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Effect of Salt Intervention on Serum Levels of Fibroblast Growth Factor 23 (FGF23) in Chinese Adults: An Intervention Study

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: Fibroblast growth factor 23 (FGF23), a prominent regulator of phosphate and calcium metabolism, regulates sodium excretion in distal tubules through sodium-chloride cotransporter. This effect regulates blood pressure. Salt intake exerts effects on serum levels of FGF23 in mice. The aim of this study was to explore whether salt intervention affects serum concentrations of FGF23 in Chinese adults.

Material/Methods: We enrolled 44 participants from Lantian, a rural community of Shaanxi, China. All participants were maintained on a three-day normal diet, which was sequentially followed by a seven-day low-Na^+ diet and seven-day high-Na^+ diet. Serum FGF23 concentrations were assessed by ELISA.

Results: Serum FGF23 concentrations elevated during low-salt diet compared with levels at baseline (66.20±44.21 pg/mL versus 86.77±53.74 pg/mL, $p<0.05$) and remarkably decreased when changed from low to high salt intake (86.77±53.74 pg/mL versus 49.26±42.67 pg/mL, $p<0.001$). Responses of FGF23 to salt intervention were more prominent in normotensive, older than 60 years, BMI <24 kg/m^2 and salt-resistant individuals. Furthermore, a significant inverse correlation was observed between 24-hour urinary sodium and serum concentrations of FGF23 after adjusting age, sex, BMI and hypertension status.

Conclusions: Dietary salt intervention significantly affects serum FGF23 in Chinese adults.

MeSH Keywords: Diet, Sodium-Restricted • Fibroblast Growth Factors • Hypertension

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Background

Overwhelming evidence showed that high salt intake is a common risk factor of hypertension. Salt overload greatly contributes to the development and progression of hypertension [1,2]. Kidney and the vasculature are two critical parts of the body that regulate sodium balance, which ultimately develop into aberrant structures and dysfunction in high-salt diets [3–5]. Despite the detrimental effects of salt on the genesis of hypertension and sodium-regulated organs, humans and animals have various compensatory pathways to maintain sodium balance under high-salt conditions. Animal data suggested high-salt intervention reduced plasma aldosterone, epithelial sodium channels, and sodium-chloride cotransporter (NCC) expression, therefore decreasing salt retention [4,6]. Therefore, a thorough recognition on the responses to different salt intakes seems important to understand the pathophysiological changes of salt-induced hypertension.

Fibroblast growth factor 23 (FGF23), a bone-derived hormone secreted by osteoblasts and osteocytes, plays a pivotal role in the regulation of renal mineral metabolism [7]. Recent experimental data suggested that it could act as a sodium-conserving hormone in renal distal tubules [8,9]. Andrukhova et al. previously demonstrated that FGF23 could increase sodium reabsorption and elevate blood pressure through upregulating the expression of renal NCC in mice. These effects of FGF23 could be abrogated by the NCC inhibitor chlorothiazide [8]. Patients with high FGF23 plasma levels tend to have high sodium concentration during low salt intake [10]. Compelling clinical studies also indicated an obvious elevation of serum concentrations of FGF23 in chronic kidney disease (CKD) and decompensated heart failure patients, often accompanied by sodium retention and volume expansion. Additionally, a positive correlation between FGF23 and blood pressure was also found in primary hyperparathyroidism patients through 24-hour ambulatory blood pressure monitoring [11]. These inspiring discoveries demonstrated the role of FGF23 on the regulation of sodium excretion and blood pressure.

Conversely, salt restriction in mice elevated serum c-terminal FGF23 [12]. Aldosterone could upregulate FGF23 expression [12]. High salt intake inhibits aldosterone secretion, whereas low salt intake stimulates it under normal condition [13]. Low-salt diet could also strengthen the effects of FGF23 [8]. A feedback loop between salt intake and FGF23 may be found. Low-salt diet could potentiate the sodium conserving effect of FGF23 through increasing serum levels of FGF23, and vice versa.

