal Science and Technology Bureau (Y20160032, Y20160127).

Disclosure of conflict of interest

None.

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