ORIGINAL

Habitual confectionery intake is associated with serum phosphorus levels : A cross-sectional study on healthy subjects

Yosuke Saito[1], Masae Sakuma[1,2], Yuri Narishima[1], Takuya Yoshida[3], Hiromichi Kumagai[3], and Hidekazu Arai[1]

[1]*Laboratory of Clinical Nutrition and Management, Graduate School of Nutritional and Environmental Sciences, The University of Shizuoka, Shizuoka, Japan,* [2]*Department of Human Nutrition, School of Life Studies, Sugiyama Jogakuen University, Aichi, Japan,* [3]*Laboratory of Clinical Nutrition, Graduate School of Nutritional and Environmental Sciences, The University of Shizuoka, Shizuoka, Japan*

Abstract : Hyperphosphatemia is associated with an increased risk of developing cardiovascular disease. Recently, it has been shown that high serum phosphorus levels are associated with increased cardiovascular events in healthy subjects, but the dietary factors determining serum phosphorus level have not been fully investigated. The study investigated the influence of habitual dietary factors on serum phosphorus levels in healthy young participants. This cross-sectional study conducted fasting blood sampling in 109 healthy young people and used a brief-type self-administered diet history questionnaire to evaluate the subject's habitual meals. Since the bioavailability of dietary phosphorus depends on the food sources, habitual phosphorus intakes from different food groups and intake frequency (times/month) of processed foods were calculated. The mean serum phosphorus level was 3.9 ± 0.5 mg/dl ; 10.1% of the subjects had serum phosphorus levels that exceeded the reference levels of ≤ 4.5 mg/dl. Total phosphorus intake and phosphorus intake from animal-based food did not differ between serum phosphorus quartiles. Higher intake of confectionery was associated with increased serum phosphorus levels. This study showed that frequent consumption of confectionery was associated with elevated serum phosphorus levels. Additional studies are needed to determine whether this is a causal relationship. J. Med. Invest. 66 : 134-140, February, 2019

Keywords : *Phosphorus, Confectionery, Food additive, Processed food*

INTRODUCTION

Hyperphosphatemia is a condition that is associated with increased risk of cardiovascular disease by promoting arterial sclerosis (1, 2). This is prevalent in patients with chronic renal failure. Several epidemiological studies in patients with chronic renal failure have shown that high serum phosphorus levels were independently associated with mortality and cardiovascular events (3-5). Interestingly, similar associations have been extended to the normal renal function population, even if the serum phosphorus level was within the normal range (6, 7). This suggests that controlling phosphorus intake is important in patients with kidney disease as well as healthy individuals.

Increased phosphorus intake is a worldwide problem. The main sources of high phosphorus levels are dairy, meat products and food additives. The amount of phosphorus intake from food additives in the American diet is estimated to be 1000 mg/day, which has doubled since 1990 (8).

Phosphorus is present in many foods, and its form varies. In plant-based foods, phosphorus is mainly present as phytates, which are poorly digested by humans (9, 10). In animal-based foods, the phosphorus is bound to amino acid side chains and is easily digested and liberated from food constituents (11). Phosphorus in food additives exists as inorganic molecules that readily dissociate in water. The phosphorus bioavailabilities from plant-based foods, animal-based foods, and food additives are ≤50%, 60%, and ≥90%, respectively. When assessing this increase in dietary phosphorus intake in nutritional counseling, it is necessary to consider both the total amount of dietary phosphorus intake and the food sources. Phosphorus intakes from different foods give different serum phosphorus levels and its regulating factors (12, 13).

Recent epidemiological studies have found no significant relationship between serum phosphorus levels and total phosphorus intake assessed from 24-hour dietary recall or dietary records (14, 15). The effects of habitual diet on serum phosphorus levels in healthy populations have not been fully elucidated. The study objective was to evaluate the associations between serum phosphorus levels and 1) phosphorus intake from different food groups and 2) intake frequency of processed foods among healthy young populations.

Received for publication November 2, 2018 ; accepted December 14, 2018.

Address correspondence and reprint requests to Masae Sakuma, Ph.D., Department of Human Nutrition, School of Life Studies, Sugiyama Jogakuen University, 17-3 Hoshigaoka Motomachi, Chikusa-ku, Nagoya 464-8662, Japan and Fax : +81-52-781-4390.

