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ORIGINAL ARTICLE

Serum phosphate in white-coat hypertensive patients: focus on dipping status and metabolic syndrome

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Recent studies indicate an association between serum phosphate levels and blood pressure in hypertensive patients. A growing body of evidence suggests that white-coat hypertension (WCH) is associated with target organ damage. Furthermore, metabolic syndrome (MS) and a non-dipping pattern are associated with increased cardiovascular risk. The purpose of this study was to explore the nocturnal blood pressure fall in patients with WCH according to their serum phosphate levels and number of MS components fulfilled. The study included 2600 patients with WCH who attended our outpatient clinics. All patients underwent repeated office blood pressure measurements, 24-h ambulatory blood pressure monitoring and full clinical and laboratory evaluation. The diagnosis of MS was made according to the Adult Treatment Panel III criteria. Dipping pattern was defined as follows: 'dippers' had a nocturnal systolic blood pressure (NSBP) fall $\geqslant$10% but $<$20%; 'non-dippers' had an NSBP fall $<$10%; 'extreme dippers' had an NSBP fall $\geqslant$20% and 'reverse dippers' had an NSBP increase. There were 314 extreme dippers, 1337 dippers, 734 non-dippers and 116 reverse dippers. Reverse dippers presented with significantly lower levels of serum phosphate, whereas extreme dippers had significantly higher levels (3.39 ± 3.29 *vs.* 3.58 ± 3.52 mg per 100 ml, $P<0.0001$). The patients were classified according to the number of MS components and the main observation was the inverse relationship of serum phosphate with MS components (3.53 ± 0.36, 3.50 ± 0.38, 3.49 ± 0.38, 3.44 ± 0.36 and 3.35 ± 0.31 mg per 100 ml, respectively, $P=0.003$). Patients with WCH and low serum phosphate levels appear to have a higher incidence of a non-dipping NSBP profile and an impaired metabolic profile. This observation may be important for the stratification of the cardiovascular risk in WCH patients.
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INTRODUCTION

Isolated office hypertension or white-coat hypertension (WCH) is defined as persistently elevated office blood pressure (BP), whereas daytime BP, 24-h BP and home BP are in the normal range.[1] The definition in some studies was based on the average 24-h ambulatory BP monitoring (ABPM),[2,3] on both systolic BP (SBP) and diastolic BP (DBP) values[4–6] or only on DBP values,[7,8] whereas in other studies, the average ABPM during the day was used.[4,6] Many studies indicate that WCH is associated with target organ damage as well as metabolic abnormalities.[9] Increased numbers of metabolic syndrome (MS) components are associated with elevated night-time SBP levels,[10] left ventricular hypertrophy[7,11–14] and increased values of intima-media thickness.[15,16]

It is known that phosphate balance is essential for various biological activities and biochemical reactions, and the molecular regulation of phosphate homeostasis has enormous clinical and biological importance.[17] Disturbed phosphate balance, such as in acute hypophosphatemia, can cause cardiac dysfunction. Also, chronic hypophosphatemia impairs bone mineralization, resulting in rickets and osteomalacia.[18] Furthermore, a growing body of evidence points to an association of serum phosphate levels and BP in hypertensive patients.[19–21]

Recently, low serum phosphate levels have been related to the development of hypertension and increased number of components of the MS.[22] These findings motivated our investigation of the hypothesis that low serum phosphate levels are associated with a non-dipping pattern and an increased number of metabolic components in WCH patients.

METHODS

Study population

The study, which was conducted in the Hypertension Unit of the 1st Cardiology Clinic, Hippokration Hospital, Athens, from the year 2000 to 2009, initially included 12 000 patients who were admitted to our clinics for BP monitoring. The study protocol was approved by the ethics committee of Hippokration Hospital.

