Reduced Serum Phosphorus Levels Were Associated with Metabolic Syndrome in Men But Not in Women: A Cross-Sectional Study among the Japanese Population

Masanori Shimodaira^{a, b} Shinji Okaniwa^a Tomohiro Nakayama^b

^aDepartment of Internal Medicine, Iida Municipal Hospital, Nagano, and ^bDivision of Companion Diagnostics, Department of Pathology of Microbiology, Nihon University School of Medicine, Tokyo, Japan

Keywords

Serum phosphorus · Metabolic syndrome · Risk factor · Gender

unexpectedly positively correlated with SP levels in women. Reduced SP levels were associated with MetS in men but not in women.

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Abstract

Background: Reduced serum phosphorus (SP) levels are reported to be associated with insulin resistance and metabolic syndrome (MetS). However, there have been a few gender-specific studies although SP levels are substantially different between men and women. **Methods:** This is a cross-sectional study. A total of 16,041 subjects (9,076 men and 6,965 women) were analyzed. The subjects were divided into 3 groups of gender-specific tertiles based on phosphorus levels: the lowest (T₁), middle (T₂), and the highest (T₃). **Results:** SP levels were significantly lower in subjects with MetS than in those without MetS in men but not in women. Waist circumference and fasting plasma glucose were negatively and high-density lipoprotein cholesterol was positively correlated with SP levels both in men and women. Blood pressure (BP) and triglycerides (TG) were negatively correlated with SP levels in men, while they were positively correlated with SP levels in women. Lower SP levels were associated with the prevalence of MetS in men (T₁; 19.9%, T₂; 16.9%, and T₃; 14.3%; $p < 0.001$) but not in women (T₁; 14.1%, T₂; 16.6%, and T₃; 15.3%; $p = 0.282$). **Conclusion:** BP and TG were

Introduction

Metabolic syndrome (MetS) is a constellation of metabolic disorders including abdominal obesity, atherogenic dyslipidemia (elevated triglyceride [TG] and/or reduced high-density lipoprotein cholesterol [HDL-C]), elevated blood pressure (BP), and high fasting plasma glucose (FPG) [1]. Phosphorus is an essential mineral required for biological activities, biochemical reactions, and energy metabolism [2]. Therefore, a phosphorus imbalance may contribute to the development of metabolic disorders [3, 4]. Several studies have found that lower serum phosphorus (SP) levels are associated with impaired glucose tolerance and insulin resistance [5–7]. Furthermore, hypertensive subjects have significantly lower phosphorus levels compared with healthy individuals [8]. In contrast, higher levels of SP are thought to be associated with lower TG and higher HDL-C levels [9, 10]. These studies indicate that a disturbance in phosphorus metabolism may represent a key feature of MetS and its components.

The prevalence of MetS and its phenotypes differs between men and women [11–13]. For example, in the Japanese population, the prevalence of MetS with elevated FPG levels is higher in men than in women [11]. Furthermore, while SP levels differ by gender, there have been a few gender-stratified studies investigating the relationship between SP levels and MetS and its components [14]. Therefore, we conducted the present gender-stratified cross-sectional study to investigate the relationship between SP and metabolic parameters in the Japanese population.

Materials and Methods

Study Subjects

This study included individuals undergoing routine health checkups at the Iida Municipal Hospital from January 2008 to December 2015. When individuals had data from multiple visits, we included only the data acquired during the first visit. Out of 16,735 individuals, we excluded individuals with a possibility of advanced renal dysfunction, such as those with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m², and evidence of albuminuria indicated by urine dipstick albumin >2+. In addition, we excluded individuals of advanced age (>80 years). Consequently, we included a total of 16,041 subjects (men, *n* = 9,076 and women, *n* = 6,965) in the present analysis. The study was approved by the Institution Ethics Review Board of Iida Municipal Hospital in agreement with the Helsinki Declaration of 1975. Informed consent was obtained from all participants.