Nevertheless, studies about the interaction of dietary salt intake and FGF23 were limited. Studies of the effects of salt intake on FGF23 were conducted on hypertensive or CKD patients and obtained nonsignificant results. These facts encouraged us to clarify the relationship between different salt intake and FGF23 in general populations. Through dietary salt intervention, we aimed at figuring out the effect of salt on serum FGF23 and whether an inverse feedback loop existed between them.

Material and Methods

Participants

In this study, we recruited 44 participants aged 18–65 years with similar dietary customs from Lantian, a rural community of Shaanxi, China. Trained staff collected basic demographic information by using a standard questionnaire. Participants with a mean systolic blood pressure (SBP) of ≥140 mm Hg, a mean diastolic blood pressure (DBP) of ≥90 mmHg, and/or a history of hypertension with current use of antihypertensive medications were defined as hypertensive patients. The exclusion criteria were as follows: 1) BP ≥160/100 mm Hg, secondary hypertension, or use of antihypertensive medication; 2) history of clinical cardiovascular disease, liver or kidney disease, diabetes mellitus, infectious diseases, vascular disease, and alcohol abuse; 3) and inability or unwillingness to participate in all aspects of the study. This study strictly followed the Declaration of Helsinki and was approved by the ethics committee of the First Affiliated Hospital of Medical School, Xi'an Jiaotong University (Code: 2015-128). Signed informed consents were obtained from all participants.

Study design and measurements

Dietary intervention

The protocol for salt loading intervention was conducted as described previously [14,15]. Briefly, the intervention protocol was separated into three periods. First, participants received normal Na^+ diet for three days as the baseline period. During this period, trained staff collected anthropometric data (including height, weight, and waist circumference). Next, participants were given seven-day low-Na^+ diet (51.3 mmol sodium or 3.0 g NaCl per day) and seven-day high-Na^+ diet (307.7 mmol sodium or 18 g NaCl per day). All participants were asked to eat in the research kitchen during the entire study period to minimize dietary variance because FGF23 concentration might be influenced by diet especially dietary phosphate [7,16]. The dieticians of the study prepared food and beverages without salt and separately prepackaged salt for each subject. The staff added the prepackaged salt to the participant's meal and stressed the importance of avoiding extra food consumption at home.

BP measurement

Random-zero BP was measured by certified physicians using standard mercury sphygmomanometers followed the protocol

recommended by the American Heart Association [17]. We obtained BP measurements at each day of baseline and the 6th and 7th day of each intervention period. Participants were instructed to sit in a resting position for more than five minutes and avoid exercise, smoking, alcohol, coffee, or tea prior to BP measurement. BP was measured three times with one minute intervals. It was measured by the same BP technician using the same sphygmomanometer to avoid observation variation. The means of nine measurements at baseline and six measurements of each salt intervention period were used as the final BP of each individual. The mean arterial pressure (MAP) was calculated using the formula: $SBP/3 + DBP \times 2/3$. Participants whose MAP increased more than 10 mm Hg while changing from low Na^+ to high Na^+ were defined as salt-sensitive (SS) individuals [15,18]. The rest were regarded as salt-resistant (SR) individuals.

Laboratory measurements

Venous blood samples were obtained under overnight fasting state at the last day of each period. The blood samples were centrifuged at 3,000 g and 4°C for 10 minutes within two hours, packaged in aliquots, and stored at -80°C for further analysis. Basic biochemistry parameters (including lipid profiles, fasting serum glucose, serum creatinine, and uric acid) were analyzed using an automatic biochemical analyzer (Hitachi, Ltd., Tokyo, Japan). Commercial enzyme-linked immunosorbent assay kits were applied to measure the serum intact FGF-23 (USCN Life Science Inc., Wuhan, China). Intra-assay and inter-assay coefficients of FGF-23 ELISA kit were reported to be <10% and <12%, respectively. The minimum detectable dose of FGF23 was typically less than 6.1 pg/mL.

Analysis of 24-hour urine

Each participant collected 24-hour urine under the guidance of staff at 8: 00 am on the 6th day of each intervention period. The concentrations of urine sodium and potassium were analyzed using ion-selective electrodes (Hitachi, Ltd., Tokyo, Japan). The sodium and potassium excretion in 24-hour urine were calculated by 24-hour total urine volume multiplied by concentrations of sodium or potassium.

