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Fibroblast Growth Factor-23 and Vegetarian Diet in India

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Abstract

Objective: Sparse data exist on population distributions of serum fibroblast growth factor 23 (FGF23) levels from developing, middle-income economies. FGF23 levels may differ substantially across regions based on differences in diet and urbanization. In a population-based study from North India, we tested the hypothesis that urinary phosphate excretion and FGF23 levels are lower among rural compared with urban participants, and among vegetarian compared with non-vegetarian participants.

Methods: We measured 24-hour urinary phosphate, and serum parathyroid hormone and FGF23 in a subsample of the population-based Cardiometabolic Risk Reduction in South Asia and Indian Council of Medical Research Coronary Heart Disease surveys. We categorized participants according to diet and residence: urban non-vegetarians (n=70), urban vegetarians (n=564), and rural vegetarians (n=558). Using least-square means, we compared the groups' 24-hour urinary phosphate (with urban vegetarians as reference) and FGF23 levels after accounting for age, sex, diabetes, and body mass index.

Results: Among 1192 study participants, mean FGF23 was 41 ± 18 pg/mL, median parathyroid hormone was 44 (interquartile range [IQR] 31–60) pg/mL, and median 24-hour urinary phosphate excretion was 419 (IQR: 47–622) mg/day. Urinary phosphate was significantly higher in rural compared with urban vegetarians (median, 503; IQR, 334–543 versus 365; IQR, 199–399 mg/day), but adjusted mean FGF23 levels did not differ across study groups.

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Conclusion: In rural and urban India, urinary phosphate excretion was low, but FGF23 levels did not differ by residence or dietary preference. Homogenously low dietary phosphate intake across different settings and diets may partly explain the lack of differences in FGF23.

Keywords

FGF23; FGF-23; phosphate; vegetarian; diet; rural

Introduction

Fibroblast growth factor 23 (FGF23) is a bone-derived hormone that promotes phosphate excretion from the kidney and counter-regulates the effects of parathyroid hormone (PTH) to suppress circulating concentrations of calcitriol, which is the active form of vitamin D¹. Elevated FGF23 levels, as observed most commonly in patients with chronic kidney disease (CKD), may have several additional off-target adverse cardiovascular effects², including contributing to left ventricular hypertrophy,^{3,4} atrial fibrillation⁵, heart failure⁶, and endothelial dysfunction⁷. Since high FGF23 predicts risk for overall mortality^{8–12} and cardiovascular events^{5,6,8} in persons with and without CKD, multiple studies have investigated approaches to lower FGF23 levels^{13–15}.

Consuming a plant protein-enriched diet is one potential non-pharmacological approach to reduce FGF23 levels¹⁶. Animal data demonstrated lower FGF23 levels and urine phosphate excretion in rats fed a plant-based versus casein-based protein diet¹⁷, and the results were confirmed in humans in a cross-over randomized trial of patients with advanced CKD stage and mean eGFR of 32.0 ml/min/1.73m². Participants fed a vegetarian, grain- and soy-rich diet had approximately 40% lower FGF23 levels compared with the corresponding time period when they ate a meat-rich diet, despite both diets containing an equal amount of total phosphate¹⁸. These results may be explained by the 2.5-fold higher phosphate absorption from meat-based versus plant-based protein sources^{18,19}. The findings from this work suggest that consuming a vegetarian diet might lower FGF23 relative to a meat-based diet, but there is a scarcity of data available on the association of FGF23 with dietary preference in the general population, and none available in the Asian Indian population, where a majority of persons consume little to no meat²⁰.

Studies have examined FGF23 levels according to degree of urbanization^{19,21}. In these studies, Africans living in Nigeria or Ghana had lower urine phosphate excretion and lower FGF23 levels compared with African Americans, possibly due to lower intake of meat-protein or processed foods. A similar gradient could exist within India, given the heterogeneity in diet and lifestyle between urban and rural areas²².

Using data from two population-based studies, we evaluated serum FGF23, urinary phosphate excretion, and fractional excretion of phosphate in persons living in rural and urban India. We hypothesized that FGF23 levels would be lower in rural than in urban environments, and lower in vegetarians than in non-vegetarians.