The inclusion criteria were patients with office SBP values $\geqslant$140 mm Hg and/or DBP $\geqslant$90 mm Hg, on three consecutive visits to our clinic, each visit

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1 week apart, plus mean 24-h ABP values <125/80 mm Hg. Patients with acute or chronic inflammatory disease, endocrine disorders, chronic obstructive pulmonary disease, malignancy, renal insufficiency (serum creatinine >1.5 mg per 100 ml), heart failure, recent (<6 months) cerebrovascular event, coronary artery disease, history of angina, past myocardial infarction, ventricular arrhythmia, sinus bradycardia (<55 b.p.m.), sinus tachycardia (>100 b.p.m.), atrioventicular conduction defects, known diabetes mellitus (earlier antidiabetic treatment) and any condition preventing technically adequate ABPM were excluded from the study. All patients included in the study underwent the following: physical examination, medical history check, repeated clinical BP measurement, blood sampling for routine laboratory examinations and 24-h ABPM. The final cohort included 2600 WCH patients.

BP measurements

The evaluation of BP was made according to the 2007 European Society of Hypertension guidelines published by the European Society of Cardiology for the management of arterial hypertension in individuals aged 18 years or more.[1] BP was measured three times with 1 min intervals after a 10–15 min relaxation period with the patient sitting comfortably. A mercury sphygmomanometer was used for all measurements with a medium- or a large-sized cuff, according to the patient's arm circumference.

All patients underwent ABPM for 24 h on the nondominant arm using a Spacelabs 90207 device (Spacelabs, Redmond, WA, USA). The recorder was calibrated with a mercury column and was set to take readings at 20 min intervals from 0600 to 2200 hours, and every 30 min from 2200 to 0600 hours. All patients were encouraged to carry out their normal daily routine after they left the hospital. Daytime and night-time readings corresponded to awake and sleep periods, respectively. The recordings were analyzed to obtain 24-h daytime and night-time average SBP, DBP and heart rates.

According to the 2007 European Society of Hypertension guidelines,[1] an average 24-h ABP of 124/79 mm Hg was considered as the upper limit of normality. Each participant was classified according to nocturnal SBP (NSBP) fall as a 'dipper' if the decrease was $\geqslant$10% but <20%; a 'non-dipper' if it was $\geqslant$0% but <10%; an 'extreme dipper' if it was $\geqslant$20% or a 'reverse dipper' if NSBP increased compared with the average daytime values.

Anthropometric and biochemical measurements

In each patient, weight, height and waist-to-hip ratio were measured, and body mass index (BMI) was calculated. Waist circumference to the nearest 0.1 cm was measured at the midpoint between the bottom of the rib cage and above the top of the iliac crest from patients at minimal respiration.

All patients underwent full laboratory evaluation (blood test, lipids, liver and kidney function indices). The blood samples were collected from the antecubital vein between 0800 and 1000 hours after a 12 h fast and alcohol abstinence. Serum phosphate and serum calcium levels were measured in the same laboratory with an autoanalyzer (Aeroset; Abbott Laboratories, Chicago, IL, USA) using the end-point photometric method. The reference values of serum phosphate and serum calcium are 2.50–4.30 mg per 100 ml and 8.0–10.6 mEq l^{-1} (or 16.0–21.20 mg per 100 ml), respectively.

The biochemical evaluation was carried out in the same laboratory, which followed the criteria of the World Health Organization Lipid Reference Laboratories.

Definition of the components of MS

MS was defined according to the Adult Treatment Panel III report[23] as three or more of the following criteria being met: (i) abdominal obesity: waist circumference >102 cm in men and >88 cm in women; (ii) hypertriglyceridemia: >150 mg per 100 ml (1.69 mmol l^{-1}); (iii) low high-density lipoprotein cholesterol: <40 mg per 100 ml (1.04 mmol l^{-1}) in men and <50 mg per 100 ml (1.29 mmol l^{-1}) in women; (iv) high BP: SBP >130 mm Hg and/or DBP >85 mm Hg; and (v) high fasting blood glucose: >110 mg per 100 ml. Because of our study inclusion criterion, SBP >140 mm Hg and/or DBP >90 mm Hg, all of our patients fulfilled at least one of the Adult Treatment Panel III criteria. Patients with hypertension only were classified as group I, whereas other groups were as follows: hypertension and one other MS criterion (group II), hypertension and two other MS criteria (group III), hypertension and three other MS criteria (group IV) or all five MS criteria (group V).

