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ORIGINAL RESEARCH

Plasma Fibroblast Growth Factor 23 as a Predictor for Fosinopril Therapeutic Efficacy in Pediatric Primary Hypertension

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BACKGROUND: Plasma fibroblast growth factor 23 (FGF23) has been reported to be a predictive biomarker for therapeutic effectiveness of angiotensin-converting enzyme inhibitors in heart failure. Higher plasma FGF23 levels have been shown in pediatric primary hypertension, but the predictive value of FGF23 for angiotensin-converting enzyme inhibitors' effectiveness in pediatric primary hypertension has not been documented.

METHODS AND RESULTS: This is a prospective study. An exploratory study with 139 patients was first conducted to determine the cutoff value of FGF23 for the prediction of treatment responsiveness. After receiving fosinopril for 4 weeks, of all 139 patients, 91 responded, while 48 did not respond to the treatment, and the responders had a significantly higher baseline plasma FGF23 level than nonresponders ($P<0.01$). Multiple regression analysis revealed a significant impact of baseline plasma FGF23 levels on fosinopril responsiveness ($P<0.05$). The receiver operating characteristic curve analysis showed that the plasma FGF23 predicted the effectiveness of fosinopril treatment with an area under the curve of 0.784 (95% CI, 0.704–0.863) for a sensitivity and a specificity of 67.0% and 89.6%, respectively, for a cutoff value of 62.08 RU/mL. Subsequently, another group of 40 patients were recruited for validation. The blood pressure control rate in those (n=22) with baseline plasma FGF23 >62.08 RU/mL was significantly higher than that in children (n=18) with FGF23 ≤62.08 RU/mL ($P<0.05$).

CONCLUSIONS: Plasma FGF23 might be a valuable biomarker to guide fosinopril therapy for primary hypertension in children.

Key Words: angiotensin-converting enzyme inhibitors ■ effectiveness ■ fibroblast growth factor ■ hypertension

The prevalence of pediatric primary hypertension is increasing.[1] Early identification and appropriate management of hypertension in children is important to prevent the development of subclinical target organ damage, which may be persistent to the adult period.[2] Angiotensin-converting enzyme inhibitors (ACEIs), one of the most prescribed antihypertensive drugs in children, target the renin-angiotensin-aldosterone system (RAAS) to achieve the therapeutic effect by blocking the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. Currently, there are no predictive biomarkers documented for the therapeutic efficacy of ACEIs.

Fibroblast growth factor 23 (FGF23) is a bone-derived hormone regulating mineral metabolism, and its special role in cardiovascular diseases has been reported in recent years. Wohlfahrt et al[3] reported that the increased FGF23 may identify a subset of patients with heart failure benefiting from ACEI therapy, suggesting that FGF23 may be a predictor for ACEIs' therapeutic efficacy in heart failure. We recently found that the plasma FGF23 level was increased in children

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CLINICAL PERSPECTIVE

What Is New?

- The present study demonstrated that 65.5% of children with primary hypertension prescribed fosinopril achieved blood pressure control.
- Children with hypertension who responded to fosinopril therapy had higher baseline plasma fibroblast growth factor 23 levels.
- Fosinopril treatment resulted in a higher blood pressure control rate in children with hypertension with higher baseline plasma fibroblast growth factor 23 levels.

What Are the Clinical Implications?

- Plasma fibroblast growth factor 23 might be a valuable predictor of therapeutic efficacy of fosinopril.
- Plasma fibroblast growth factor 23 may be used to guide the fosinopril therapy for pediatric primary hypertension.

Nonstandard Abbreviations and Acronyms

DBP	diastolic blood pressure
FGF23	fibroblast growth factor 23
RAAS	renin-angiotensin-aldosterone system
SBP	systolic blood pressure

with primary hypertension.[4] It has been shown that FGF23 may participate in the pathogenesis of hypertension through the activation of RAAS.[5,6] Thus, we hypothesized that children with hypertension with higher FGF23 levels might have a better response to ACEIs. This study was designed to explore the value of plasma FGF23 in predicting the therapeutic efficacy of fosinopril in children with primary hypertension.

