Original Article

Fibroblast growth factor-23 and phosphorus related factors in young Japanese women: a cross-sectional study

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Phosphorus homeostasis is determined by dietary intake, intestinal absorption, and renal tubular reabsorption of phosphorus. Serum fibroblast growth factor-23 (FGF-23) is considered to be a sensitive early biomarker of disordered phosphorus metabolism in both patients with chronic kidney diseases and healthy subjects. However, the number of studies evaluating serum FGF-23 concentrations in healthy subjects is limited. The objective of this cross-sectional study was to examine the relationship between serum FGF-23 concentrations and phosphorus related factors in 182 young Japanese women (mean age, 19.5±0.4 years). We found that higher serum concentrations of inorganic phosphorus and lower serum concentrations of 1,25-dihydroxy vitamin D as well as lower fat but higher phosphorus and calcium intake were weakly but significantly associated with high serum concentrations of FGF-23, adjusted for postmenarcheal age and body weight. These results suggested that in young Japanese women, serum FGF-23 might be indicative of phosphorus nutrition status. However, it is worthy of note that maturity factors, including postmenarcheal age and physical attributes, such as body weight, might be related to serum FGF-23 concentrations.

Key Words: fibroblast growth factor-23, phosphorus, calcium, bone mineral density, young Japanese women

INTRODUCTION

Phosphorus is an important mineral, playing a vital role in energy metabolism, cellular signaling, nucleic acid metabolism, platelet aggregation, and bone mineralization.[1] Phosphorus homeostasis is determined by dietary intake, intestinal absorption, and renal tubular reabsorption of phosphorus.[2] Thus, in healthy subjects, morning fasting serum phosphorus concentration is maintained within the normal range via hormonal mechanisms even in cases of excess dietary phosphorus intake.

Such hormonal mechanisms, primarily mediated by parathyroid hormone (PTH) and the bone-derived hormone fibroblast growth factor-23 (FGF-23), are usually activated to reduce post-meal elevation of serum phosphorus concentration.[3] PTH acts on the bone to increase an efflux of calcium and phosphate and in the kidneys to increase active vitamin D synthesis.[4] FGF-23 is a 251-amino acid phosphatonin that promotes phosphaturia by decreasing phosphorus reabsorption in the proximal tubules and phosphorus absorption in the gut via the inhibition of active vitamin D generation.[5] Several epidemiologic studies have suggested that a high-phosphorus diet is a risk factor for bone health, cardiovascular diseases, and mortality, not only in patients with chronic kidney diseases (CKD) but also in the general population.[6,7] Such a dietis thought to induce PTH and FGF-23 release, resulting in significant pathogenic cardiovascular effects, such as arterial calcification, endothelial dysfunction, and left ventricular hypertrophy.[6]

In CKD patients, an increase in serum FGF-23 concentration precedes that of PTH and serum phosphate concentration.[8] Thus, FGF-23 might be a sensitive early biomarker of disordered phosphorus metabolism in not only CKD patients and also healthy subjects.[8] However, the number of studies assessing serum FGF-23 concentrations in healthy people is limited. In community-living Caucasian men aged 40 to 75 years with largely preserved kidney functions, older age, high BMI and phosphorus intake, current smoking status, and history of hypertension were independently associated with high serum FGF-23 concentrations.[9] Furthermore, in elderly Swedish men aged 69 to 80 years without any known renal diseases, there was a positive association between serum FGF-23 concentrations and body weight.[10] Additionally, the weak correlation between serum FGF-23 concentrations and bone mineral density (BMD) was mainly due to the association between serum FGF-23 concentrations and body weight. The same authors of the above mentioned studies also reported a positive relationship between serum FGF-23 concentrations and body fat mass, adverse lipid me-

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Manuscript received 02 April 2015. Initial review completed 14 June 2015. Revision accepted 25 June 2015.
doi: 10.6133/apjcn.092015.22

tabolism, and fracture risk in elderly Swedish indivisuals.[11,12]

However, all the above-mentioned studies were conducted in Western men. Thus, the relationship between FGF-23 and anthropometric or phosphorus related factors have not been clearly demonstrated in healthy subjects, particularly those of Asian background. The objective of this study was to examine the relationship between serum FGF-23 concentrations and phosphorus related factors in young Japanese women.