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics 22.0 (IBM Corp., Chicago, IL, USA). Data are presented as mean ± standard deviation for continuous variables and expressed as frequencies with percentages [n (%)] for categorical variables. As the concentrations of FGF23 were right skewed and normally distributed after natural log(ln) transformation, FGF23 levels were shown as geometric mean ± standard deviation and ln transformed during correlation analysis. Differences in biochemical parameters among different intervention periods

Table 1. Demographic and clinical characteristics of baseline.

Paremeters	Values
Age (y)	51.2±12.4
Sex (M/F)	11/33
BMI (kg/m²)	24.85±3.12
SBP (mmHg)	124±16
DBP (mmHg)	77±10
Glucose (mmol/L)	5.37±0.73
Total cholesterol (mmol/L)	4.60±0.87
Triglycerides (mmol/L)	1.35±0.74
LDL-cholesterol (mmol/L)	2.59±0.65
HDL-cholesterol (mmol/L)	1.47±0.42
Serum creatinine (umol/L)	54.70±9.33
Serum UA (umol/L)	263.93±81.94

Values are means ± SD. BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; LDL – low-density lipoprotein; HDL – high-density lipoprotein; UA – uric acid.

were assessed using one-way ANOVA with repeated measures in case of normal distribution. Pearson's and Spearman's correlation tests were used to explore the correlations of FGF23 and other variables as appropriate. A two-sided *p*-value of 0.05 was used to evaluate statistical significance.

Results

Characteristics of participants

All 44 participants completed the whole trial. Baseline clinical characteristics are outlined in Table 1. The mean age of the study population was 51.2±12.4 years, and the mean BMI was 24.85±3.12 kg/m². Nine participants (25.7%) were hypertensive, but none were taking medicines. Nine of the participants were defined as SS individuals.

Changes of BP, urinary sodium and potassium excretion, and serum sodium during each period

Compared with baseline, SBP significantly decreased during the low-salt period (*p*=0.009) and increased while changing from low- to high-Na^+ diet (*p*=0.001). However, no obvious changes of DBP were observed during dietary intervention. The sodium excretion of 24-hour urine was evaluated by the end of each intervention period and well reflected dietary changes, which decreased in low-Na^+ diet (*p*<0.001) and increased in

Table 2. Levels of different parameters at baseline and during dietary interventions.

Parameters	B	LS	HS
SBP (mmHg)	124±16	116±12[a]	128±18[b]
DBP (mmHg)	79±9	77±8	80±9
UNa+ (mmol/24h)	168.98±77.00	79.08±32.90[a]	281.86±77.31[ab]
UK+ (mmol/24h)	27.79±10.66	25.25±8.82	34.13±10.65[a]
Serum Na+ (mmol/L)	140.3±1.5	141.6±1.1[a]	142.0±2.02[a]

Values are mean ± =SD. [a] $p<0.01$ versus baseline; [b] $p<0.01$ versus low-salt diet. B – baseline; LS – low salt; HS – high salt; SBP – systolic blood pressure; DBP – diastolic blood pressure; U_{Na+} – 24h urinary sodium excretion; U_{K+} – 24h urinary potassium excretion.
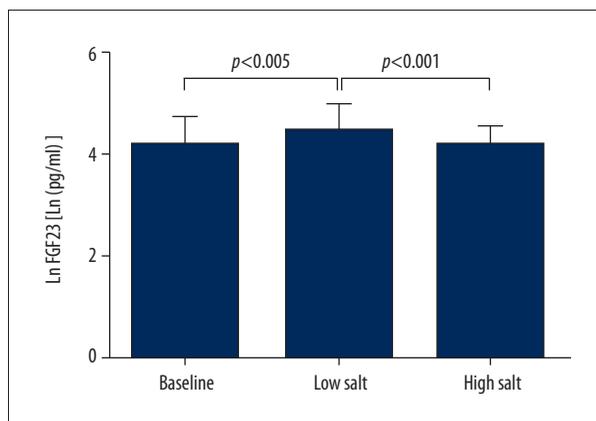
Figure 1. The effects of low salt and high salt intake on ln-transformed concentrations of serum FGF23.

high-salt intake ($p<0.001$) (Table 2). The 24-hour urinary potassium also increased with the change from low to high salt diet ($p<0.001$). These results strongly indicated that subjects had good compliance with the dietary intervention protocol.