MATERIALS AND METHODS

Study population

One hundred nine healthy young participants from the University of Shizuoka and the Yamagata Prefectural Yonezawa University of Nutrition Sciences participated in this study (21 males, 88 females ; age : 19-25 years). The participants performed physical measurements and blood sampling, and there was no abnormality in any of the subjects' renal function. The clinical and biological characteristics of the subjects are shown in Table 1. All participants gave written informed consent, and the Ethics Committee of the University of Shizuoka approved this study. The protocol conformed to the Helsinki Declaration. The trial was registered in the University Hospital Medical information Network (UMIN) Center system. The UMIN accession number is UMIN000034352.

Table 1. Characteristics of study subjects

All subjects (*N* = 109)	
Age (year)	20.9 ± 1.4
Sex (% females)	80.7 (n = 88)
Height (cm)	161 ± 8
Body weight (kg)	54.3 ± 7.5
BMI (kg/m²)	20.8 ± 2.1
Blood	
Albumin (g/dl)	4.7 ± 0.3
Triglyceride (mg/dl)	65 ± 32
LDL-Cho (mg/dl)	96 ± 24
HDL-Cho (mg/dl)	66 ± 12
Urea nitrogen (mg/dl)	11.5 ± 2.7
Creatinine (mg/dl)	0.70 ± 0.12
Sodium (mEq/L)	141 ± 2
Potassium (mEq/L)	4.3 ± 0.3
Calcium (mg/dl)	9.4 ± 0.3
Phosphorus (mg/dl)	3.9 ± 0.5
iPTH (pg/ml)	35 ± 9
1,25(OH)$_2$VD$_3$ (pg/ml)	60.9 ± 16.3
iFGF-23 (pg/ml)	49.7 ± 40.3
cFGF-23 (RU/ml)*	15.1 ± 13.3

Values are % or mean ± standard deviation. Abbreviations : BMI, body mass index ; LDL-Cho, low-density lipoprotein cholesterol ; HDL-Cho, high-density lipoprotein cholesterol ; iPTH, intact parathyroid hormone ; 1,25(OH)$_2$VD$_3$, 1α,25-dihydroxyvitamin D$_3$; iFGF-23, intact fibroblast growth factor 23 ; cFGF-23, C-terminal fibroblast growth factor 23. *Serum cFGF-23 levels were available in 108 subjects.

Protocol

The participants received three examinations within 1 week : 1) questionnaires about habitual diet (brief-type self-administered diet history questionnaire : BDHQ), 2) blood sampling in the morning fasting, and 3) anthropometric measurements. They were instructed to live normally throughout the study period, without any restrictions on physical activity and dietary intake.

Brief-type self-administered diet history questionnaire (BDHQ)

Habitual diet during the preceding month was assessed using a BDHQ (16, 17). Macronutrient intakes were expressed as a ratio to the total energy intake. Phosphorus and calcium intakes were energy-adjusted by using the energy density model and expressed as density (mg per 1000 kcal energy intake).

Phosphorus intakes from different food groups

The BDHQ included questions about the frequency of consumption of 58 foods and beverages. Phosphorus intakes were calculated by using a commercial computer algorithm for the BDHQ, which was based primarily on the Standard Tables of Food Composition in Japan (18). The phosphorus intakes were grouped into 13 food groups (*Fish and shellfish, Meat, Eggs, Dairy products, Cereals, Potatoes, Pulses, Green and yellow vegetables, Other vegetables, Fruits, Confectioneries, Beverages, and Condiments*), mainly according to definitions of food groups outlined by Kobayashi *et al.* (16), with the following modifications : *Sugar* and *Oils* were excluded because they poorly absorb phosphorus ; *Pickled vegetables, Mushrooms*, and *Seaweeds* were included in *Other vegetables ; Alcoholic beverages* and *Non-alcoholic beverages,* excluding *Fruit and vegetable juice*, were included in *Beverages* ; and *Fruit and vegetable juice* was included in *Fruits*. The phosphorus intakes from the 13 food groups were further divided into three food categories : 1) Animal-based foods, including *Fish and shellfish, Meat, Eggs,* and *Dairy products,* 2) Plant-based foods, including *Cereals, Potatoes, Pulses, Green and yellow vegetables, Other vegetables, and Fruits,* and 3) Other foods, including *Confectioneries, Beverages*, and *Condiments*. All phosphorus intakes were energy-adjusted by using the energy density model and expressed as density (mg per 1000 kcal energy intake).