METHODS

Study design

The subjects of this study were first-year female students enrolled at Kagawa Nutrition University in 2011. The study purposes and protocol were explained to all participants prior to their enrollment. Written informed consent was obtained from each subject. The procedures used in this study were approved by the Human Research Ethics Committee of Kagawa Nutrition University. A total of 197 subjects participated in the study. Of these, 12 were excluded because their energy intake from a three-day dietary record was less than 1,000 kcal/day, and three subjects were excluded for missing data. Finally, 182 subjects (92.4%) with all the required data were analyzed.

Age and postmenarcheal age, and physical assessments

Age and postmenarcheal age (defined as age at the time of survey subtracting that at menarche) were reported in a questionnaire.

All participants' body height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively, while they were wearing light clothes and no shoes. BMI was calculated as body weight (kg) divided by the square of body height (m).

Bone mineral content (BMC), BMD, body fat mass, and body fat percentage were measured by dual-energy X-ray absorptiometry (Lunar Prodigy, GE Healthcare, Wisconsin, USA).

Serum and 24-hour urine samples

Serum samples were obtained from blood drawn under fasting condition. Subjects were asked not to eat or drink with the exception of water after 10 pm on the day prior to blood sampling.

A single 24-hour urine sample was collected. Subjects were instructed orally and in writing on the method of urine collection and the necessity of obtaining a complete 24-hour urine collection. We requested the subjects to eat and drink normally during the collection period and to follow their usual pattern of activity. Subjects were then provided with a bag, two or three 1-liter plastic bottles (containing no additives) and ten 500-mL cups. They were asked to discard the specimen collected around noon on the collection day and record that time on a sheet as the start of the collection period. Subsequently, they were instructed to collect all specimens produced during a 24-hour period. When a specimen was missed, the participants were asked to record the estimated volume of missing urine and the time. The last specimen was collected around noon on the following day at approximately the same time as the start of the collection period, and the participants were asked to record that time point on the data sheet as the end of the collection period. All recording sheets were reviewed by our research staff when the collection bottles were submitted, and any missing information was obtained from the subjects. The height of urine concentration in each bottle was measured and later converted into volume using an empiric formula generated from repeated measurements of volumes in identical bottles.[13] All urine samples from the 24-hour collection period were then combined and mixed thoroughly by vigorous stirring, and several urinary aliquots were taken for analysis. Total 24-hour excretion of phosphorus and calcium was calculated by multiplying the measured concentration by the total volume of collected urine.

Serum FGF-23 concentrations were measured in our laboratory using an ELISA kit (Kainos Laboratories International; Tokyo, Japan) that recognizes only the biologically active full-length FGF-23.[14] Serum and urinary inorganic phosphorus concentrations were determined via a direct method using molybdic acid.[15] Serum and urinary calcium concentrations were determined via the orthocresolphthalein complex one method.[16] Serum whole PTH concentrations were measured by the immunoradiometric assay.[17] Serum 1,25-dihydroxy vitamin D ($1,25(OH)_2D$) concentrations were measured by the double antibody radioimmunoassay method.[18] All serum and urinary samples except those used for FGF-23 measurement were maintained at −20°C while being transported to a laboratory in Tokyo (SRL Inc., Tokyo, Japan).

Dietary assessments

Subjects were asked to record all foods and beverages consumed over a consecutive three-day period including one weekend and two week days that included the 24-hour urine sampling day. They were recommended to weight all foods but advised to report the portion size of foods consumed when the weight was not available. All subjects were interviewed about their unclear records by skilled registered dietitians. A computer program with Japanese food composition tables[19] was used to analyze diet records.

Statistical analysis

Pearson's product-moment correlation coefficient was calculated to test for linear correlation between serum FGF-23 concentrations and other measurements. Multiple regression analysis was used to assess the influence of phosphorus related measurements on serum FGF-23 concentrations, adjusted for postmenarcheal age and body weight. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 19.0 (IBM Japan, Ltd., Tokyo, Japan).