Definition of the Variables

According to the National Cholesterol Education Program, Adult Treatment Panel III criteria [1], MetS was defined by the fulfillment of 3 or more components of the 5 following abnormalities: (1) waist circumference (WC) ≥90 and ≥80 cm in Japanese men and women, respectively; (2) systolic BP ≥130 mm Hg and/or diastolic BP ≥85 mm Hg, or treatment for previously diagnosed hypertension; (3) TG ≥150 mg/dL or receiving specific treatment for hypertriglyceridemia; (4) HDL-C <40 mg/dL in men and <50 mg/dL in women, or receiving specific treatment for low HDL-C; and (5) FPG ≥100 mg/dL or previously diagnosed diabetes. The individuals with fewer than 3 criteria for the diagnosis of MetS served as the controls. SP levels were categorized by tertiles with tertile 1 (T₁) representing the lowest phosphorus levels; T₂: middle phosphorus levels; and T₃: the highest phosphorus levels.

Clinical and Anthropometric Measurements

Height and weight were measured with the subjects wearing light clothing and no shoes using a fixed stadiometer and a digital scale, which was used to calculate the body mass index (BMI). WC was measured between the lower rib margin and the iliac crest after a normal expiratory breath. Systolic and diastolic BP was measured using an automated measuring device (HEM-7080IT, Omron Co., Tokyo, Japan). Two separate BP measurements were taken after 15 min of rest, with at least a 30-s interval between the 2, and the mean of these was considered to be the participant's BP.

Information regarding various comorbid conditions, including hypertension, dyslipidemia, and diabetes was collected by conducting in-person interviews. The smoking status and alcohol consumption of the study participants were assessed using a standardized questionnaire. Smoking status was categorized as either current smokers (daily and occasional smoking) or non-smokers (never and former smoking). Alcohol consumption was classified as current drinkers (at least once per week) and non-current drinkers.

Laboratory Measurements

Blood samples were obtained after an overnight fast. The measurements of the total serum cholesterol, TG, HDL-C, low density lipoprotein cholesterol, uric acid, high sensitivity C-reactive protein (hs-CRP), and creatinine were determined using standard methods (Hitachi 47 automatic analyzer, Hitachi Ltd., Japan). eGFR was calculated using the formula of the Japanese Society of Nephrology according to the equation: $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$ mL/min/1.73 m², which was further multiplied by 0.739 for female subjects [15]. FPG was measured using the hexokinase method (GLU-HK, Shinotest Inc., Japan). SP was measured by the enzymatic method with maltose phosphorylase (Kainos Laboratory Inc., Japan). The coefficient of variation for SP determination was less than 1.0 and 0.6% for low- and high-level quality control specimens, respectively.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 21.0 (SPSS Inc. IL, USA). Gender-specific characteristics of the study population were analyzed using independent *t* tests for continuous variables and the chi-square test for dichotomous variables. Skewed distribution variables were analyzed after a logarithmic transformation. The correlation between the SP levels and the variables of the MetS components was analyzed using Pearson's correlation analysis, and a partial correlation analysis was performed to control confounding factors (e.g., age, BMI, hs-CRP, eGFR, smoking and alcohol status, and the use of antihypertensive, antidiabetic, and hypolipidemic drugs). The differences in the mean values of the MetS components according to SP level tertiles were evaluated using an analysis of covariance. To determine the adjusted ORs for the incidence of MetS and its components between the tertile categories, a logistic regression analysis was used to adjust the confounding factors.

Results

Characteristics of the Subjects with and without MetS

The physical and biochemical characteristics of the study subjects are summarized in Table 1. The prevalence of MetS in men and women were 17.0 and 15.4%, respectively. Of the men, the subjects with MetS exhibited significantly lower SP levels than those without MetS (3.04 ± 0.44 vs. 3.13 ± 0.42 mg/dL, respectively). Conversely, in women, there was no difference in SP levels between the 2 groups.