Statistical analysis

Statistical analysis was performed using the SPSS package for windows version 13.0 (SPSS, Chicago, IL, USA). Values were expressed as mean ± s.d. or as percentages. Means were compared using the independent samples Student's *t*-test or after analysis of variance when appropriate. Analysis of categorical data was carried out with the χ^2-test. Values without normal distribution were analyzed with the Kruskal–Wallis test.

Pearson's correlation coefficients were calculated to examine the univariate relation of phosphate to continuous variables. Comparisons between quartiles of phosphate were performed separately for the five MS groups after analysis of variance and analysis of covariance. Finally, a multivariate logistic analysis of the four groups' dipping status and the five groups of MS components was performed using phosphate as the dependent variable and age, BMI, waist-to-hip ratio, total cholesterol, triglycerides, high-density lipoprotein, glucose and eGFR as the independent variables. The limit of statistical significance was set at $P<0.05$.

RESULTS

The study cohort was divided into four groups according to NSBP fall: group 1, extreme dippers (n=413); group 2, dippers (n=1337); group 3, non-dippers (n=734) and group 4, reverse dippers (n=116). In the study population, reverse dippers were older and had higher BMI and waist-to-hip values, and significantly lower values of serum phosphate compared to the other three groups. Extreme dippers presented with significantly higher levels of phosphate in comparison to the other three groups. Patients' baseline characteristics are presented in Table 1. In group 1 (extreme dippers), a strong negative correlation with BMI was noticed (r=−0.1, P=0.043). In group 2 (dippers), there was a negative correlation between waist-to-hip ratio and dipping pattern (r=−0.107, $P<0.0001$) (Table 2).

Table 1 Baseline characteristics of the study population according to dipping status

	Extreme dippers	*Dippers*	*Non-dippers*	*Reverse dippers*	P *(for trend)*
N (males)	413 (156)	1337 (558)	734 (320)	116 (49)	NS
Age (years)	53.3 ± 11.4	51.9 ± 13.3	53.1 ± 13.2	58.4 ± 13.4	<0.001
BMI (kg m^{-2})	27.0 ± 4.2	27.0 ± 4.0	27.8 ± 4.4	28.3 ± 4.9	<0.001
W/H	0.845 ± 0.752	0.846 ± 0.744	0.869 ± 0.776	0.879 ± 0.732	<0.001
Serum P (mg per 100 ml)	3.58 ± 3.52	3.52 ± 3.69	3.44 ± 3.82	3.39 ± 3.29	<0.001
Serum Ca (mEq lt^{-1})	9.54 ± 4.62	9.54 ± 4.79	9.47 ± 5.04	9.41 ± 4.39	0.001
Serum K (mEq lt^{-1})	4.41 ± 3.90	4.37 ± 3.71	4.40 ± 3.95	4.31 ± 4.20	0.037
Serum Na (mEq lt^{-1})	142.2 ± 3.0	142.0 ± 3.2	142.4 ± 3.4	142.1 ± 3.2	NS
Serum Mg (mg per 100 ml)	2.05 ± 2.19	2.08 ± 1.57	2.06 ± 1.47	2.05 ± 1.47	NS
Glucose (mg per 100 ml)	95.3 ± 12.9	94.1 ± 16.6	98.3 ± 19.5	102.4 ± 27.9	<0.001

Abbreviations: BMI, body mass index; Ca, serum calcium; K, serum potassium; Mg, serum magnesium; Na, serum sodium; NS, not significant; P, serum phosphate; W/H, waist-to-hip ratio.