RESULTS

All subjects' demographic and physical characteristics, serum and urinary measurements, and nutrient intakes are presented in Table 1. The subjects' body height and weight were not significantly different from the values reported for those aged 18 to 20 years in the National Nutrition Survey, Japan.[20] The mean FGF-23 concentration was 30.4±11.1 pg/mL. Serum phosphorus and calcium concentrations were not significantly different from

Table 1. Characteristics of study subjects (n=182)†

Variable	Mean±SD	Coefficient of variation (%)
Age (years)	19.5±0.4	(2.1)
Postmenarcheal age (years)	7.1±1.4	(19.7)
Body height (cm)	158±5.2	(3.3)
Body weight (kg)	53.9±8.0	(14.8)
BMI (kg/m^2)	21.5±2.6	(12.1)
BMC (kg)	2.3±0.4	(17.4)
BMD (g/cm^2)	1.14±0.07	(6.1)
Body fat mass (kg)	15.7±5.1	(32.5)
Body fat percentages (%)	28.5±5.8	(20.4)
Serum FGF-23 (pg/mL)	30.4±11.1	(36.5)
Serum Pi (mg/dL)	3.8±0.4	(10.5)
Serum calcium (mg/dL)	9.7±0.3	(3.1)
Serum whole PTH (pg/mL)	17.6±3.8	(21.6)
Serum 1,25(OH)$_2$D (ng/mL)	73.5±20.9	(28.4)
Urinary Pi (mg/day)	651±143	(22.0)
Urinary Pi (mg/day/kg body weight)	12.2±2.7	(22.1)
Urinary calcium (mg/day)	92±42	(45.7)
Urinary calcium (mg/day/kg body weight)	1.7±0.8	(47.1)
Nutrient intakes		
Energy (kcal/day)	1534±310	(20.2)
Protein (g/day)	53.3±12.6	(23.6)
Protein (% energy)	14.0±2.4	(17.1)
Fat (g/day)	45.2±16.6	(36.7)
Fat (% energy)	26.2±6.0	(22.9)
Carbohydrate (g/day)	223±45.2	(20.3)
Carbohydrate (% energy)	58.4±6.5	(11.1)
Vitamin D (μg/day)	5.3±4.7	(88.7)
Vitamin D (μg/1,000 kcal)	3.5±3.5	(100)
Phosphorus (mg/day)	779±202	(25.9)
Phosphorus (mg/1,000 kcal)	511±104	(20.4)
Calcium (mg/day)	406±176	(43.3)
Calcium (mg/1,000 kcal)	265±104	(39.2)
Calcium/phosphorus ratio (mg/mg)	0.51±0.13	(25.5)

BMI: body mass index; BMC: bone mineral content; BMD: bone mineral density; FGF-23: fibroblast growth factor-23; Pi: inorganic phosphorus; PTH: parathyroid hormone; 1,25(OH)$_2$D: 1,25-dihydroxyvitamin D.
†Values are presented as mean±standard deviation (coefficient of variation).

those reported for young Japanese women aged 19.0±0.5 years in another cross-sectional study.[21] The mean urinary inorganic phosphorus concentration was 651±143 mg/day (12.2±2.7 mg/day/kg body weight), and the mean phosphorus intake was 779±202 mg/day (511±104 mg/1,000 kcal).

Table 2 shows the correlation coefficients of serum FGF-23 concentrations with other measurements. Serum FGF-23 concentrations positively correlated with body height and weight, BMI, BMD, body fat mass, serum inorganic phosphorus, whole PTH, urinary inorganic phosphorus, phosphorus intake per 1,000 kcal, calcium intake, and calcium/phosphorus intake ratio, while negatively correlated with postmenarcheal age, serum 1,25(OH)$_2$D concentrations, urinary calcium, and fat intake (% energy).

Table 3 shows the results of linear regression models used to examine the relationship between serum FGF-23 concentrations and phosphorus related measurements adjusted for postmenarcheal age and body weight. Higher serum inorganic phosphorus concentrations, phosphorus intake per 1,000 kcal, and calcium intake per 1,000 kcal, but lower 1,25(OH)$_2$D concentrations and fat intake (% energy) were independently associated with higher serum FGF-23 concentrations.