Intake Frequency Score (IFS) of processed foods

Phosphorus-containing food additives are extensively used in food processing. However, much of the phosphorus contained in food additives is not included in the Standard Tables of Food Composition in Japan (18). Thus, of the phosphorus intakes from 58 items estimated by BDHQ, those from processed foods may have been underestimated from the true phosphorus intake. Furthermore, even with similar foods, the content of phosphorus in food additives may vary greatly by manufacturer (19). In general, information on the phosphorus content of foods cannot be used because it is not described on the food label. Therefore, to evaluate dietary phosphorus intake from food additives, we focused on the intake frequency of processed foods. We chose eight items related to processed food from the BDHQ : 1) Ham, sausages, and bacon ; 2) Dried fish and salted fish (including salted mackerel, salted salmon, and dried horse mackerel) ; 3) Breads (including white bread and Japanese bread with a sweet filling) ; 4) Instant noodles and Chinese noodles ; 5) Rice crackers, rice cakes, and Japanese-style pancakes ; 6) Japanese sweets ; 7) Cakes, cookies, and biscuits ; and 8) Ice cream. We calculated the IFS per month from the individual responses to the intake frequency for each item. That is, the category of intake frequency reported in each item (≥2 times/day, 1 time/day, 4-6 times/week, 2-3 times/week, 1 time/week, 0-1 time/week, and did not eat) were assigned a numerical value as the midpoint of the upper and lower bound. Whenever the category was open-ended at the upper bound, the assigned value recorded was the lower bound value of the category (i.e., 2 times/day, 1 time/day, 5 times/week, 2.5 times/week, 1 time/week, 0.5 time/week, and 0 time/month, respectively). Subsequently, each numerical value was converted to the equivalent frequency per month (i.e., 60, 30, 21.4, 10.7, 4.3, 2.1, and 0 times/month, respectively), termed the IFS. We defined three categories of processed foods. These were animal-based processed foods : 1) ham, sausages, and bacon and 2) dried fish and salted fish ; plant-based processed foods : 3) breads and 4) instant noodles and Chinese noodles ; and confectionery : 5) rice crackers, rice cakes, and Japanese-style pancakes, 6) Japanese sweets, 7) cakes, cookies, and biscuits, and 8) ice cream. The IFS of the eight processed foods categories were summed and divided into the three categories.

Measurements of anthropometric and biochemical blood parameters

After measuring the body weight and height of each subject, the body mass index (BMI) was calculated. Blood samples were dispensed into vacuum blood collection tubes and centrifuged (4°C, 3000 rpm, 10 min) immediately. Serum samples were separated and stored at –80°C until use. Triglyceride, total cholesterol, high-density lipoprotein cholesterol, albumin, urea nitrogen, creatinine, sodium, potassium, calcium, phosphorus, intact parathyroid hormone (iPTH), and 1α,25-dihydroxyvitamin D$_3$ (1,25(OH)$_2$VD$_3$) levels were measured by SRL Inc. (Tokyo, Japan). Low-density lipoprotein cholesterol levels were estimated by using the Friedewald formula (20). Serum intact fibroblast growth factor-23 (iFGF-23) and C-terminal fibroblast growth factor-23 (cFGF-23) levels were measured by using an FGF-23 ELISA Kit (KAINOS Laboratories, Inc. Tokyo, Japan) and a Human FGF-23 (C-Term) ELISA Kit

(Quidel, San Diego, CA, USA), respectively, according to the manufacturer's instructions.

Statistical analysis

The baseline and dietary characteristics of the study subjects are presented as the mean ± standard deviation (SD). Gender differences regarding serum levels of phosphorus and phosphate-regulating factors (iPTH, 1,25(OH)$_2$VD$_3$, iFGF-23, and cFGF-23) were assessed by independent student's t-test and Mann-Whitney U test for normally and non-normally distributed variables, respectively. To investigate the relationship between serum phosphorus levels and phosphorus intake from each food group and IFS of the processed foods, the subjects were divided into quartiles based on the serum phosphorus levels of the target population. For each subgroup of serum phosphorus quartiles, data for all continuous variables were tested for normal distribution by using the Shapiro-Wilk test. Parametric one-way analysis of variance (parametric ANOVA) was used to test for differences in variables that were normally distributed in the subgroups among the serum phosphorus quartiles, and values are presented as the mean ± SD. The Kruskal-Wallis ANOVA was used to test for differences in variables that were non-normally distributed even in one subgroup among serum phosphorus quartiles, and values are presented as medians (25th to 75th interquartile range). Spearman's rank correlation coefficient was calculated to test for linear correlations between the IFS's of the processed foods and serum levels of phosphate-regulating factors. All analyses were only repeated for females due to the small number of male subjects. All statistical analyses were performed by using SPSS Statistic, version 22.0 for Windows (IBM SPSS, Inc., Chicago, IL, USA) and were considered statistically significant at $P < 0.05$.