METHODS

The authors declare that all supporting data are available within the article, and further inquiries are available from the corresponding author upon reasonable request.

Ethics Statement

This study was approved by the Capital Institute of Pediatrics Ethics Committee, Beijing, China (No: SHERLL2019003), in compliance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all study subjects/patients or guardians of the minors.

Subjects

Two independent groups of children with primary hypertension requiring antihypertensive pharmacotherapy were recruited, with 139 patients from Children's Hospital, Capital Institute of Pediatrics, for the exploratory study to establish an FGF23 cutoff value for drug efficacy prediction, and 40 children from Beijing Children's Hospital for external validation. Inclusion criteria for all subjects were as follows: (1) based on the instruction for drug use that recommends fosinopril for patients aged ≥12 years of age, the patients were aged 12 to 18 years; and (2) the patients required antihypertensive drug therapy and had at least 1 indication of: (a) stage 2 hypertension; (b) symptomatic hypertension; (c) hypertensive target organ damage; and (d) stage 1 hypertension with insufficient response to 6-month lifestyle modification. Those with hypertension secondary to renal disease, cardiovascular disease, or endocrine and central nervous system disease were excluded. Secondary hypertension was diagnosed by past medical history, physical exam, and the following tests, whichever were deemed necessary for a patient: blood testing (urea, creatinine, albumin, thyroid-stimulating hormone, aldosterone, or cortisol), urine vanillylmandelic acid measurement, 24-hour urine protein testing, kidney ultrasound, ultrasound of aorta, carotid artery and subclavian artery, or cranial magnetic resonance imaging.

Clinical Data Collection and Blood Pressure Measurement

We collected the data of sex, age, height, weight, and body mass index (BMI) of all subjects. Blood urea and serum creatinine were measured before treatment. Calculation of estimated glomerular filtration rate was done as described elsewhere.[7] All blood pressure (BP) measurements were performed using the auscultation method as recommended by the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents.[8] Ambulatory BP monitoring was performed in all participants to exclude white coat hypertension. Hypertension was diagnosed and staged according to "2018 Chinese Guidelines for Prevention and Treatment of Hypertension";[9] that is, hypertension was diagnosed when average clinic measured systolic blood pressure (SBP) or diastolic blood pressure (DBP) were ≥95th percentile for sex, age, and height on ≥3 occasions; hypertension stage 1 was defined as average clinic measured SBP or DBP ≥95th but <99th percentile+5 mm Hg for sex, age, and height; and hypertension stage 2 was defined as

average clinic measured SBP or DBP ≥99th percentile+5 mm Hg for sex, age, and height.

Plasma FGF23 Measurement

The venous blood samples were drawn after overnight fasting. Plasma FGF23 levels were measured by a 2-site ELISA using the second-generation Human FGF-23 (C-Term) ELISA Kit. The assay was performed according to the manufacturer's instructions (Quidel Corporation, San Diego, CA).[4]

Protocol of Treatment and Follow-Up

All subjects were prescribed fosinopril with an initial dosage of 10 mg daily, with the goal BP of the 95th percentile for sex, age, and height. The BP reduction response was evaluated weekly, and drug dosage adjustment was started the second week after the initiation of treatment, with a maximum of 40 mg daily. Additionally, according to the Chinese guidelines,[9] a special diet with maximum daily consumption of 3 g of salt was prescribed for all participants from the Department of Nutrition of the participating hospitals. The last follow-up was completed with BP measured at 4 weeks after treatment.

Criteria for Evaluating Therapeutic Effects

The responders were defined as those with the BP reduction to the goal of SBP and DBP <95th percentile for sex, age, and height after 4 weeks of treatment, and nonresponders were defined as those with SBP and DBP ≥95th percentile for sex, age, and height after 4 weeks of treatment. The BP control rate was calculated by the numbers of responders to the total numbers in each group.