Table 2 Pearson's correlation coefficients of serum phosphate according to dipping pattern with clinic-laboratory variables

	Extreme dippers		*Dippers*		*Non-dippers*		*Reverse dippers*	
Dipping pattern	r	P	r	P	r	P	r	P
Age (years)	−0.009	NS	0.044	NS	0.005	NS	0.031	NS
BMI ($kg\,m^{-2}$)	−0.100	0.043	−0.024	NS	0.007	NS	−0.054	NS
W/H	0.032	NS	−0.107	<0.0001	−0.022	NS	−0.004	NS
P (mg per 100 ml)	−0.055	NS	−0.013	NS	0.006	NS	0.130	NS
Ca ($mEq\,lt^{-1}$)	0.012	NS	−0.016	NS	−0.038	NS	−0.098	NS
K ($mEq\,lt^{-1}$)	−0.052	NS	0.010	NS	−0.013	NS	−0.070	NS
Na ($mEq\,lt^{-1}$)	−0.034	NS	−0.027	NS	0.025	NS	−0.117	NS
Mg (mg per 100 ml)	−0.340	NS	0.012	NS	−0.013	NS	0.145	NS
Glucose (mg per 100 ml)	−0.015	NS	−0.023	NS	−0.023	NS	−0.135	NS

Abbreviations: BMI, body mass index; Ca, calcium; K, potassium; Mg, magnesium; Na, sodium; NS, not significant; P, phosphate; W/H, waist-to-hip ratio.

Table 3 Baseline characteristics of the study population according to metabolic syndrome components

MS components	*1*	*2*	*3*	*4*	*5*	P *(for trend)*
N (males)	1081 (469)	858 (353)	438 (178)	191 (67)	32 (16)	NS
Age (years)	52.3 ± 13.9	52.1 ± 12.9	53.4 ± 11.9	56.6 ± 10.9	53.9 ± 10.8	0.000
BMI ($kg\,m^{-2}$)	25.4 ± 3.1	27.4 ± 3.8	29.6 ± 4.3	31.0 ± 4.6	32.1 ± 4.1	0.000
W/H	0.830 ± 0.070	0.860 ± 0.070	0.880 ± 0.080	0.900 ± 0.072	0.930 ± 0.060	0.000
P (mg per 100 ml)	3.53 ± 0.36	3.50 ± 0.38	3.49 ± 0.38	3.44 ± 0.36	3.35 ± 0.31	0.003
Ca ($mEq\,lt^{-1}$)	9.53 ± 0.47	9.51 ± 0.48	9.53 ± 0.52	9.49 ± 0.51	9.46 ± 0.39	0.037
K ($mEq\,lt^{-1}$)	4.39 ± 0.38	4.38 ± 0.39	4.40 ± 0.36	4.38 ± 0.41	4.27 ± 0.43	NS
Na ($mEq\,lt^{-1}$)	142.0 ± 3.1	142.3 ± 3.4	142.1 ± 3.0	142.5 ± 3.6	141.1 ± 3.2	0.021
Mg (mg per 100 ml)	2.08 ± 0.16	2.06 ± 0.17	2.06 ± 0.20	2.04 ± 0.18	1.99 ± 0.13	0.002
Glucose (mg per 100 ml)	90.4 ± 8.7	94.8 ± 13,37	100.4 ± 18.6	115.0 ± 37.2	130.6 ± 24.7	0.000

Abbreviations: BMI, body mass index; Ca, calcium; K, potassium; Mg, magnesium; MS, metabolic syndrome; Na, sodium; NS, not significant; P, phosphate; W/H, waist-to-hip ratio.

Table 4 Pearson's correlation coefficients of serum phosphate according to metabolic syndrome components with clinic-laboratory variables

	1		*2*		*3*		*4*		*5*	
MS components	r	P	r	P	r	P	r	P	r	P
Age (years)	−0.063	0.039	0.080	0.020	0.035	NS	−0.036	NS	0.750	NS
BMI ($kg\,m^{-2}$)	−0.098	0.001	−0.064	NS	0.144	0.003	−0.130	NS	−0.242	NS
W/H	−0.090	0.003	−0.013	NS	−0.086	NS	−0.104	NS	0.333	NS
Ca ($mEq\,lt^{-1}$)	0.288	<0.001	0.294	<0.001	0.294	<0.001	0.028	NS	0.449	0.01
K ($mEq\,lt^{-1}$)	0.006	NS	0.021	NS	0.070	NS	−0.049	NS	−0.227	NS
Na ($mEq\,lt^{-1}$)	−0.027	NS	−0.036	NS	0.011	NS	−0.240	NS	0.008	NS
Mg (mg per 100 ml)	0.107	<0.001	0.080	0.019	−0.650	NS	0.640	NS	0.627	<0.001
Glucose (mg per 100 ml)	−0.036	NS	−0.095	0.005	−0.002	NS	−0.050	NS	−0.306	NS

Abbreviations: BMI, body mass index; Ca, calcium; K, potassium; Mg, magnesium; MS, metabolic syndrome; Na, sodium; NS, not significant; P, phosphate; W/H, waist-to-hip ratio.