Table 1. Demographic and metabolic characteristics of study participants

	Men (<i>n</i> = 9,076)			Women (<i>n</i> = 6,965)		
	MetS (<i>n</i> = 1,544)	non-MetS (<i>n</i> = 7,532)	<i>p</i> value	MetS (<i>n</i> = 1,072)	non-MetS (<i>n</i> = 5,893)	<i>p</i> value
Serum phosphorus, mg/dL	3.04±0.44	3.13±0.42	<0.001	3.53±0.41	3.54±0.41	0.590
Age, years	56.2±10.8	53.4±11.4	<0.001	59.4±9.9	52.4±11.2	<0.001
BMI, kg/m ²	26.2±3.2	22.9±2.8	<0.001	25.6±3.9	21.3±3.0	<0.001
Waist circumference, cm	91.8±8.5	81.1±7.4	<0.001	87.5±8.0	75.2±8.3	<0.001
eGFR, mL/min/1.73 m ²	72.1±14.7	74.8±13.9	<0.001	76.7±15.7	77.7±14.0	0.073
Uric acid, mg/dL	6.5±1.3	6.0±1.2	<0.001	5.0±1.1	4.4±0.9	<0.001
hs-CRP, mg/L	1.7±7.2	1.2±4.6	0.019	1.5±2.5	0.7±2.8	<0.001
Calcium, mg/dL	9.3±0.4	9.2±0.3	<0.001	9.4±0.4	9.3±0.4	<0.001
Blood pressures						
SBP, mm Hg	136.4±13.8	122.9±15.8	<0.001	138.5±13.6	118.9±16.6	<0.001
DBP, mm Hg	84.2±10.7	75.2±11.5	<0.001	80.8±10.5	70.7±11.3	<0.001
Lipids, mg/dL						
TC	205.8±33.6	199.3±31.5	<0.001	213.5±37.6	207.3±34.1	<0.001
TG	212.7±143.4	110.0±65.3	<0.001	145.7±80.6	78.1±36.0	<0.001
HDL-C	47.7±11.4	58.4±13.7	<0.001	55.5±12.4	69.8±14.6	<0.001
LDL-C	121.1±31.0	118.1±29.5	<0.001	128.6±32.3	117.8±30.5	<0.001
Glucose parameters						
HbA1c, %	5.9±0.6	5.6±0.5	<0.001	6.0±0.8	5.5±0.4	<0.001
FPG, mg/dL	113.5±22.5	100.0±15.8	<0.001	113.0±27.9	94.1±11.0	<0.001
Medication use, %						
Antihypertensive drugs	20.3	15.4	<0.001	24.1	13.8	<0.001
Antidiabetic drugs	11.2	6.2	<0.001	15.8	5.8	<0.001
Hypolipidemic drugs	15.6	10.9	<0.001	19.4	13.3	<0.001
Current drinker, %	39.3	35.8	0.010	25.6	22.7	<0.001
Current smoker, %	24.3	22.5	0.127	8.7	8.1	0.032

MetS, metabolic syndrome; BMI, body mass index; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; hs-CRP, high sensitive C-reactive protein; TC, total cholesterol; TG, triglycerid; HDL-C, HDL-cholesterole; LDL-C, LDL-cholesterol; FPG, fasting plasma glucose.

Correlations between Serum Phosphorus Levels and MetS Components

In both genders, WC and FPG were negatively correlated and HDL-C was positively correlated with SP levels even after an adjustment for the confounding factors (Table 2). Interestingly, there were gender-related differences in the correlation between SP levels and systolic and diastolic BP and TG levels – a negative correlation among male subjects but a positive correlation among female subjects.

Prevalence of MetS and Values of the MetS Components According to Serum Phosphorus Level Tertiles

The prevalence of MetS and mean values of the MetS components adjusted for the confounding factors between the different SP level tertiles are shown in Table 3.