Methods and Materials

We used data from a subset of participants of two population-based studies: 1) Centre for Cardiometabolic Risk Reduction in South Asia (CARRS) cohort study in urban Delhi²³; and 2) Indian Council of Medical Research coronary heart disease repeat (CHD) survey in rural Haryana²⁴. The detailed methodology of the urban CARRS²³ and rural CHD repeat survey²⁴ have been previously published. Both studies employed population-representative sampling of adults and collected data on demography, medical history, anthropometry, and blood pressure at the participants' homes using standard questionnaires and procedures. In both studies, a randomly selected subset completed 24-hour urine collections between 2010–12. The Institutional Review Board of the Centre for Chronic Disease Control, New Delhi provided ethical approval for the studies.

Serum FGF23, Parathyroid hormone, and Phosphate

Once collected in the field, we transported blood and urine to a Randox International Quality Assessment Scheme-certified central laboratory. The blood samples were centrifuged and immediately stored in -80°C freezers. For this analysis, we thawed samples to measure intact FGF23 using a two-site enzyme-linked immunosorbent assay (Immutopics, Inc., San Clemente, California, US). Parathyroid hormone (PTH) was analyzed by electrochemiluminescence immune assay (Roche Diagnostics, Rotkreuz, Switzerland). Phosphate in plasma and urine was analyzed by forming ammonium phosphomolybdenum complex on c311 (Roche) using reagents from Roche Diagnostics, Switzerland. All calibrators and controls were run in duplicates. The coefficient of variation for FGF23, PTH, phosphate and urine phosphate assays were below 10%.

24-hour Urine Measures

We provided each participant with a five-liter container to collect urine and standard instructions regarding 24-hour urine collection. Participants were asked to note the starting and ending times of their collections. The 24-hour urine samples were transported in whole to the central laboratory, where volume was measured, and the urine was aliquoted and stored in -80°C freezers. Urinary phosphate, potassium, and sodium were measured using direct measurement by ion-selective electrode. Urine creatinine was measured using the modified kinetic Jaffe method. We corrected urinary phosphate, potassium and sodium excretions for collection times, as previously described²⁵. We calculated fractional excretion of phosphate as $100 \times (\text{urine phosphate} \times \text{serum creatinine}) / (\text{serum phosphate} \times \text{urine creatinine})$.

Statistical Analysis

We present descriptive statistics according to urban versus rural residence, and dietary preference. We defined participants as non-vegetarian if they had habitual meat intake (i.e., ate 4 or more servings of meat per week). Since only 3 of 561 persons living in rural areas reported habitual meat intake, we excluded them from our analysis. Thus, participants were categorized into three groups: urban non-vegetarians, urban vegetarians, and rural vegetarians. For subsequent analyses, we used urban vegetarians as the reference category,

and compared urban non-vegetarians to urban vegetarians, and rural vegetarians to urban vegetarians.

Continuous variables are presented as mean $\pm$ standard deviation (SD) for normally distributed variables or median (interquartile range [IQR]) for non-normally distributed variables. Categorical variables are presented as counts and corresponding percentages. We first describe the unadjusted means of serum phosphate, 24-hour urinary phosphate excretion, and urinary fractional excretion of phosphate, FGF23, and PTH.

To examine differences in FGF23 levels by study groups, we calculated least-square means adjusted values of FGF23, after accounting for age, sex, diabetes, and body mass index. We also examined differences in urinary fractional excretion of phosphate by diet and urban status, after accounting for age, sex, diabetes, and body mass index. In a sensitivity analysis, we used South Asian-specific urine creatinine excretion cut offs²⁶, and determined 24-hour urinary phosphate excretion in the sub-sample of participants with biologically plausible urine creatinine excretions of at least 9 mg/kg/day for men and 7 mg/kg/day for women (n=969). To test the hypothesis that higher intake of fresh fruits and vegetables would be associated with lower FGF23 levels¹⁶, we evaluated the association between FGF23 and urinary potassium excretion, which is a surrogate of fruit and vegetable intake. All analyses were performed with R (version 3.5.2). For all analyses, a p-value (two-tailed) < 0.05 was considered to indicate statistical significance.