Patients were also divided into five groups according to MS components, as described above, and the number of patients in each group was as follows: group I, n=1081; group II, n=858; group III, n=438; group IV, n=191 and group V, n=32. It was observed that as the number of components of MS rose, BMI and waist-to-hip ratio did as well, but the levels of phosphate were significantly higher in the first three groups in comparison to groups IV and V (P=0.003) (Table 3).

In each group, the correlation of phosphate to other parameters was studied. In group I, there was a strong positive correlation of phosphate to calcium and magnesium (r=0.288, P<0.0001; and r=0.107, P<0.001, respectively) and a negative correlation to age, BMI and waist-to-hip ratio (r=−0.063, P=0.039; r=−0.098, P=0.001; and r=−0.09, P=0.003, respectively). In group II, a significant correlation between phosphate and age, calcium and magnesium was observed (r=0.08, P=0.02; r=0.294, P<0.001; and r=0.08, P=0.019, respectively). In group III, a strong positive correlation between phosphate and calcium and BMI was seen (r=0.294, P<0.0001; and r=0.144 P=0.003, respectively), whereas in group V a positive correlation was observed between phosphate and calcium and magnesium (r=0.449, P=0.01; and r=0.627, P<0.001, respectively) (Table 4).

A multivariate analysis was performed in the four groups with dipping status and in the five groups of MS components in which phosphate was set as the dependent variable and age, total cholesterol,

Table 5 Independent effect of age, BMI, waist-to-hip ratio, glucose, total cholesterol, triglycerides, HDL and eGFR in phosphate levels in the four dipping pattern groups and in the five groups of metabolic syndrome component accumulation

	Extreme dippers			*Dippers*			*Non-dippers*			*Reverse dippers*		
	R^2=*0.015*			R^2=*0.023*			R^2=*0.034*			R^2=*0.128*		
Serum phosphate	*β*	*s.e.*	P	*β*	*s.e.*	P	*β*	*s.e.*	P	*β*	*s.e.*	P
Age	0.000	0.002	NS	0.000	0.001	NS	0.002	0.001	NS	0.03	0.528	NS
Waist-to-hip ratio	0.221	0.247	NS	0.065	0.148	NS	0.254	0.203	NS	0.22	0.45	NS
Total cholesterol	0.001	0.001	NS	0.0	0.0	NS	0.0	0.0	NS	−0.001	0.001	0.04
HDL	0.000	0.002	NS	0.002	0.001	0.05	0.02	0.001	NS	0.05	0.003	NS
Triglycerides	0.0	0.0	NS	0.0	0.0	NS	0.01	0.00	0.004	0.000	0.001	NS
eGFR	0.0	0.001	NS	0.001	0.001	0.04	0.01	0.001	NS	0.01	0.002	NS
Glucose	0.000	0.001	NS	0.01	0.001	NS	−0.001	0.001	NS	−0.001	0.001	NS
BMI	0.004	0.004	NS	0.008	0.003	0.005	0.007	0.003	NS	0.002	0.006	NS