As for the serum sodium, serum sodium levels rose significantly in the high salt diet period compared with those observed at baseline period ($p<0.01$). By contrast, in the low salt diet period, serum sodium was elevated rather than decreased compared with the baseline period ($p<0.01$) and showed no significant difference with that of the HSD period.

Effect of dietary salt intervention on serum FGF23

At baseline, serum FGF23 was 66.20±44.21 pg/mL. It increased with the change from baseline to low-Na+ diet (66.20±44.21 pg/mL versus 86.77±53.74 pg/mL, $p<0.05$) and decreased significantly when changed from low- to high-Na+ intake (86.77±53.74 pg/mL versus 49.26±42.67 pg/mL, $p<0.001$) (Figure 1). To clarify the influence of confounding factors on the response of FGF23, we divided participants into groups based on the tertiles of age (tertile range: 47–60), sex, BMI, and hypertension status. We found FGF23 was significantly higher in female and BMI >28 kg/m² participants at baseline. There was a positive correlation between BMI and FGF23 (r=0.389, $p=0.009$). Age and hypertension status didn't exert obvious

Table 3. The influence of age, sex, BMI, hypertension status on the response of FGF23 to salt intervention.

Indexes	Baseline	Low salt	High salt	P values
Age <47, n=14	57.69±45.89	77.67±50.97	43.94±40.47	P=0.196
47≤ Age <60, n=19	74.75±44.24	96.60±57.21	59.93±50.63	P=0.119
60≤ Age <65, n=11	63.86±44.24	85.35±53.03	41.89±23.05	P=0.035
Male, n=11	48.15±26.05	73.46±27.75	41.31±18.59	P=0.009
Female, n=33	73.13±46.59	92.04±58.92	52.43±47.21	P=0.013
BMI <24, n =19	52.30±34.60	80.82±52.70	45.23±35.22	P=0.014
24≤ BMI <28, n=17	73.34±44.90	91.21±51.79	53.87±48.79	P=0.149
28≤ BMI, n=8	94.68±51.59	93.53±64.53	50.99±49.13	P=0.295
Normal, n=35	63.40±45.40	86.76±56.56	52.22±43.65	P=0.011
Hypertension, n=9	77.57±40.77	86.81±42.54	38.42±38.91	P=0.091
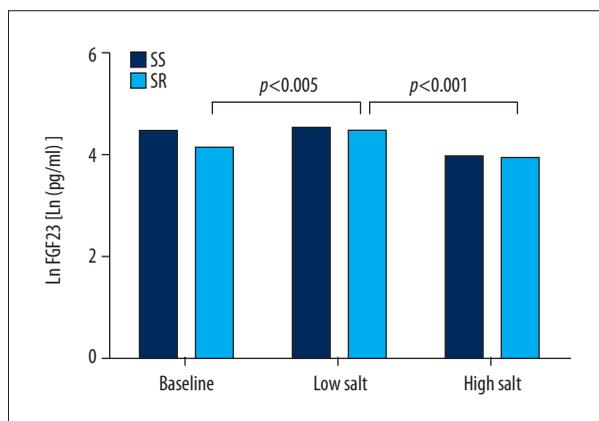
Figure 2. The ln-transformed concentrations of FGF23 among different salt interventions in subjects with different salt sensitivities.

influence on serum FGF23 levels. The responses of FGF23 to salt intervention were more pronounced in normotensive, older than 60 years and BMI <24 kg/m² participants. Both male and female showed significant changes among different intervention period (Table 3).