In men, the prevalence of MetS increased as SP levels decreased. However, in women, there was no difference in the prevalence of MetS between the 3 groups. In both genders, as SP levels decreased, WC and FPG levels increased and HDL-C levels decreased. On the other hand, gender differences were identified for the relationship between systolic and diastolic BP and TG levels and SP levels; there was a negative association among male subjects but a positive association among female subjects.

ORs of the MetS and Its Components According to Serum Phosphorus Level Tertiles

The unadjusted and adjusted ORs for the presence of MetS and its components according to SP levels are presented in Table 4. In both genders, the ORs of elevated FPG increased according to a decrease in SP levels. Only in men, the ORs of elevated WC, elevated TG, and

Table 2. Correlation coefficients between serum phosphorus levels and values of MetS traits

	Men				Women			
	unadjusted		adjusted*		unadjusted		adjusted*	
	<i>r</i>	<i>p</i> value	<i>r</i>	<i>p</i> value	<i>r</i>	<i>p</i> value	<i>r</i>	<i>p</i> value
WC, cm	−0.085	<0.001	−0.066	<0.001	−0.053	<0.001	−0.095	<0.001
SBP, mm Hg	−0.110	<0.001	−0.096	<0.001	0.031	0.025	0.055	<0.001
DBP, mm Hg	−0.096	<0.001	−0.092	<0.001	0.049	<0.001	0.095	<0.001
TG, mg/dL [†]	−0.019	0.011	−0.025	0.012	0.049	0.001	0.047	0.002
HDL-C, mg/dL	0.048	<0.001	0.031	0.014	0.098	<0.001	0.083	<0.001
FPG, mg/dL	−0.054	<0.001	−0.052	<0.001	−0.037	0.008	−0.102	<0.001

MetS, metabolic syndrome; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerid; HDL-C, HDL-cholesterole; FPG, fasting plasma glucose.

[†] Log-transformed

* Partial correlation analysis adjusted for age, BMI, high sensitivity C-reactive protein, estimated glomerular filtration rate, smoking and alcohol status, and use antihypertensive, antidiabetic, and hypolipidemic drugs.

Table 3. Prevalence of MetS and adjusted mean values of MetS components according to serum phosphorus level tertiles

	Men				Women			
	T ₁ (<i>n</i> = 2,905)	T ₂ (<i>n</i> = 3,155)	T ₃ (<i>n</i> = 3,016)	<i>p</i> for trend	T ₁ (<i>n</i> = 2,211)	T ₂ (<i>n</i> = 2,022)	T ₃ (<i>n</i> = 2,732)	<i>p</i> for trend
Phosphorus, mg/dL	≤2.9	3.0–3.3	≥3.4		≤3.3	3.4–3.7	≥3.8	
MetS, %	19.9	16.9	14.3	<0.001	14.1	16.6	15.3	0.282
WC, cm	84.1±8.1	83.0±9.0	82.4±8.7	<0.001	77.6±9.6	77.0±9.0	76.8±9.1	0.030
SBP, mm Hg	127.5±15.9	125.3±15.5	123.7±16.8	<0.001	120.0±17.6	121.8±17.6	122.4±17.2	<0.001
DBP, mm Hg	78.0±11.6	77.0±11.4	75.7±12.2	<0.001	71.2±11.6	71.9±11.6	72.1±11.5	0.010
TG, mg/dL	131.2±101.1	127.7±95.5	120.5±73.5	0.002	82.6±40.9	85.3±44.9	86.4±48.5	0.049
HDL-C, mg/dL	55.5±13.5	57.1±13.7	57.9±14.7	0.004	66.5±13.7	67.6±15.2	68.3±16.1	0.035
FPG, mg/dL	103.4±18.5	102.1±16.2	101.6±18.6	0.003	98.8±19.6	96.5±14.3	95.5±13.3	<0.001

MetS, metabolic syndrome; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerid; HDL-C, HDL-cholesterole; FPG, fasting plasma glucose.

