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THE ROLE OF DISTUBANCES OF PHOSPHATE METABOLISM IN METABOLIC SYNDROME

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Abstract

Background and Aims: *Metabolic syndrome represents a cluster of cardiovascular risk factors and reached epidemic proportions. It was hypothesized that disturbances in phosphate metabolism may represent a feature of the metabolic syndrome. The aim of the study was to investigate the relationship between phosphate levels and the presence of metabolic syndrome components, as well as the putative mechanism for reduced phosphate level in metabolic syndrome.* ***Materials and Methods:*** *We enrolled 155 subjects: 64 with metabolic syndrome and 91 controls. Biochemical parameters of the metabolic syndrome study population were compared with the healthy population.* ***Results:*** *Patients with metabolic syndrome showed significantly lower phosphate (46%) and magnesium levels compared with controls (22.7%) ($p<0.001$). Women showed significantly greater serum phosphate levels than men (3.32 mg/dl versus 3.18 mg/dl) ($p<0.03$). Serum magnesium levels did no differ significantly between men and women. Fractional phosphate excretion rates in patients with metabolic syndrome were similar with controls (10.1±10.2% vs 13.1±9.9%), as well as fractional magnesium excretion (3.1±1.6% vs 2.8±1.3%).* ***Conclusions:*** *Patients with metabolic syndrome show significantly lower phosphate and magnesium concentrations compared to controls. This reduction is likely to be attributed to internal redistribution of phosphate and is more pronounced as the number of components of metabolic syndrome increases.*

key words: *metabolic syndrome, phosphate concentration, magnesium concentration.*

Background and aims

Metabolic syndrome is a complex of cardiovascular risk factors possibly arising from insulin resistance accompanying abnormal adipose tissue distribution and function [1]. javascript:showrefcontent('refrenceslayer');It is a risk factor for coronary heart disease, as well as diabetes, fatty liver, and several cancers. The clinical manifestations of this syndrome may include hypertension, hyperglycemia, hypertriglyceridemia, reduced high-density lipoprotein cholesterol (HDL-C), and abdominal obesity. Under the current guidelines of the Adult Treatment Panel III revised in 2005 by the National Heart, Lung and Blood Institute (NHLBI) and the American Heart Association (AHA) [2], metabolic syndrome is diagnosed

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when a patient has at least 3 of the following 5 features:

- Fasting glucose ≥100 mg/dL (or receiving drug therapy for hyperglycemia);
- Blood pressure ≥130/85 mm Hg (or receiving drug therapy for hypertension);
- Triglycerides ≥150 mg/dL (or receiving drug therapy for hypertriglyceridemia);
- HDL-C < 40 mg/dL in men or < 50 mg/dL in women (or receiving drug therapy for reduced HDL-C);
- Waist circumference ≥102 cm (40 in) in men or ≥88 cm (35 in) in women; if Asian American, ≥90 cm (35 in) in men or ≥80 cm (32 in) in women.

Many data suggest that patients meeting these diagnostic criteria have a greater risk of significant clinical consequences, the 2 most prominent of which are the development of diabetes mellitus [3] and of coronary heart disease. Pooled data from 37 studies involving more than 170,000 patients have shown that metabolic syndrome doubles the risk of coronary artery disease [4]. It also increases the risk of stroke, fatty liver disease, and cancer [5].

Metabolic syndrome is increasing in prevalence, paralleling an increasing epidemic of obesity. In the United States, where almost two thirds of the population is overweight or obese, more than one fourth of the population meets the diagnostic criteria for metabolic syndrome [6]. Approximately one fourth of the adult European population is estimated to have metabolic syndrome, with a similar prevalence in Latin America [6]. It is also considered an emerging epidemic in East Asian countries, including China, Japan, and Korea .The prevalence of metabolic syndrome in East Asia may range between 8-13% in men and 2-18% in women, depending on the population and definitions used [7-9]. In Japan, the Ministry of Health, Labor, and Welfare has instituted a screening and interventional program for metabolic syndrome [10] while this condition has been recognized as a highly prevalent problem in many other countries worldwide [11-16].

The pathogenesis of metabolic syndrome remains uncertain. It is not known whether the individual components of metabolic syndrome share underlying causes (with insulin resistance as the most important) or if they merely represent a cluster of unrelated risk factors.

May the disturbances in phosphate metabolism represent a feature of the metabolic syndrome? Some studies [17,18] show that phosphate is involved directly in carbohydrate metabolism. Hypophosphatemia can result in impaired utilization of glucose, insulin resistance, and hyperinsulinemia [19]. So, reduced phosphate levels may contribute directly to the development of the obesity, hypertension, and dyslipidemia that characterize metabolic syndrome [20].

The present study investigates the relationship between phosphate levels and the presence of the characteristics of metabolic syndrome, as well as the mechanism that may be responsible for reduced phosphate level in patients with this syndrome.