Table 2. Dietary characteristics of study subjects

All subjects (*N* = 109)	
Daily energy (kcal/day)	1522 ± 562
Energy per body weight (kcal/kg)	28.1 ± 9.3
Protein (% Energy)	13.8 ± 2.4
Fat (% Energy)	27.4 ± 5.7
Carbohydrate (% Energy)	58.9 ± 7.4
Daily calcium (mg/day)	368 ± 174
Daily phosphorus (mg/day)	764 ± 314
Calcium (mg/1000 kcal)	244 ± 77
Total phosphorus (mg/1000 kcal)	500 ± 83
Animal-based foods*	253 ± 84
Fish and shellfish	72 ± 45
Meat	92 ± 47
Eggs	32 ± 21
Dairy products	58 ± 52
Plant-based foods*	190 ± 39
Cereals	101 ± 24
Potatoes	10 ± 9
Pulses	31 ± 25
Green and yellow vegetables	17 ± 14
Other vegetables	25 ± 13
Fruits	6 ± 6
Other foods*	57 ± 24
Confectioneries	39 ± 21
Beverages	11 ± 13
Condiments	7 ± 5

Values are means ± standard deviations. *Phosphorus intake from different food groups (mg/1000 kcal).

RESULTS

Subject characteristics

The characteristics of the subjects are shown in Table 1. The study population consisted of 109 participants with a mean age of 20.9 years ; 80.7% were women, and 87.1% were ideal body weight ($18.5 \leq$ BMI < 25). The mean serum phosphorus level was 3.9 mg/dl, 10.1% had high serum phosphorus levels that exceeded the reference levels (2.5-4.5 mg/dl), and no subject had serum phosphorus levels below the reference levels. In the study population, we assessed the gender differences regarding serum levels of phosphorus and phosphate-regulating factors because the gender was not distributed equally. Serum phosphorus, iPTH, 1,25(OH)$_2$VD$_3$, iFGF-23, and cFGF-23 levels were not significantly different between genders (data not shown). Serum cFGF-23 concentration of one subject among 109 subjects exceeded the detection limit, so it was excluded, and 108 subjects were analyzed.

Habitual dietary phosphorus intake

The characteristics of the habitual diets of the subjects are shown in Table 2. The means ± SDs for total phosphorus intake in the habitual diets were 500 ± 83 mg/1000 kcal. The means ± SDs for phosphorus intake from animal-based foods were 253 ± 84 mg/1000 kcal, which accounted for 51% of dietary phosphorus. Of the 13 food groups, *Cereals* was the main source of phosphorus (20%).

Subject characteristics according to serum phosphorus level quartiles

To evaluate whether or not the subject characteristics differed among serum phosphorus quartiles, clinical and laboratory characteristics were compared by ANOVA (Table 3). Serum 1,25(OH)$_2$VD$_3$ levels were significantly different among serum phosphorus quartiles ($P = 0.004$, Kruskal-Wallis ANOVA), with the lowest being the fourth quartile. This difference was also observed for females (median serum 1,25(OH)$_2$VD$_3$ levels in serum phosphorus quartiles 1, 2, 3, and 4 were 63.5 (55.9, 79.1), 60.5 (53.5, 76.4), 61.2 (47.4, 68.0), and 48.0 (43.1, 61.4) pg/ml, respectively ; Kruskal-Wallis ANOVA, $P = 0.004$; data not shown). There were no differences in the other clinical and laboratory characteristics.