External Validation

Forty patients from another institution, that is, Beijing Children' Hospital, were recruited for validation. According to the cutoff value of FGF23 established in the drug responsiveness study as described above, the patients were divided into 2 groups: group 1 with FGF23 higher than the cutoff value, and group 2 with FGF23 lower than or equal to the cutoff value. To test the therapeutic efficacy, the children were treated with fosinopril for 4 weeks, and the BP control rates were compared between the 2 groups.

Statistical Analysis

All statistical analyses were done using SPSS 25.0 software (IBM Corporation, Armonk, NY). Data normality was determined by the Shapiro-Wilk test. The continuous variables were expressed as mean±SD or median (interquartile range). An independent *t* test was applied for the analysis of parametric data and the Mann-Whitney *U* test for nonparametric data. Categorical data were analyzed by the chi-square test. Multivariate regression analysis was performed to determine the effect of independent variables on treatment responsiveness. The receiver operating characteristic curve was used to evaluate the predictive value of FGF23 in assessing the fosinopril therapeutic effect. The area under the curve was used to assess the predictive value, with an area of 0.5 to 0.7 indicating low predictive value, 0.7 to 0.9 indicating moderate predictive value, and >0.9 indicating high predictive value. $P<0.05$ was considered statistically significant.

RESULTS

Assessment of Plasma FGF23 as a Biomarker to Predict Responsiveness to Fosinopril Treatment

Of all 139 patients receiving fosinopril for 4 weeks, 91 patients responded, while 48 did not respond to the treatment, with a BP control rate of 65.5%. At week 4, the initial fosinopril dosage of 10 mg remained unchanged in 29 children, 15 mg in 2, 20 mg in 74, 30 mg in 32, and 40 mg in 2. There were no statistically significant differences in age, sex, height, weight, BMI, BMI *z* score, baseline BP, blood urea, serum creatinine, estimated glomerular filtration rate, and fosinopril dose between responders and nonresponders (Table 1). The responders had a significantly higher baseline plasma FGF23 level and a greater proportion of stage 1 hypertension (Table 1). Further multiple logistic regression analysis revealed that only baseline FGF23 levels significantly predicted the effect of fosinopril treatment (Table 2).

Although both responders and nonresponders achieved a significant BP reduction after treatment, the former had a significantly higher decrease in SBP (Table 3). The receiver operating characteristic curve analysis showed that plasma FGF23 predicted the effectiveness of fosinopril treatment with an area under the curve of 0.784 (95% CI, 0.704–0.863) ($P<0.01$) for a sensitivity and a specificity of 67.0% and 89.6% respectively for a cutoff value of 62.08 RU/mL (Figure).

External Validation

Of the 40 patients recruited for the validation study, 22 (group 1) had a plasma FGF23 level >62.08 RU/mL, and 18 (group 2) had a plasma FGF23 level ≤62.08 RU/mL. At week 4, the initial fosinopril dosage of 10 mg remained unchanged in 6 children, 15 mg in 1, 20 mg in 24, and 30 mg in 9. The baseline parameters and fosinopril doses between the 2 groups of children are summarized in Table S1. After 4 weeks of treatment with fosinopril, the BP control rate of group 1 was

Table 1. Comparison of Baseline Parameters and Drug Doses Between Responders and Nonresponders

	Responders (n=91)	Nonresponders (n=48)	*P* value
Age, y	13 (3)	13 (2)	0.216
Sex, M/F	72/19	41/7	0.365
Weight, kg	82.02±17.76	77.81±14.80	0.163
Height, cm	170.00 (12.00)	172.50 (10.75)	0.653
BMI, kg/m^2	28.42±4.54	26.94±3.87	0.058
BMI *z* score	2.38 (0.98)	2.30 (1.32)	0.177
Obesity/nonobesity	68/23	34/14	0.622
SBP, mm Hg	140.00 (10.00)	141.00 (8.75)	0.265
DBP, mm Hg	82.00 (18.00)	80.00 (11.50)	0.934
Stage 1/Stage 2	18/73	0/48	0.001
Blood urea, mmol/L	4.38 (1.14)	4.14 (1.73)	0.851
Scr, μmol/L	52.0 (16.9)	53.4 (15.3)	0.581
eGFR, mL/min per 1.73 m^2	118.22 (29.80)	117.82 (27.75)	0.505
Fosinopril dose, mg/kg	0.25±0.10	0.27±0.08	0.145
FGF23, RU/mL	66.98 (33.07)	45.57 (18.93)	<0.01