DISCUSSION

In the present cross-sectional study, the relationship between serum FGF-23 concentration and phosphorus related measurements were examined in young Japanese women. The mean serum FGF-23 concentration in this study was 30.4±11.1 pg/mL, which was lower than the value measured using the same kit in elderly Swedish men (42 to 49 pg/mL).[10-12] Orito et al reported that serum calcium concentrations remained constant between the ages of 12 and 30 years, while serum phosphorus concentrations gradually decreased from 12 to 18 years of age and remained constant thereafter.[22] Since the mean age of this study's participants was 19.5±0.4 years, their serum inorganic phosphorus and calcium concentrations were expected to be stable. However, in this study, serum inorganic phosphorus concentrations, but not serum calcium concentrations, negatively correlated with postmenarcheal age (r=-0.15, p<0.05) (data not shown), but not with age. Furthermore, serum FGF-23 concentrations also negatively correlated with postmen-

Table 2. Pearson's correlation coefficients for serum FGF-23† concentrations and other measures (n=182)

	Serum FGF-23 (pg/mL)	
	r	*p*
Age (years)	0.05	0.493
Postmenarcheal age (years)	-0.16	<0.05
Body height (cm)	0.18	<0.05
Body weight (kg)	0.22	<0.001
BMI (kg/m^2)	0.18	<0.05
BMC (kg)	0.13	0.091
BMD (g/cm^2)	0.15	<0.05
Body fat mass (kg)	0.19	<0.05
Body fat percentages (%)	0.14	0.058
Serum Pi (mg/dL)	0.29	<0.001
Serum calcium (mg/dL)	0.14	0.067
Serum whole PTH (pg/mL)	0.16	<0.05
Serum 1,25(OH)$_2$D (ng/mL)	-0.15	<0.05
Urinary Pi (mg/day)	0.15	<0.05
Urinary Pi (mg/day/kg body weight)	0.16	0.833
Urinary calcium (mg/day)	-0.10	0.174
Urinary calcium (mg/day/kg body weight)	-0.16	<0.05
Nutrient intakes		
Energy (kcal/day)	-0.03	0.675
Protein (g/day)	0.04	0.616
Protein (% Energy)	0.10	0.194
Fat (g/day)	-0.11	0.125
Fat (% Energy)	-0.17	<0.05
Carbohydrate (g/day)	0.04	0.616
Carbohydrate (% Energy)	0.13	0.082
Vitamin D (μg/day)	0.11	0.151
Vitamin D (μg/1,000 kcal)	0.10	0.178
Phosphorus (mg/day)	0.11	0.134
Phosphorus (mg/1,000 kcal)	0.18	<0.05
Calcium (mg/day)	0.16	<0.05
Calcium (mg/1,000 kcal)	0.22	<0.01
Calcium/phosphorus ratio (mg/mg)	0.15	<0.05

FGF-23: fibroblast growth factor-23; BMI: body mass index; BMC: bone mineral content; BMD: bone mineral density; Pi: inorganic phosphorus; PTH: parathyroid hormone; 1,25(OH)$_2$D: 1,25-dihydroxyvitamin D.

archeal age (r=-0.16, p<0.05), but not with age. These results indicated that serum inorganic phosphorus and FGF-23 concentrations might change with maturity rather than actual age in young women.

Serum FGF-23 concentrations positively correlated with physical attributes such as body height, weight, BMI and body fat mass in the present study. These findings were consistent with the reports on elderly Swedish men that serum FGF-23 concentrations exhibited a positive association with body weight and on Polish perimenopausal women that obese subjects had higher serum FGF-23 concentrations than non-obese participants.[9,23]