Association between serum phosphorus levels and phosphorus intake from different food groups

To investigate the influence of habitual dietary factors affecting the serum phosphorus levels, we compared the habitual nutrient intakes and phosphorus intakes from different food groups among serum phosphorus quartiles by ANOVA (Table 4). Macronutrient intake, calcium intake, and total phosphorus intake did not differ among serum phosphorus quartiles. Phosphorus intake from animal-based foods that had a relatively high bioavailability of phosphorus did not differ among serum phosphorus quartiles, but phosphorus intake from other foods (the sum of *Confectioneries, Beverages,* and *Condiments*) differed significantly ($P = 0.032$, Kruskal-Wallis ANOVA), with the first quartile being the lowest. Notably, *Confectioneries* was the main source of other foods, and phosphorus intake from *Confectioneries* tended to be different among serum phosphorus quartiles ($P = 0.074$, Kruskal-Wallis ANOVA). These associations were also observed for females (median phosphorus intake from other foods in the serum phosphorus quartiles 1, 2, 3, and 4 were 38 (23, 66), 47 (32, 70), 58 (44, 75), and 59 (42, 77) mg/1000 kcal, respectively ; Kruskal-Wallis ANOVA, $P = 0.029$; data not shown).

Table 3. Participants' demographic, clinical, and laboratory characteristics according to serum phosphorus level quartiles

	S-Pi Quartile 1	S-Pi Quartile 2	S-Pi Quartile 3	S-Pi Quartile 4	*P*
n (109)	23	28	32	26	
Sex (% females)	82.6 (n = 19)	71.4 (n = 20)	78.1 (n = 25)	92.3 (n = 24)	
BMI (kg/m^2)	21.2 (19.5, 23.2)	20.2 (19.1, 20.9)	20.4 (19.5, 22.7)	20.4 (19.0, 21.2)	0.156
Blood					
Urea nitrogen (mg/dl)	10.7 (8.6, 11.6)	10.7 (9.6, 13.2)	11.6 (9.6, 14.4)	11.4 (9.8, 13.8)	0.398
Creatinine (mg/dl)	0.67 (0.62, 0.76)	0.69 (0.62, 0.77)	0.68 (0.60, 0.78)	0.70 (0.63, 0.76)	0.816
Calcium (mg/dl)	9.4 ± 0.3	9.4 ± 0.2	9.4 ± 0.3	9.5 ± 0.3	0.581
Phosphorus (mg/dl)	3.4 (3.2, 3.5)	3.8 (3.6, 3.8)	4.1 (4.0, 4.2)	4.5 (4.3, 4.6)	
iPTH (pg/ml)	32 (28, 37)	35 (28, 43)	36 (29, 41)	34 (27, 40)	0.745
1,25(OH)$_2$VD$_3$ (pg/ml)	63.5 (52.6, 79.1)	60.5 (51.7, 76.5)	64.6 (48.0, 69.0)	48.4 (43.2, 58.4)	0.004
iFGF-23 (pg/ml)	44.0 (28.9, 55.8)	39.5 (27.7, 58.4)	41.9 (34.5, 58.4)	46.4 (33.5, 61.4)	0.643
cFGF-23 (RU/ml)	9.6 (7.8, 13.1)*	11.8 (7.2, 16.1)	15.1 (8.9, 21.2)	13.5 (10.0, 19.7)	0.099

Serum phosphorus (S-Pi) level quartiles ; Quartile 1, <3.6 mg/dl ; Quartile 2, 3.6-3.9 mg/dl ; Quartile 3, 4.0-4.2 mg/dl ; Quartile 4, >4.2 mg/dl. Values are means ± standard deviations or medians (25th to 75th interquartile range). Abbreviations : BMI, body mass index ; iPTH, intact parathyroid hormone ; 1,25(OH)$_2$VD$_3$, 1α,25-dihydroxyvitamin D$_3$; iFGF-23, intact fibroblast growth factor 23 ; cFGF-23, C-terminal fibroblast growth factor 23. *Serum cFGF-23 levels in the lowest serum phosphorus quartile were available in 22 subjects.