	1			*2*			*3*			*4*			*5*		
	R^2=*0.03*			R^2=*0.025*			R^2=*0.02*			R^2=*0.36*			R^2=*0.36*		
MS components	*β*	*s.e.*	P	*β*	*s.e.*	P	*β*	*s.e.*	P	*β*	*s.e.*	P	*β*	*s.e.*	P
Age	0.000	0.001	NS	0.001	0.001	NS	0.001	0.002	NS	0.03	0.003	NS	0.005	0.006	NS
Waist-to-hip ratio	−0.360	0.177	0.04	0.039	0.180	NS	0.382	0.247	NS	0.413	0.376	NS	2.126	0.984	0.04
Total cholesterol	0.0	0.0	NS	0.0	0.0	NS	0.0	0.0	NS	−0.001	0.001	NS	0.00	0.001	NS
HDL	0.002	0.001	0.04	0.002	0.001	NS	0.02	0.002	NS	0.004	0.003	NS	0.002	0.01	NS
Triglycerides	0.0	0.0	NS	0.0	0.0	NS	0.0	0.0	NS	0.0	0.0	NS	0.001	0.001	NS
eGFR	0.002	0.001	0.01	0.01	0.001	NS	0.0	0.001	NS	0.0	0.002	NS	0.0	0.003	NS
Glucose	0.000	0.001	NS	−0.002	0.001	0.01	0.0	0.001	NS	0.0	0.001	NS	−0.006	0.003	0.03
BMI	0.009	0.004	0.009	0.008	0.004	0.028	0.004	0.005	NS	0.005	0.006	NS	0.018	0.014	NS

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; MS, metabolic syndrome; NS, not significant.

Table 6 Baseline characteristics and NSBP fall of the study population according to calcium×phosphate (Ca×P) multiplication divided in quartiles

Ca×P	*First*	*Second*	*Third*	*Fourth*	P *(for trend)*
Age (years)	54.3 ± 12.4	54.1 ± 12.7	51.2 ± 12.9	51.5 ± 14.0	<0.001
BMI (kg m^{-2})	27.8 ± 4.5	27.5 ± 4.1	27.0 ± 4.1	26.9 ± 3.9	<0.001
W/H	0.860 ± 0.070	0.860 ± 0.080	0.850 ± 0.080	0.850 ± 0.070	0.02
NSBP fall (mm Hg)	11.7 ± 7.9	12.3 ± 8.0	13.7 ± 7.4	13.9 ± 7.2	<0.001
P (mg per 100 ml)	3.04 ± 0.26	3.43 ± 0.15	3.64 ± 0.14	3.90 ± 0.23	<0.001
Ca (mEq lt^{-1})	9.14 ± 0.45	9.41 ± 0.35	9.59 ± 0.36	9.93 ± 0.39	<0.001
K (mEq lt^{-1})	4.37 ± 0.40	4.36 ± 0.40	4.37 ± 0.34	4.42 ± 0.58	0.02
Na (mEq lt^{-1})	142.0 ± 3.5	142.2 ± 3.1	142.3 ± 2.9	142.1 ± 3.3	NS
Mg (mg per 100 ml)	2.03 ± 0.19	2.06 ± 0.19	2.08 ± 0.14	2.10 ± 0.17	<0.001
Glucose (mg per 100 ml)	97.7 ± 21.4	96.8 ± 20.0	93.8 ± 12.9	95.0 ± 15.0	<0.001

Abbreviations: BMI, body mass index; Ca, calcium; K, potassium; Mg, magnesium; MS, metabolic syndrome; Na, sodium; NS, not significant; NSBP, nocturnal systolic blood pressure; P, phosphate; W/H, waist-to-hip ratio.

high-density lipoprotein, triglycerides, BMI, waist-to-hip ratio and eGFR were the independent variables. Phosphate levels in both models were not significantly affected by these parameters (Table 5).

After analysis of covariance, in which phosphate was set as the dependent variable and the model was adjusted for calcium levels, the four groups did not differ in phosphate levels (P=0.712). Finally, calcium and phosphate were multiplied (Ca×P) and divided into quartiles (first <61.38 mg^2 dl^{-2}; second 61.38–67.20 mg^2 dl^{-2}; third 67.20–72.20 mg^2 dl^{-2}; fourth $\geqslant 72.20$ mg^2 dl^{-2}). Nocturnal BP fall was significantly greater in the highest quartile of Ca×P ($P<0.001$), whereas there was no correlation among the four dipping pattern groups and Ca×P (P=NS) (Table 6).