In the multiple regression analysis, we adopted postmenarcheal age and body weight as the adjusting factors, because there were significant relationships between serum FGF-23 concentrations and maturity, and also between those and physical attributes. As a result, the positive relationship between serum FGF-23 concentrations and BMD diminished, which was consistent with results by the study on elderly Swedish men.[9] Meanwhile, serum FGF-23 concentrations exhibiteda weak but significantly positive correlation with serum inorganic phosphorus concentrations and phosphorus intake per 1,000 kcal after adjusted for postmenarcheal age and body weight. These results indicated that serum FGF-23 concentrations might partially reflect phosphorus homeostasis in healthy subjects. Dietary phosphorus is absorbed from the intestine, and the excess is excreted in the urine. If phosphorus homeostasis in the body is maintained, the absorbed amount is nearly equal to or closely correlates with the amount excreted in the urine.[24] However, in our study, serum FGF-23 concentrations did not correlate with urinary phosphorus concentrations adjusted for postmenarcheal age and body weight. One possible reason for such a result might be that our urinary sampling period was only for a day.

In the present study, serum 1,25(OH)$_2$D concentrations, but not serum PTH, exhibited a weak but significantly negative correlation with serum FGF-23 concentrations, adjusted for postmenarcheal age and body weight, via multiple regression analysis. Antoniucci et al conducted a four-week dietary phosphorus intervention study in 13 healthy men and found that serum 1,25(OH)$_2$D concentrations significantly and inversely varied with FGF-23 concentrations, although there was no relationship between serum FGF-23 concentrations and intact PTH.[2] In this intervention study, serum 1,25(OH)$_2$D concentrations were at the highest when dietary phosphorus was restricted (625 mg/day) and lowest when phosphorus was supplemented (2,300 mg/day).[2] Our results were consistent with the findings of this intervention study despite the differences in study design.

We found the dietary fat intake (% energy) and calcium intake (mg/1,000 kcal) were weakly but significantly correlated with serum FGF-23 concentrations via multiple regression analysis. The positive correlation between calcium intake and serum FGF-23 concentrations might be owing to the strong positive correlation between calcium intake (mg/1,000 kcal) and phosphorus intake (mg/1,000 kcal) (r=0.80, p<0.001) (data not shown). However, the negative correlation between fat intake (% energy) and serum FGF-23 concentrations was intriguing and might require further investigation.

In this study, serum FGF-23 concentrations positively correlated with body fat mass. Mirza et al indicated that serum FGF-23 concentrations were associated with increased fat mass and dyslipidemia in elderly Swedish individuals.[11] Moreover, Tsuji et al reported that leptin directly stimulated serum FGF-23 expression in bone in leptin-deficient mice.[25] Kadowaki et al indicated that serum FGF-23 concentrations were inversely related to adiponectin, which is highly expressed in adipose tissue.[26] The results of present study support the findings of those reports. Further investigation is needed to clarify the relationship between serum FGF-23 and lipid metabolism.

Our study has several limitations. First, serum sampling was conducted under morning fasting condition. Thus, we could not detect the circadian rhythms of serum measures. Second, the participants were not diverse with limited age range and sex group. Third, phosphorus intake might be underestimated because most phosphorus contained in food additives was not included in the nutrient composition tables.[27] Phosphorus from food additives has been estimated to contribute more than 30% of total phosphorus in Western diets.[28] In addition, phosphorus

Table 3. Multiple regression analysis of serum FGF-23† concentrations against each measurement adjusted for post-menarcheal age and body weight (n=182)