Table 4. Dietary characteristics of the participants according to serum phosphorus level quartiles

	S-Pi Quartile 1	S-Pi Quartile 2	S-Pi Quartile 3	S-Pi Quartile 4	*P*
n (109)	23	28	32	26	
Protein (%Energy)	14.4 ± 3.0	14.4 ± 2.7	13.1 ± 2.1	13.2 ± 1.6	0.062
Fat (%Energy)	28.1 ± 5.3	27.6 ± 5.1	27.2 ± 6.0	26.7 ± 6.4	0.870
Carbohydrate (%Energy)	57.5 ± 7.9	58.0 ± 7.3	60.0 ± 7.5	60.0 ± 7.2	0.550
Calcium (mg/1000 kcal)	241 ± 79	250 ± 83	230 ± 75	256 ± 72	0.598
Total phosphorus (mg/1000 kcal)	514 ± 98	520 ± 89	478 ± 83	495 ± 57	0.222
Animal-based foods*	255 (202, 319)	261 (200, 317)	219 (162, 286)	244 (198, 292)	0.231
Fish and shellfish	57 (38, 100)	70 (41, 95)	59 (42, 83)	60 (46, 90)	0.890
Meat	105 (65, 130)	82 (65, 144)	78 (59, 121)	76 (45, 102)	0.112
Eggs	29 (14, 35)	29 (20, 53)	27 (13, 41)	34 (22, 41)	0.516
Dairy products	34 (10, 89)	46 (5, 96)	40 (8, 98)	66 (31, 111)	0.338
Plant-based foods*	287 ± 94	280 ± 80	252 ± 95	271 ± 62	0.159
Cereals	105 (76, 115)	104 (93, 117)	102 (77, 118)	108 (84, 118)	0.823
Potatoes	4 (3, 10)	8 (4, 18)	6 (3, 9)	8 (3, 14)	0.453
Pulses	27 (20, 53)	25 (11, 47)	20 (9, 35)	26 (15, 35)	0.311
Green and yellow vegetables	17 (8, 30)	16 (9, 23)	13 (7, 19)	15 (9, 21)	0.588
Other vegetables	24 (18, 37)	25 (18, 33)	26 (18, 35)	18 (12, 28)	0.136
Fruits	3 (2, 8)	5 (2, 8)	5 (2, 8)	5 (3, 8)	0.857
Other foods*	38 (25, 67)	47 (35, 63)	57 (44, 74)	60 (45, 77)	0.032
Confectioneries	27 (16, 50)	31 (18, 48)	37 (22, 53)	43 (33, 56)	0.074
Beverages	6 (3, 13)	8 (5, 12)	9 (6, 14)	7 (5, 15)	0.384
Condiments	5 (2, 8)	6 (4, 9)	7 (4, 11)	6 (3, 8)	0.148

Serum phosphorus (S-Pi) level quartiles ; Quartile 1, <3.6 mg/dl ; Quartile 2, 3.6-3.9 mg/dl ; Quartile 3, 4.0-4.2 mg/dl ; Quartile 4, >4.2 mg/dl. Values are means ± standard deviations or medians (25th to 75th interquartile range). *Phosphorus intake from different food groups (mg/1000 kcal).

Associations between serum phosphorus levels and IFS's of processed foods

To evaluate the dietary phosphorus intake from food additives, we focused on the intake frequency of processed foods per month. We compared the IFS's of processed foods among serum phosphorus quartiles by using ANOVA (Table 5). The IFS of confectionery differed significantly among serum phosphorus quartiles (P = 0.035, Kruskal-Wallis ANOVA), and the median for the IFS of confectionery was 2.3-fold higher in the highest quartile than in the lowest

Table 5. Intake frequency scores (IFS's) of processed foods according to serum phosphorus level quartiles