Salt sensitivity influences the response of serum FGF23

Subsequently, we explored the influence of salt sensitivity on the response of serum FGF23. At baseline, FGF23 was non-significantly higher in SS than in SR participants (83.84±50.19 pg/mL versus 62.07±41.76 pg/mL, p>0.05). Serum levels of FGF23 between SS and SR individuals also showed no significant difference during each intervention period. However, the responses of serum FGF23 to salt intervention were more prominent in SR than in SS individuals. Serum FGF23 of SR individuals increased from 62.07±41.76 pg/mL to 84.10±57.26 pg/mL (p<0.05) from baseline to low salt intake and declined to 48.32±42.44 pg/mL during high-salt period

(compared with low-Na⁺ period, p<0.001). Serum FGF23 showed no obvious difference from low- to high-salt diet in SS participants (Figure 2).

Correlations between the excretion of 24-hour urinary sodium, potassium, and serum FGF23

Furthermore, we performed correlation analysis between the ln-transformed concentrations of FGF23 and 24-hour urinary sodium excretion and found an inverse correlation during low- and high-Na⁺ periods (r=-0.377, p<0.001) (Figure 3A). The correlation was strengthened after adjusting for age, sex, BMI, hypertension status (r=-0.397 p<0.001). Additionally, the ln-transformed concentrations of FGF23 was negatively correlated with 24-hour urinary potassium excretion (r=-0.227, p=0.03; adjusted r=-0.259, p=0.018) (Figure 3B). However, we failed to observe any correlation between ln-transformed concentrations of FGF23 and BP indexes.

Discussion

The results of the present study demonstrated an inverse correlation between dietary salt intervention and serum FGF23 in Chinese adults. Low salt intake contributed to an increment of serum FGF23, whereas high salt intake decreased serum FGF23 from the levels observed at low-salt period. The responses of FGF23 were more pronounced in normotensive, older than 60 years, BMI <24 kg/m² and SR individuals. The negative correlation between 24-hour urinary sodium excretion and serum FGF23 further indicates the pivotal role of FGF23 in the maintenance of sodium balance.

FGF23 was traditionally regarded as a bone-derived hormone that regulated mineral metabolism [19]. Recent data clarified that FGF23-deficient mice were in sodium-wasting and
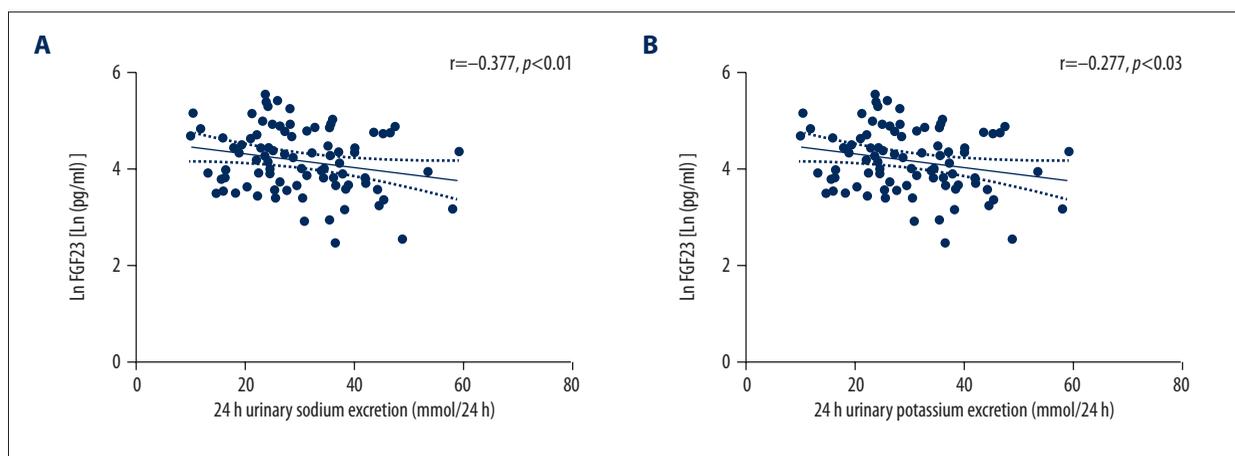
Figure 3. 24-hour urinary sodium (**A**) and potassium (**B**) excretion are negative correlates of ln-transformed concentration of serum FGF23 in low salt and high salt periods.