Values of MetS components were adjusted for age, BMI, high sensitivity C-reactive protein, estimated glomerular filtration rate, smoking and alcohol status, and use of antihypertensive, antidiabetic, and hypolipidemic drugs.

reduced HDL-C increased in accordance with a decrease in SP levels. Gender differences were found in the association between the ORs of elevated BP and SP levels; a positive association was found in men, whereas there was a negative association in women. These relationships remained significant after adjusting for the confounding factors. In men, because of the significant association between the MetS components and SP levels, ORs of MetS decreased with SP levels. The adjusted ORs in T₂ and T₁ were 1.19 and 1.23, respectively, using T₃ as a reference.

Discussion

This gender-stratified analysis conducted in a large general population that represents a single ethnicity demonstrated gender differences in the association between SP levels and the incidence of MetS; decreased phosphorus levels were related to an increased incidence of MetS only among male subjects. We also identified a negative association between systolic and diastolic BPs and TG among male subjects; however, an inverse association was observed among female subjects.

Table 4. OR and 95% CI for the prevalence of MetS and its components according to serum phosphorus level tertiles

	Men				Women			
	unadjusted		adjusted*		unadjusted		adjusted*	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
MetS								
T ₃	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
T ₂	1.21 (1.11–1.33)	0.011	1.19 (1.08–1.32)	0.001	0.92 (0.83–1.03)	0.139	0.93 (0.83–1.04)	0.120
T ₁	1.25 (1.14–1.37)	<0.001	1.23 (1.12–1.35)	<0.001	0.97 (0.82–1.05)	0.418	0.97 (0.88–1.06)	0.261
Elevated WC ^a								
T ₃	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
T ₂	1.07 (0.98–1.16)	0.132	1.06 (0.97–1.16)	0.413	1.05 (0.97–1.14)	0.201	1.06 (0.98–1.16)	0.032
T ₁	1.09 (1.02–1.19)	0.036	1.08 (1.01–1.18)	0.015	1.04 (0.98–1.11)	0.211	1.07 (1.00–1.14)	0.010
Elevated BP ^b								
T ₃	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
T ₂	1.18 (1.11–1.26)	<0.001	1.19 (1.11–1.27)	0.002	0.90 (0.84–0.97)	0.014	0.91 (0.84–0.98)	0.002
T ₁	1.21 (1.13–1.29)	<0.001	1.22 (1.13–1.31)	<0.001	0.93 (0.87–0.98)	0.023	0.94 (0.88–0.99)	0.036
Elevated TG ^c								
T ₃	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
T ₂	1.10 (1.02–1.18)	0.015	1.08 (1.01–1.15)	0.032	0.99 (0.88–1.14)	0.931	1.04 (0.89–1.23)	0.638
T ₁	1.13 (1.05–1.21)	0.007	1.12 (1.03–1.20)	0.012	0.93 (0.84–1.03)	0.165	0.94 (0.84–1.04)	0.844
Reduced HDL-C ^d								
T ₃	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
T ₂	1.18 (1.04–1.34)	0.006	1.19 (1.05–1.34)	0.001	1.02 (0.90–1.67)	0.124	1.02 (0.89–1.18)	0.055
T ₁	1.27 (1.12–1.44)	<0.001	1.27 (1.11–1.14)	0.001	1.09 (0.98–1.22)	0.109	1.06 (0.94–1.19)	0.099
Elevated FPG ^e								
T ₃	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
T ₂	1.09 (1.04–1.15)	0.014	1.06 (1.02–1.12)	0.019	1.15 (1.06–1.23)	0.026	1.14 (1.03–1.22)	<0.001
T ₁	1.20 (1.12–1.28)	<0.001	1.12 (1.10–1.27)	0.007	1.28 (1.15–1.36)	<0.001	1.24 (1.17–1.37)	0.001

MetS, metabolic syndrome; WC, waist circumference; BP, blood pressure; TG, triglycerid; HDL-C, HDL-cholesterole; FPG, fasting plasma glucose.