The continuous variables were presented as mean±standard deviation or median (interquartile range). BMI indicates body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FGF23, fibroblast growth factor 23; M/F, male/female; SBP, systolic blood pressure; and Scr, serum creatinine.

72.7% (16/22), significantly higher than 33.3% (6/18) of group 2 (*P*=0.013).

DISCUSSION

Children with primary hypertension, especially those with target organ damages, have a high risk of cardiovascular events during adulthood.[10] Therefore, treatment and control of primary hypertension in children is of great importance. ACEIs remain the first-line antihypertensive agents, and currently there have been no biomarkers documented for the prediction of therapeutic efficacy of ACEIs in pediatric primary hypertension. Therefore, we aimed to investigate ACEI therapeutic efficacy for pediatric primary hypertension and identify a novel biomarker that predicts the responsiveness to ACEI therapy. We now report the following findings: (1) In the exploratory study, the BP control rate was 65.5% (91/139); the baseline plasma FGF23 level in responders was significantly higher than that in nonresponders; and the receiver operating characteristic curve analysis revealed that a cutoff value of 62.08 RU/mL for plasma FGF23 had a sensitivity of 67.0% and a specificity of 89.6% in predicting the therapeutic efficacy of fosinopril; and (2) external validation in the second cohort of patients showed that those with a baseline plasma FGF23 level >62.08 RU/mL had a significantly higher BP control rate with fosinopril therapy.

Table 2. Multiple Logistic Regression Analysis of Treatment Effect

Variables	Wald	Exp (B)	95% CI	*P* value
Plasma FGF23	5.450	0.981	0.965–0.997	0.020
Age	3.764	0.742	0.549–1.003	0.052
Sex	0.577	0.674	0.244–1.864	0.448
BMI *z* score	2.081	0.704	0.438–1.134	0.149
Pretreatment SBP	1.902	1.033	0.986–1.083	0.168
Blood urea	0.182	1.039	0.872–1.237	0.670
eGFR	0.139	0.997	0.978–1.015	0.710

The male group is taken as the reference group. BMI indicates body mass index; eGFR, estimated glomerular filtration rate; Exp (B), the exponentiation of the B coefficient; FGF23, fibroblast growth factor 23 and SBP, systolic blood pressure.

Fosinopril was chosen for the present study because it is a drug in the Food and Drug Administration Pediatric Priority List, and it is safe and effective for the treatment of pediatric hypertension.[11,12] The 2018 Chinese Guidelines for Prevention and Treatment of Hypertension recommend that clinicians refer to the medication guides to confirm whether or not antihypertensive medicine is appropriate in children,[9] where fosinopril is indicated for patients aged ≥12 years. In the present study, we observed a response rate of 65.5% in 139 children after 4 weeks of fosinopril administration. In a previous study, different fosinopril doses, namely, low (0.1 mg/kg), medium (0.3 mg/kg), or high (0.6 mg/kg), were applied to treat children with primary hypertension or high-normal BP with an associated medical condition requiring treatment, and the highest response rate of 47% was recorded at 4 weeks for

Table 3. BP Changes in Responders and Nonresponders

	Responders (n=91)	Nonresponders (n=48)	*P* value
Posttreatment SBP, mm Hg	124.00 (9.00)	130.00 (9.75)	<0.001
Posttreatment DBP, mm Hg	73.00 (12.00)	74.50 (10.00)	0.122
d-SBP, mm Hg	16.00 (12.00)	10.00 (8.75)	0.001
d-DBP, mm Hg	8.00 (17.00)	5.00 (13.50)	0.227