Results

Of the 1203 eligible participants, we excluded 11 with missing serum creatinine values. Table 2 describes the 1,192 study participants by living environment and dietary preference. Compared with urban participants, participants from rural areas had lower rates of diabetes and obesity. Median urine sodium and potassium excretion were both higher in rural than in urban participants. A majority (94%) of participants were vegetarian. Urban non-vegetarians were younger than urban or rural vegetarians.

Overall median urine phosphate excretion was 419 (IQR: 247–622) mg/day (Table 2). Urine phosphate excretion was higher in rural compared with urban participants. In a sensitivity analysis restricted to participants with urine creatinine at or above expected levels, overall median urine phosphate excretion was slightly higher at 473 (330–674) mg/day. Fractional excretion of phosphate was highest in rural vegetarians and lowest in urban non-vegetarians.

Mean and median FGF23 levels in the study population were 41.0 ± 18.2 and 38.7 (IQR: 26.6–52.9) pg/mL, respectively (Figure 1). Median FGF23 levels were higher in women than men (39.7 versus 37.1 pg/mL; $p = 0.04$), but did not differ in those with versus without diabetes (38.2 versus 39.1; $p = 0.32$), or by age categories (< 45 years: 42.5 pg/ml versus 45 years: 42.1; $p = 0.81$). Furthermore, unadjusted and adjusted FGF23 levels did not differ by vegetarian or non-vegetarian status in the urban area, nor by rural versus urban residence among vegetarians (Figure 2). In contrast, adjusted fractional excretion of phosphate was higher in rural vegetarians, compared with urban vegetarians, and lower in urban non-

vegetarian compared with urban vegetarians (Figure 3). There was a weak correlation between FGF23 and fractional excretion of phosphate ($r^2 = 0.06$; $p = 0.04$).

We tested the hypothesis that participants with higher urinary potassium excretion and thereby higher intake of fresh fruits and vegetables would have lower FGF23 levels. However, there was no correlation between FGF23 levels and urine potassium excretion ($r^2 = 0.02$, p value=0.47).

Discussion

We hypothesized that a vegetarian diet would be associated with lower FGF23 levels than a non-vegetarian diet. However, we found similar FGF23 levels across the dietary groups in this study. In addition, unlike the notable differences seen along the urbanization spectrum in prior studies, we found no differences in FGF23 levels between urban versus rural areas in India. However, overall 24-hour urinary excretion of phosphate, and thus dietary intake of phosphate were extremely low in all groups. Thus the homogenously low phosphate intake may partly explain the lack of variation in FGF23 levels across the dietary and rural-urban axis in India.

In the community-based Multi-Ethnic Study of Atherosclerosis of persons without preexisting cardiovascular disease, mean FGF23 levels were 40.0 (15.2) pg/mL and did not differ across ethnicities²⁷. Similar levels are reported from other population-based studies, including from elderly persons with normal kidney function in Sweden (median FGF23 levels of 41.5 [IQR: 25.1–67.3] pg/mL)²¹, and in patients with diabetes but normal kidney function in China (median FGF23 levels of 42.1 [35.6–49.2] pg/mL)²⁸. Therefore, despite a majority of participants reporting little to no animal-based protein intake, overall FGF23 levels in our study of Indian participants are similar to those reported from other regions.

In a comparison of individuals of African descent living in rural Nigeria and urban U.S., urban U.S. participants had median FGF23 levels that were 5-to-7 fold higher than rural Nigerians¹⁹. The authors hypothesized that this difference was driven by lower dietary phosphate intake or gut phosphate absorption in rural populations that ingest less animal-based proteins and processed foods. This was supported by parallel differences in urinary phosphate excretion, which was much higher in the U.S. versus Nigerian participants. There are several potential explanations for the discrepant results between that study and the current one. First, few participants consumed daily servings of meat-protein, thus limiting heterogeneity of the dietary exposure between the vegetarians and non-vegetarians. In addition, intake of phosphate as estimated by urine phosphate excretion was extremely low overall and varied little across urban and rural participants or across the dietary preference groups. Dietary data from the U.S. National Health and Nutrition Examination Survey describe median phosphate intake more than double the urinary excretion of phosphate seen in our Indian participants (1166 [IQR: 823–1610] versus 419 [IQR: 247–622] mg/day)²⁹. Higher estimates of phosphate excretion—generally exceeding 700mg/day—are reported from participants of the Nurses Health Study³⁰, Health Professional Follow Up Study³¹, and from participants with near-normal eGFR in the Chronic Renal Insufficiency Cohort.³² The

overall extremely low phosphate intake in our participants may have limited our ability to detect differences in FGF23 levels by rural-urban status, and by diet.