	S-Pi Quartile 1	S-Pi Quartile 2	S-Pi Quartile 3	S-Pi Quartile 4	*P*
n (109)	23	28	32	26	
Total IFS (times/month)	34.4 (21.5, 55.7)	45.0 (30.0, 62.2)	42.9 (29.0, 51.4)	44.0 (26.8, 62.1)	0.405
Animal-based processed foods*	6.5 (4.3, 12.9)	9.7 (4.3, 15.0)	4.3 (4.3, 8.6)	5.4 (2.2, 13.4)	0.196
1) Ham, sausages, and bacon	4.3 (2.2, 10.7)	4.3 (2.2, 10.7)	2.2 (2.2, 4.3)	3.2 (2.2, 10.7)	0.131
2) Dried fish and salted fish	2.2 (0.0, 4.3)	2.2 (2.2, 3.8)	2.2 (2.2, 2.2)	2.2 (0.0, 2.2)	0.534
Plant-based processed foods*	10.7 (6.5, 21.4)	12.9 (6.5, 25.2)	9.7 (6.5, 23.6)	12.9 (6.5, 21.9)	0.726
3) Breads	10.7 (4.3, 21.4)	10.7 (4.3, 21.4)	4.3 (2.2, 21.4)	4.3 (2.2, 21.4)	0.228
4) Instant noodles and Chinese noodles	2.2 (2.2, 4.3)	2.2 (0.5, 3.8)	2.2 (2.2, 4.3)	3.2 (1.6, 5.9)	0.449
Confectionery*	10.8 (8.6, 23.6)	17.2 (8.6, 27.9)	19.3 (11.3, 27.3)	24.6 (14.5, 34.8)	0.035
5) Rice crackers, rice cakes, and Japanese-style pancakes	2.2 (2.2, 4.3)	2.2 (0.5, 4.3)	3.2 (2.2, 4.3)	4.3 (2.2, 10.7)	0.150
6) Japanese sweets	0.0 (0.0, 2.2)	2.2 (0.0, 2.2)	2.2 (0.0, 2.2)	2.2 (0.0, 2.2)	0.434
7) Cakes, cookies, and biscuits	4.3 (2.2, 4.3)	7.5 (2.2, 10.7)	10.7 (4.3, 10.7)	4.3 (3.8, 10.7)	0.198
8) Ice cream	4.3 (2.2, 10.7)	4.3 (2.2, 9.1)	4.3 (2.2, 10.7)	10.7 (2.2, 10.7)	0.357

Serum phosphorus (S-Pi) level quartiles ; Quartile 1, <3.6 mg/dl ; Quartile 2, 3.6-3.9 mg/dl ; Quartile 3, 4.0-4.2 mg/dl ; Quartile 4, >4.2 mg/dl. Values are medians (25th to 75th interquartile range). 2) Dried fish and salted fish include salted mackerel, salted salmon, and dried horse mackerel. 3) Breads include white bread and Japanese bread with a sweet filling. * Intake frequency score (IFS, times/month)

(10.8 vs. 24.6 times/month). Moreover, this association was observed for females (median IFS of confectionery in the serum phosphorus quartiles 1, 2, 3, and 4 were 10.8 (8.6, 19.3), 11.8 (7.0, 27.9), 19.3 (11.8, 25.7), and 22.5 (13.4, 33.7) times/month, respectively ; Kruskal-Wallis ANOVA, $P = 0.036$; data not shown). The total IFS and IFS of animal- and plant-based processed foods did not differ among quartiles. Furthermore, we analyzed the associations among the IFS's of confectionery and phosphate-regulating factors (iPTH, $1{,}25(OH)_2VD_3$, iFGF-23, and cFGF-23) by using Spearman's correlation analysis (Table 6). The IFS of confectionery was inversely correlated with serum $1{,}25(OH)_2VD_3$ levels (Spearman $r = -0.220$, $P = 0.022$) and positively correlated with serum iFGF-23 levels (Spearman $r = 0.193$, $P = 0.045$). These association were also observed for females ($1{,}25(OH)_2VD_3$: Spearman $r = -0.246$, $P = 0.021$; iFGF-23 : Spearman $r = 0.276$, $P = 0.009$; data not shown).

DISCUSSION

Serum phosphorus levels > 3.9 mg/dl, even if normal, may be a risk factor for coronary artery atherosclerosis in healthy young adults (21). In this study, serum phosphorus levels in 53% of the participants was > 3.9 mg/dl. Higher IFS's of confectionery were associated with higher serum phosphorus levels.

Karp *et al*. investigated the acute effects of dietary phosphorus from meat, cheese, and whole grains and a phosphate supplement on calcium and bone metabolism. Despite the similar intakes of phosphorus, only phosphate supplements significantly increased serum parathyroid hormone concentrations (13). Kemi *et al*. reported that higher habitual phosphorus intake from processed cheese was associated with higher mean serum parathyroid hormone concentrations, whereas the effects of phosphorus from milk and cheese on serum parathyroid hormone concentrations were contradictory (22). Therefore, food additive phosphorus may impose a larger burden than natural source phosphorus.