All data are presented as median (interquartile range). BP indicates blood pressure; DBP, diastolic blood pressure; d-DBP indicates decrease of DBP; d-SBP, decrease of SBP; and SBP, systolic blood pressure.

the medium dose,[11] lower than what we achieved. Of note, among the total of 87 children receiving 0.3 mg/kg of fosinopril, 72 had primary hypertension and 15 had high-normal blood pressure with a medical condition[11]; this heterogeneity of conditions, we speculate, leads to the lower response rate as an associated medical condition may affect the efficacy of fosinopril treatment, although the dose is similar to that received by our patients.

FGF23, a bone-derived hormone regulating calcium and phosphorus metabolism, has been implicated in cardiovascular disease.[13–16] In the ARIC (Atherosclerosis Risk in Communities) study, Fyfe-Johnson et al[17] examined the impact of FGF23 on the development of incident hypertension and revealed that 2152 of 7948 middle-aged participants who were normotensive developed hypertension during a median follow-up of 5.9 years, and high plasma FGF23 levels were associated with an increased risk of incident hypertension independent of kidney function. Similar findings were reported in the CARDIA (Coronary Artery Risk Development in Young Adults) study.[18] We recently found that children with primary hypertension had a significantly higher plasma FGF23 level than controls who were normotensive.[4]

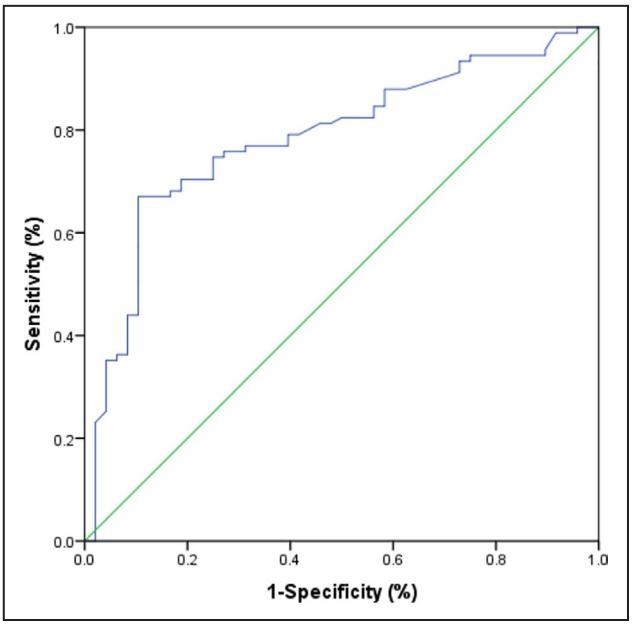

Figure 1. Receiver operating characteristic curve of plasma FGF23 levels for predicting the therapeutic efficacy of fosinopril.
The *y* axis represents the sensitivity to predict the effectiveness of different plasma FGF23 levels in fosinopril therapy. The *x* axis represents the false-positive rate (1–specificity) of the prediction. The green line is the reference line, indicating sensitivity=specificity. FGF23 indicates fibroblast growth factor 23.

Despite the findings from above clinical studies suggesting a role of FGF23 in the pathogenesis of hypertension, the mechanisms by which FGF23 regulates blood pressure remain to be fully elucidated. Animal studies have revealed that FGF23 promotes sodium and calcium reabsorption, resulting in hypertension.[19,20] Moreover, FGF23 has been found to regulate the RAAS. Dai et al[21] reported that FGF 23 activated the RAAS through the suppression of angiotensin-converting enzyme 2 in the kidney of genetically engineered mice overexpressing FGF23. RAAS activation by FGF23 was also observed in rat cardiomyocytes and cardiac fibroblasts.[22] Interestingly, activation of the RAAS in turn upregulates FGF23. Leifheit-Nestler et al[23] reported that angiotensin II and aldosterone, components of the RAAS, up-regulated FGF23 in rat cardiac myocytes. Pi et al[5] showed that rats and mice receiving angiotensin II through a subcutaneous pump for 4 weeks developed hypertension and had a significantly higher serum FGF23 level than animals treated with vehicle. These data suggest that interactions between FGF23 and the RAAS may contribute to hypertension, and higher FGF23 levels resulting from greater RAAS activation may indicate a better response to ACEIs. On the other hand, will blockade of the RAAS lead to the reduction of FGF23? Unfortunately, our current study is unable to answer this question, as plasma FGF23 was not measured at 4 weeks after antihypertensive treatment with fosinopril. Klotho, the essential component of the FGF23 receptor complex, is required for the high-affinity binding of FGF23 to its cognate receptor.[24] In this study, the soluble Klotho was not assayed and the correlation between Klotho levels and treatment effectiveness remains to be explored.