We also unexpectedly found that the urine sodium to potassium ratios in rural versus urban participants, and vegetarian versus non-vegetarians were similar and much higher than the target of <1 that is recommended by World Health Organization. Thus, we speculate that processed food intake may also have been similar across our comparator groups. Consistently, urban participants reported similar fresh fruit and vegetable intake to rural participants and no higher fried food intake, suggesting that contrary to our hypothesis, processed food intake was likely not higher in urban compared with rural study participants. Alternatively, the rural vegetarian group could have relatively higher dairy intake, compared with the urban vegetarians. In comparing non-vegetarian to vegetarian urban participants, a relatively higher contribution from sources other than animal protein (e.g., dairy or processed foods³³—rich in inorganic phosphate, most of which are readily absorbed¹⁹) could obscure small differences related to other aspects of the diet.

Our study has several limitations. We did not measure vitamin D levels, which could also differ by diet preference and rural/urban residence, and could have helped to explain the lower parathyroid hormone levels seen in the rural participants, who presumably spend a larger portion of their time outdoors. We rely on single 24-hour urine collections, but two 24-hour urine collections have been demonstrated to have better reliability in estimating phosphate excretion³⁴. Our study is small and cross-sectional. Thus we lack any outcome data.

The strengths of our analysis include representative, community-based participants, standardized procedures in the surveys, availability of 24-hour urine collections, and use of a central, certified laboratory. We evaluated 24-hour urine collections using ethnicity-specific urine creatinine excretion threshold and found minor differences between the subset and overall complete dataset. Since we had data from two settings, both of which had available data on dietary preference, we were able to assess for differences across the urban-rural and vegetarian -and non-vegetarian spectrum in a single country.

We report data on FGF23 levels and urine phosphate excretion from a previously understudied population. Both may be expected to differ substantially from other regions based on differences in diet and urbanization. However, we found minimal difference in FGF23 levels overall when compared to other regions, and by diet and urban-rural status within India, despite the low urine phosphate excretion compared to other developed countries. We find that low intake of animal protein alone is not associated with lower population distribution of FGF23 levels.

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Practical Application

Despite relying on diet with extremely low animal intake, healthy participants in India had mean FGF23 levels similar to those of residents of high income countries. Thus, while animal protein is a major source of inorganic phosphate with high intestinal absorption in high-income countries, its low intake does not result in lower FGF23 levels in India.

Figure 1:
Distribution of FGF23 levels in India: Mean and median FGF23 levels in the study population were 41.0 ± 18.2 and 38.7 (IQR: 26.6–52.9) pg/mL, respectively.

Figure 2:

FGF23 levels according to residence and dietary preference in India: FGF23 levels were similar when compared between rural (45.3 [95%CI: 41.3–49.3] pg/mL) and urban vegetarians (46.7 [95%CI: 43.4–50.0] pg/mL), and urban non-vegetarians (48.7 [41.6–55.8] pg/mL), after accounting for age, sex, diabetes, and body mass index.

Figure 3:

Fractional excretion of phosphate according to residence and dietary preference: Fractional excretion of phosphate was highest in rural vegetarians, after accounting for age, sex, diabetes, and body mass index. Urban non-vegetarians had lowest fractional excretion of phosphate ($p < 0.0001$ in comparison with rural vegetarians).