Many of the studies regarding phosphate-containing food additives have focused on processed meat, fish, and cheese (15, 19, 22-24). However, chemical analyses of the phosphorus content of 24 confectioneries, 33 prepared foods, 15 beverages, and eight seasoning products purchased from grocery stores in Japan showed that confectioneries had higher phosphorus contents per food weight than those of prepared foods, including processed meat and fish (25). In this study, snacks, confectionery included rice crackers, Japanese sweets, cookies or cakes, and ice cream. León *et al*. researched the prevalence of phosphorus-containing food additives in best-selling grocery products in northeast Ohio and compared the difference in the phosphorus content of top-selling food products with and without phosphorus additives. Of the 116 snack products researched, approximately 30% of the products contained phosphorus-containing food additives. Moreover, phosphorus content substantially differed between products with and without phosphorus additives (26). Baked goods contain a phosphate-containing leavening agent (sodium polyphosphate), and industrial muffins containing sodium phosphate as a leavening agent reportedly contained digestible phosphorus at a higher concentration than that in cookies without sodium phosphate (27). Ice creams contain disodium phosphate, tetrasodium pyrophosphate, or sodium hexametaphosphate to prevent defects in texture (28). Furthermore, a recent study investigated primary sources of dietary phosphorus by using dietary intake data from the National

Table 6. Spearman's correlation coefficients between intake frequency scores (IFS) of confectionery and serum levels of phosphorus and phosphate-regulating factors.

	IFS of confectionery	
	R	*P*
Phosphorus	0.261	0.006
iPTH	−0.085	0.379
$1{,}25(OH)_2VD_3$	−0.220	0.022
iFGF-23	0.193	0.045
cFGF-23*	0.067	0.491

Abbreviations : IFS, intake frequency scores ; iPTH, intact parathyroid hormone ; $1{,}25(OH)_2VD_3$, 1α,25-dihydroxyvitamin D_3 ; iFGF-23, intact fibroblast growth factor 23 ; cFGF-23, C-terminal fibroblast growth factor 23. *Serum cFGF-23 levels were available in 108 subjects.

Health and Nutrition Examination Survey, and the results highlighted that non-dairy snacks and sweets were an important source of dietary phosphorus (29). Jiamg *et al*. found that in peritoneal dialysis patients, hyperphosphatemic patients had greater phosphorus intake from confectioneries than that of patients with normal serum phosphorus, which suggested that peritoneal dialysis patients should limit their intake of confectioneries (30).

In this study, we found that higher IFS's of confectioneries were associated with higher serum phosphorus. In the digestive tract, phosphorus can form an insoluble complex with other minerals in the presence of calcium, which results in lower phosphorus absorption (31-33). Trautvetter *et al*. compared the differential effects of supplementation with calcium phosphate or phosphate alone by combining pooled results of their randomized human intervention studies with those of reported randomized human intervention studies. Calcium phosphate supplementation increased fecal but not urinary phosphorus, whereas phosphate supplementation alone increased urinary excretion (34). Because processed meat, fish, and cereal are consumed with other foods, their phosphorus may interact with other digestive tract minerals, whereas, confectioneries may be consumed only as snacks. In addition, confectioneries have a high phosphorus content per food weight (25), so their digestive products may flow into the small intestine in a very high phosphorus density state.

Moreover, because dietary phosphorus loading has been shown to cause postprandial elevation of serum phosphorus (2, 35), snacking may increase daily serum phosphorus levels. Previous studies have reported that increased daily serum phosphorus levels (24-hour mean of replicates) may decrease the production of $1,25(OH)_2VD_3$ (36), which is downregulated by FGF-23 (37, 38). In our study, the IFS of confectionery was negatively correlated with serum $1,25(OH)_2VD_3$ and positively correlated with iFGF-23, suggesting an association between higher confectionery intake and increased daily serum phosphorus levels.

Our study had some limitations. First, the number of study subjects was relatively small. Second, the BDHQ did not allow observation of true dietary habits, so reporting bias was possible. Third, the validity of the IFS in this study was not evaluated. However, in some studies, intake frequencies of foods have been assessed based on the same method as the IFS used in this study (39, 40). Finally, this was a cross-sectional study, which precluded evaluation of causality. Further studies should determine if habitual intake of confectioneries affects morning fasting serum phosphorus levels.

In conclusion, we found that the higher habitual intake of confectionery was associated with higher serum phosphorus levels in healthy young individuals. Further studies are needed to determine whether frequent consumption of confectionery induces increase in serum phosphorus levels.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

ACKNOWLEDGMENTS

This work was supported by the Grant-in-Aid for Young Scientists (B) [grant number 26750046] from the Ministry of Education, Culture, Sports, Science and Technology in Japan (for MS).

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