A positive correlation between plasma FGF23 levels and obesity has been described in both adults and children.[25,26] In the present study, we observed a trend (*P*=0.058) for higher BMI in the responders in the exploratory study. In view of this, the BMI *z* score for each individual patient was computed and compared, and no significant difference was found in the BMI *z* score between the responders and nonresponders. Furthermore, multiple regression analysis showed that BMI *z* score did not impact treatment responsiveness. Salt intake may

affect plasma FGF23 levels. A recent study demonstrated an inverse correlation between 24-hour urinary sodium levels and serum FGF23 concentrations in healthy adults.[27] As all participants of this study were prescribed a special diet restricting salt consumption during the treatment, we felt it was unlikely that salt intake played a confounding role in the antihypertensive treatment.

We found in the exploratory study that the baseline plasma FGF23 level in responders was significantly higher than that in nonresponders. Receiver operating characteristic analysis showed that plasma FGF23 predicted the efficacy of fosinopril, which was further confirmed in the external validation study. FGF23 in plasma is stable,[28] and ELISA kits for FGF23 measurement are commercially available. Once our results are validated in a large patient population, plasma FGF23 may serve as a novel biomarker to guide the treatment of pediatric primary hypertension with fosinopril in the future, although routine testing of FGF23 is currently unavailable in many labs.

Study Limitations

There are several limitations of this study, including (1) short-term follow up; (2) a small sample size; (3) FGF23 measurement at a single time point and currently unavailable in many labs; and (4) no measurement of Klotho, a coreceptor for FGF23.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Table S1

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SUPPLEMENTAL MATERIAL

Table S1. Comparison of baseline parameters and drug doses between the two groups of the validation study.

	Group 1 (n=22)	Group 2 (n=18)	P value
Age (year)	12 (2)	12.5 (2)	0.636
Sex (M/F)	16/6	14/4	0.714
Weight (kg)	75.33 ± 17.89	78.82 ± 20.95	0.573
Height (cm)	167.36 ± 9.86	172.33 ± 12.11	0.160
BMI (kg/m^2)	26.63 ± 4.17	26.16 ± 4.51	0.736
BMI z-score	2.10 ± 0.89	1.88 ± 0.89	0.452
Obesity/non-obesity	13/9	11/7	0.897
SBP (mm Hg)	141.00 (13.75）	142.00 (13.00）	0.892
DBP (mm Hg)	80.18 ± 8.05	82.39 ± 10.11	0.447
Stage 1/Stage 2	11/11	3/15	0.028
Blood urea (mmol/L)	4.20 (1.16)	4.18 (1.61)	0.704
Scr (μmol/L)	51.71 ± 13.43	54.45 ± 11.04	0.512
eGFR ($ml/min/1.73m^2$)	124.92 ± 31.02	118.77 ± 22.15	0.503
Fosinopril dose (mg/kg)	0.25 (0.21)	0.26 (0.13)	0.505
FGF 23 (RU/mL)	102.73 (54.84)	44.20 (16.92)	< 0.001

Scr: serum creatinine. eGFR: estimated glomerular filtration rate. The continuous variables were presented as mean ± standard deviation or median (interquartile range).