Dependent variable/predictors	b (SE)†	*p* value	$R^{2‡}$
BMC (kg)	-5.26 (3.79)	0.167	0.082
BMD (g/cm^2)	7.51 (13.3)	0.572	0.074
Body fat mass (kg)	-0.03 (0.35)	0.938	0.072
Body fat percentages (%)	0.01 (0.18)	0.970	0.072
Serum Pi (mg/dL)	6.99 (1.99)	<0.001	0.132
Serum calcium (mg/dL)	5.06 (2.68)	0.060	0.090
Serum whole PTH (pg/mL)	0.36 (0.21)	0.094	0.087
Serum 1,25(OH)$_2$D (ng/mL)	-0.08 (0.04)	<0.05	0.096
Urinary Pi (mg/day)	0.01 (0.01)	0.225	0.080
Urinary Pi (mg/day/kg body weight)	0.43 (0.31)	0.168	0.082
Urinary calcium (mg/day)	-0.03 (0.02)	0.176	0.082
Urinary calcium (mg/day/kg body weight)	-0.13 (1.05)	0.209	0.080
Nutrient intakes			
Energy (kcal/day)	-0.00 (0.00)	0.621	0.073
Protein (g/day)	0.04 (0.06)	0.515	0.074
Protein (% energy)	0.51 (0.34)	0.129	0.084
Fat (g/day)	-0.08 (0.05)	0.094	0.087
Fat (% energy)	-0.31 (0.13)	<0.05	0.099
Carbohydrate (g/day)	0.01 (0.02)	0.680	0.073
Carbohydrate (% energy)	0.21 (0.12)	0.095	0.087
Vitamin D (μg/day)	0.17 (0.17)	0.319	0.077
Vitamin D (μg/1,000 kcal)	0.23 (0.23)	0.316	0.077
Phosphorus (mg/day)	0.01 (0.00)	0.140	0.083
Phosphorus (mg/1,000 kcal)	0.02 (0.01)	<0.05	0.104
Calcium (mg/day)	0.01 (0.01)	0.050	0.092
Calcium (mg/1,000 kcal)	0.02 (0.01)	<0.01	0.114
Calcium/phosphorus ratio (mg/mg)	12.4 (6.29)	0.051	0.092

FGF-23: fibroblast growth factor-23; BMC: bone mineral content; BMD: bone mineral density; Pi: inorganic phosphorus; PTH: parathyroid hormone; 1,25(OH)$_2$D: 1,25-dihydroxyvitamin D.
†Multiple regression coefficient (standard error).
‡Coefficient of determination.

from food additives is mostly in inorganic form, and thus absorbed faster and more efficiently than organic phosphorus mainly found in natural foods.[26]

In conclusion, we found that in young Japanese women, higher serum inorganic phosphorus concentrations and lower serum 1,25(OH)$_2$D concentrations as well as lower fat and higher phosphorus and calcium intake were weakly but significantly associated with higher serum FGF-23 concentrations, adjusted for postmenarcheal age and body weight. Thus, serum FGF-23 concentrations might reflect phosphorus nutrition status in healthy young Japanese women. However, it is worthy of note that maturity factors, including postmenarcheal age and physical attributes, such as body weight, might be related to serum FGF-23 concentrations. Further studies are needed to clarify the relationship between serum FGF-23 concentrations and dietary phosphorus as well as more accurately determine the amounts of dietary phosphorus or its bioavailability in all life stages.

ACKNOWLEDGEMENTS
We would like to thank all study participants. We thank Michihiro Ito, Waseda University, for helpful discussions.

AUTHOR DISCLOSURES
The authors declare no conflict of interest. This work was supported by the Japan Society for the Promotion of Science (JSPS) Grant-in-Aid for Research Activity Start-up (No. 23800056).

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Original Article

Fibroblast growth factor-23 and phosphorus related factors in young Japanese women: a cross-sectional study

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日本年轻女性中成纤维细胞生长因子 23 和磷相关因子的横断面研究

磷平衡是由饮食摄入量、肠道吸收和肾小管对磷的重吸收来确定的。血清成纤维细胞生长因子 23（FGF-23）被认为是慢性肾脏病患者和健康人磷代谢紊乱的一个早期敏感生物标志物。然而，评估健康人 FGF-23 血清浓度的研究数量有限。本横断面研究的目的是：在 182 名日本年轻女性（平均年龄为 19.5±0.4 岁）中研究血清 FGF-23 与磷相关因子之间的关系。校正初潮年龄和体重之后，我们发现较高的血清无机磷浓度与较低的血清 1,25-二羟基维生素 D 浓度和脂肪、较高的磷和钙摄入存在弱相关，但与较高的血清 FGF-23 显著相关。这些结果表明，在日本年轻女性中，FGF-23 可能反映磷的营养状态。然而，值得注意的是包括初潮年龄和身体状况（如体重）等反映成熟的指标，可能与血清 FGF-23 浓度有关。

关键词：成纤维细胞生长因子 23、磷、钙、骨密度、日本年轻女性