hypovolemic conditions accompanied with down-regulated NCC expression [8]. Conversely, recombinant FGF23 could enhance the abundance and phosphorylation of NCC in wild-type mice, resulting in a threefold increase in sodium concentration of distal tubule epithelium and contributing to sodium retention, volume expansion, and BP elevation [8]. Based on these results, Zhang et al. verified that low salt diet (<0.2%) for seven days significantly elevated serum concentration of FGF23 in mice [12]. We also found that dietary salt intervention could influence serum levels of FGF23 in humans. These results strongly indicated that dietary salt intake is a negative feedback regulator of FGF23. High salt diet suppressed the function of FGF23 in distal tubules to attenuate sodium reabsorption, while low salt intake enhanced the sodium retention function of FGF23. These results partially explain the abnormal elevation of serum sodium in low salt period compared with baseline, which has also been reported by Humalda et al. [10].

However, a recent study tried to figure out whether acute and chronic volume intervention influenced the concentrations of FGF23 in hypertensive and diabetic nephropathy patients. Acute saline infusion did not change FGF-23 concentrations, nor did six-week hydrochlorothiazide and/or low salt diet [20]. Low salt diet also failed at changing serum FGF23 in nondiabetic proteinuric CKD patients [10]. Different individuals enrolled may account for the conflicting results. FGF23 was different form conventional fibroblast growth factors for the lack of heparin-binding domain, which contributed to a significant decrease in its affinity to FGF receptors [21]. Thus, FGF23 was known to require klotho as co-receptor. Klotho, an anti-aging protein, has soluble and membrane-bound forms. Soluble klotho could attenuate oxidative stress and apoptosis and alleviate the progression of hypertension [22,23]. Membrane-bound klotho binds with FGF receptors as co-receptor, which extremely enhanced the affinity of FGF23 to its receptors. Therefore, many physiological functions of FGF23 were klotho dependent [24]. Nevertheless, klotho decreased significantly in aged individuals and CKD patients [25]. The decrease of klotho resulted in the resistance to FGF23 in distal tubule epithelium and abnormal elevation of serum FGF23 [26]. Therefore, the feedback loop in individuals with basic diseases might be aberrant. We excluded individuals with severe basic diseases or taking medicines to avoid the influences of these factors and reached positive results. However, further studies are needed to investigate any differences in the regulation of FGF23 in healthy and unhealthy individuals.

Previous study indicated that FGF23 expression could be up-regulated by aldosterone in mice [12]. In SR individuals, aldosterone decreased in high-salt period compared with low-salt period. However, salt intervention did not significantly impact aldosterone concentration in SS participants [27,28]. In the present study, we found that the response of serum FGF23 to salt intervention was more pronounced in SR than in SS participants. This result suggested that low-salt intake might indirectly elevate serum FGF23 by up-regulating aldosterone. High salt diet depressed the expression of aldosterone, decreasing the serum concentration of FGF23. Therefore, changes in serum FGF23 were more obvious in SR than in SS individuals. Previous data have also suggested that dietary salt intake might affect the abundance of NCC through an aldosterone-dependent WNK4–ERK1/2 signaling pathway, and ERK1/2 or SGK1 inhibitors suppressed FGF23-induced upregulation of NCC [8,28,29]. These results might partially explain the responses of FGF23 to salt intervention. However, the mechanism of salt intake in regulating serum FGF23 was far from clear. Additional studies are needed to demonstrate the exact mechanism and whether salt-induced changes of FGF23 were involved in the regulation of salt on NCC.

This study had several limitations that should be addressed. First, this study was restricted in Northern China, and the number of participants was quite small. Therefore, large and multiethnic clinical trials were required to determine whether our results could be generalized to populations with multiple backgrounds. Moreover, we paid little attention to the underlying mechanisms of changes in serum FGF23. Therefore, further studies are required to explore the exact mechanisms.

Conclusions

This study suggest that low salt diet contributed to an increment of circulating FGF23, while high sodium intake decreased serum FGF23 from levels observed at low salt period in Chinese adults. Changes of FGF23 are more pronounced in SR than in SS participants. These findings are helpful for providing better understanding of the physiological role of FGF23 and the interaction between FGF23, sodium, and BP.

Conflict of interest

None.

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