DISCUSSION

In this cross-sectional study, we investigated the relationship between different APBM dipping patterns and serum phosphate levels in patients with WCH. It has been reported that low serum phosphate may be related to the development of hypertension and MS.[22] We also explored the possible relation of serum phosphate and NSBP dipping status to different distributions of MS components in patients with WCH.

The key finding of this study was that WCH patients with an extreme dipping pattern had higher levels of serum phosphate compared to reverse dippers. Furthermore, when patients were grouped according to the number of the components of the MS fulfilled, individuals with the lowest serum phosphate levels had the highest number of components. In addition, when we used the quartiles of the Ca×P product, the NSBP fall magnitude increased as the levels of the product rose.

The possible mechanisms of the association between low serum phosphate and decreased dipping status in WCH are not yet well established. It is known that WCH may not be entirely benign and that the observed sympathetic hyperactivity may be responsible for the development of target organ damage in these patients.[24] Conversely, low serum phosphate has been associated with the development of hypertension explained by the increased sympathoadrenal activity presented in hypertensive patients, because it has been reported that epinephrine leads to a net shift of phosphate from the extracellular to the intracellular compartment.[25] In addition, hypophosphatemia in patients with mild essential hypertension appears to be inversely related to sympathetic adrenal tone and may be caused by increased plasma epinephrine within pathophysiologic arterial concentrations.[20] Furthermore, serum phosphate is inversely related to BP in normotensive individuals[26] when they are compared with age-, sex- and race-matched controls; in our study, serum phosphate levels were lowest in hypertensives.[27]

The relationship between MS components and low levels of serum phosphate may be causative. It has been previously observed that an unbalanced diet, characterized by low phosphate and high carbohydrate consumption, may lead to reduced serum phosphate levels in patients at risk for the development of MS.[28] Increased insulin levels in patients with MS may be a major determinant in this process since insulin stimulates intramyocellular phosphate transport into skeletal muscle, which accounts for much of its hypophosphatemic effects *in vivo*. Thus reduced phosphate levels may be the consequence of increased tranfer of phosphate from the extracellular to the intacellular compartment.[29,30]

The inclusion of Ca×P product in our study was made to add further information to the relation between ion metabolism and WCH. It is known that calcium is essential to neurohumoral control,[27] volume regulation[31] and vascular smooth muscle function.[32] The diverse effects of calcium on BP control reflect its central role in both membrane- and cytosol-associated events. In conjunction with membrane receptors and intracellular calmodulin, calcium regulates cell-to-cell communication, neurotransmitter synthesis and release, and hormone receptor interactions that initiate cytosolic metabolism.[33,34]

The role of phosphate in normal cardiovascular physiology is equally as diverse and important as that of calcium and magnesium. In all cells and organs, phosphate is a prerequisite for normal plasma membrane synthesis and integrity.[35] In addition, most energy-requiring metabolic functions of a cell are dependent upon phosphate through the formation and degradation of the high energy bonds of ATP. As a consequence, membrane-associated ion pumps, as well as receptor-ion channel interactions, involve phosphate.[36] Furthermore, the synthesis, storage and release of local and systemic hormones that regulate cardiac output and vascular resistance require phosphate. In vascular tissue, phosphate is a vital co-factor in the processes outlined above for calcium and magnesium. Thus, the functional role of these ionic species in vascular cell physiology is highly interrelated and the use of Ca×P product may be of more clinical importance.

Study limitations

First, after multivariate analysis, the differences initially observed were not significant. Perhaps the other factors may be stronger in the prediction of dipping status in WCH. Still, this study points to a possible relation between serum phosphate, dipping status and MS components in WCH patients. Second, serum parathyroid hormone

levels were not evaluated. Thus, further studies should be performed to elucidate the clinical significance of low serum phosphate values.

In conclusion, patients with WCH and decreased levels of serum phosphate or Ca×P product present with an increased number of MS components and higher night-time SBP levels. This observation may be important because of its prognostic significance in the assessment of the cardiovascular risk of WCH patients. Furthermore, the different phosphate and Ca×P product levels, according to the number of MS components, may reveal various relationships attributed to this syndrome.

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