* adjusted for age, BMI, high sensitivity C-reactive protein, estimated glomerular filtration rate, smoking and alcohol status, and use of anti-hypertensive, antidiabetic, and hypolipidemic drugs.

^a WC ≥90 cm in men and ≥80 cm in women.

^b systolic BP ≥130 mm Hg and/or diastolic BP ≥85 mm Hg.

^c TG ≥150 mg/dL.

^d HDL-C <40 mg/dL in men and <50 mg/day in women.

^e FPG ≥100 mg/dL

Elevated TG and reduced HDL-C levels have been referred to as atherogenic dyslipidemia and is thought to be a significant predictor of future high BP and diabetes [16]. This study demonstrated that the correlations of SP and TG were different between both genders. Onat et al. [16] have reported that CRP was independently related to MetS of atherogenic dyslipidemia in men but not in women. This suggests that atherogenic dyslipidemia in women with MetS was closely associated with inflammation/oxidative stress. Lipoprotein(a) is associated with inflammatory markers, while elevated TG is linked to high lipoprotein(a) in men and low lipoprotein(a) in women [17]. As shown in Table 1, the female subjects had lower hs-CRP levels than

the male subjects. However the exact reason for this phenomenon is still unclear; the different associations of SP levels and TG between men and women may be attributable to the differences in the impact of chronic low-grade inflammation on lipid metabolism in MetS.

Several studies have reported a negative correlation between SP levels and BP [10]; however, the correlation remains inconclusive [18, 19]. According to Haglin et al. [3], the correlation was not significant in women. In their study, the mean SP and BMI of women were 3.28 mg/dL and 31.4 kg/m², respectively, whereas our study, they were 3.54 mg/dL and 22–23 kg/m², respectively. These differences in SP and/or BMI values may explain

the differences regarding the association between SP levels and BP in the 2 populations. However, we could not identify a clear rationale for the gender-related differences concerning the association of SP levels with BP in this study.

In accordance with previous studies [10, 7], we demonstrated that higher SP levels were associated with lower FPG levels in both genders. The relationship between SP and glucose is believed to be mediated by insulin, which increases the transfer of phosphate from extracellular to intracellular compartments. In humans, chronic hypophosphatemia results in decreased tissue insulin sensitivity, even in a euglycemic state [5]. Phosphorus infusion to healthy volunteers improves insulin sensitivity under euglycemic conditions [20], and phosphorus supplementation for hypophosphatemic patients with glucose intolerance ameliorates glucose tolerance [21]. Therefore, a reduction in phosphate levels may decrease the peripheral utilization of glucose, thus, leading to the development of insulin resistance, a major determinant of MetS [4].

The strengths of our study include a relatively large, well-characterized, community-based population. In addition, to decrease the influence of diurnal variation in SP levels [22], all phosphorus measurements were conducted under conditions of morning fasting. Furthermore, the available diverse variables, including hs-CRP, an inflammatory marker, were used to minimize confounding in the multivariable-adjusted models. However, the pres-

ent study also has some limitations. First, this study had a cross-sectional design, which did not permit the determination of causality. Second, nutritional records were not available, and we could not include phosphorus intake in the analyses. Third, we lacked measurements of urinary phosphorus excretion. Finally, the study population consisted only a section of the Japanese population; therefore, it is uncertain whether these findings can be generalized to other ethnic groups.

In conclusion, lower SP levels were found to be associated with the incidence of MetS only in men. Furthermore, systolic and diastolic BP and TG were negatively correlated with SP levels in men, whereas the inverse correlation was found in women. Our results suggest that there may be gender-related differences in the association of decreased SP levels with MetS and its components.

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Disclosure Statement

All authors declare no conflicts of interest.

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