Table 1:

Study sample description, stratified by residence and dietary preference*

	Urban		Rural	Overall
	Non-vegetarian 70	Vegetarian 564	Vegetarian 558	
N				1192
Age	41 (11)	47 (13)	47 (15)	47 (14)
Women	34 (49)	286 (51)	338 (61)	658 (55)
Diabetes ^Q	9 (13)	87 (15)	9 (2)	105 (9)
Fruit & vegetable intake (times/day)	2.8 (1.5, 4.1)	2.4 (1.6, 3.4)	2.5 (2.2, 3.7)	2.4 (1.9, 3.0)
<2	23(33)	211 (37)	78 (14)	312 (26)
2-3	27(39)	254 (21)	429 (77)	710 (60)
4	20(29)	99 (18)	14 (3)	133 (11)
Missing	0	0	37 (7)	37 (3)
Fried food intake				
<once a week	52 (74)	381 (68)	436(78)	869(73)
Weekly	15 (21)	163 (29)	117 (21)	295 (25)
Daily	3 (5)	20 (4)	5 (1)	28 (2)
Systolic blood pressure (mmHg)	125 (17)	127 (20)	122 (21)	125 (21)
Diastolic blood pressure (mmHg)	84 (10)	84 (13)	82 (13)	83 (13)
Quetlet's BMI ^Q (kg/m ²)	26 (5)	26 (5)	23 (4)	24 (5)
Normal	35 (52)	237 (45)	397 (71)	669 (58)
Overweight	22 (32)	170 (32)	138 (25)	330 (29)
Obese	11(16)	121 (23)	23 (4)	155(13)
Serum creatinine (mg/dL)	0.75 (0.18)	0.80 (0.33)	0.85 (0.26)	0.82 (0.29)
24 hour urine ^β				
Creatinine, unadjusted (mg)	672 (537, 927)	754 (523, 1034)	724 (501, 1004)	799 (387)
Creatinine (mg)	1290 (996, 1483)	1205 (991, 1428)	1028 (872, 1282)	1151 (296)
Sodium (mg)	1804 (1294, 3201)	2081 (1226, 3259)	3455 (2225, 5044)	2625 (1592, 4097)
Potassium (mg)	765 (506, 1098)	1015 (636, 1546)	1515 (1026, 2101)	1210 (770, 1825)

	Urban		Rural	Overall
N	Non-vegetarian 70	Vegetarian 564	Vegetarian 558	1192
Sodium: Potassium ratio	2.70 (1.39)	2.20 (1.14)	2.47 (0.96)	2.36 (1.09)

* Continuous data presented as mean (standard deviation) or median (25th, 75th percentile), categorical data as number (%).

Ω Diabetes defined as self-reported diabetes, or fasting glucose ≥ 126 mg/dL or A1c $\geq 6.5\%$. Body mass index (BMI) defined as overweight if 23–27 kg/m², and as obese if > 27 kg/m².

β Data are adjusted to a 24 hour time period unless otherwise specified.

Table 2:

Serum and urinary phosphate parameters, stratified by study site and dietary preference

	Urban		Rural	Overall
N	Non vegetarian 70	Vegetarian 564	Vegetarian 558	1192
Serum tests				
Parathyroid hormone (pg/mL)	53 (41, 70) ^β	59 (44, 82) [*]	34 (25, 46)	44 (31, 60)
Plasma phosphate (mg/dL)	3.7 (3.4, 4.2)	3.7 (3.3, 4.2) [*]	3.9 (3.5, 4.3)	3.8 (3.8, 4.2)
24 hour urine				
Phosphate (mg)	338.3 (162.6–360.1)	364.8 (198.6–399.2) [*]	503.0 (333.7–542.9)	423.2 (250.3–624.8)
Phosphate (mg) [^]	361.1 (175.6–513.5)	408.3 (256.0–588.0)	561.6 (401.1–759.9)	472.6 (329.6–673.9)
Fractional phosphate excretion (%)	8(6,12) ^β	10 (7, 14) [*]	15 (11, 19)	12 (8, 16)

Data are presented as median (25th, 75th percentile)^β indicate that log-transformed values are different when comparing urban non-vegetarians versus urban vegetarians at p<0.05.^{*} indicate that log-transformed values are different when comparing urban versus rural vegetarians at p<0.05.[^] restricted to women and men with urine creatinine excretion > 7 mg/kg/day and > 9 mg/kg/day respectively (n=969).