Material and Methods

Two hundred forty subjects from Dr I Cantacuzino Hospital were evaluated for inclusion in the study from January to December 2009. To avoid the potential confounder effect of antihypertensive and hypolipidemic medications on our results, only incident cases of hypertension and dyslipidemia were included. We excluded patients with known preexisting liver or kidney diseases, patients with thyroid dysfunction, individuals consuming more than 30 g/week of alcohol and patients administered drugs that may interfere with glucose or lipid metabolism (corticoids, beta-blockers, hormonal replacement therapy, selective estrogen receptor

modulators) or drugs that may affecting serum concentrations of electrolytes (bisphosphonates, antacids, diuretics, beta-blockers, non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, recent use of antibiotic as aminoglycosides). No study participants had diabetes (fasting glucose level > 126 mg/dl) or clinical/electrocardiographic evidence of coronary heart disease. Because nicotine consumption may affect insulin sensitivity, as well as sympathetic nervous system activity, smokers were instructed to avoid smoking in the morning before sample collection. The diagnosis of metabolic syndrome was made according to Adult Treatment Panel III guidelines [2]. Otherwise healthy individuals with fewer than 3 criteria for the diagnosis of metabolic syndrome served as controls. The final study group included 155 subjects: 64 with metabolic syndrome and 91 controls.

Serum parameters measured were: glycaemia, insulin, creatinine, uric acid, total cholesterol, HDL cholesterol and triglycerides, phosphate concentration, magnesium concentration, albumin. LDL cholesterol was calculated using the formula: total cholesterol – HDL-cholesterol – triglycerides/5 (in cases with triglycerides under 400 mg/dL). In cases of hypoalbuminemia, the corrected serum magnesium was calculated using the formula of Kroll and Elin [21]:

Corrected serum magnesium (mmol/L) =measured total serum magnesium (mmol/L) +0.005+ [40-serum albumin (g/L)]

We assessed insulin sensitivity using the homeostasis model assessment (HOMA)-IR index as a surrogate marker of insulin resistance. The HOMA-IR index was calculated using the following formula [22]:

Serum insulin (mU/mL) x plasma glucose (mmol/l)/22.5

Standard formulae were used for calculation of the fractional excretion of electrolytes. Fractional excretion of magnesium was derived from total serum magnesium, rather than ultrafiltrable magnesium, and therefore is an approximation. However, because ultrafiltrable magnesium makes up a reasonably constant part of the total concentration in serum, the latter values were used for calculation.

Statistical Analysis

Data are expressed as mean ± SD. Unpaired *t*-test was used for comparison between study groups, whereas differences in proportions were assessed by using chi-square test; $p<0.05$ is considered significant. Qulitative variables were comparated by χ^2 test and Fischer's Exact Test (2-tailed, *p*-level < 0.05). EpiInfo and Statgraphics Plus 6.0. software were used for statistical analyses.

Results

Patient clinical characteristics are listed in Table 1. There were no differences in age, sex distribution, or proportion of active smokers between study groups; however, patients with metabolic syndrome had significantly greater body mass index (BMI) and waist circumference values compared with controls.

Table 1. Clinical characteristics of the study population.

	Metabolic Syndrome	**Controls**	***p***
No. of patients	64	91	
Sex (male/female)	40/24	46/41	Not significant
Smokers/nonsmokers	26/38	30/61	Not significant
Age (year)	48.8	48.7	Not significant
BMI (kg/m²)	28.6	24.7	<0.001
Waist circumference (cm)	100.1	88. 8	<0.001

Biochemical characteristics of study participants are listed in Table 2. As expected, patients with metabolic syndrome had greater fasting glucose and insulin concentrations, as well as elevated HOMA-IR index values (p<0.001). In addition, these patients showed significantly greater blood pressure values (both systolic and diastolic) and increased heart rate. Finally, patients in the metabolic syndrome group had greater uric acid values and an adverse lipid profile, characterized by elevated concentrations of total cholesterol, LDL-cholesterol, and triglycerides, as well as lower concentrations of HDL- cholesterol.

Table 2. Biochemical characteristics of the study population.

	Metabolic Syndrome	**Controls**	***p***
Glucose (mg/dL)	107±17	92 ± 9	≤ 0.001
Insulin (µU/mL)	13.3 ± 6.1	8.8 ± 5.1	≤ 0.001
Systolic blood pressure (mm Hg)	157.9±17.8	133.3±23.9	≤ 0.001
Diastolic blood pressure (mm Hg)	95.0 ± 10.1	83.1 ± 14.1	≤ 0.001
Heart rate (beats/min)	77.8 ± 9.49	73.5 ± 8.78	≤ 0.005
Total cholesterol (mg/dL)	242 ± 45	226 ± 41	≤ 0.001
Triglycerides (mg/dL)	177 ± 77	107 ± 52	≤ 0.001
HDL cholesterol (mg/dL)	38 ± 8	51 ± 12	≤ 0.001
LDL cholesterol (mg/dL)	169 ± 42	154 ± 36	≤ 0.007
Creatinine (mg/dL)	0.91 ± 0.13	0.92 ± 0.15	Not significant
Uric acid (mg/dL)	5.3 ± 1.6	4.6 ± 1.6	≤ 0.010

Table 3. Electrolytes concentrations and their fractional excretion in the study groups.

	Normal Value	**Metabolic Syndrome**	**Controls**	***p***
K (mEq/L)	3.5-5.3	4.5 ± 0.3	4.4 ± 0.4	Not significant
Ca (mg/dL)	8.2-10.6	9.5 ± 0.4	9.5 ± 0.4	Not significant
Na (mEq/L)	135-145	142.1 ± 1.8	142.1 ± 1.8	Not significant
Magnesium (mEq/L)	1.3-2.1	1.6 ± 0.1	1.7 ± 0.1	0.050
Phosphate (mg/dL)	3-4.5	3.0 ± 0.5	3.3 ± 0.5	0.001
Fractional excretion phosphate (%)		10.1 ±10.2	13.1 ± 9.9	Not significant
Fractional excretion magnesium (%)		3.1 ± 1.6	2.8 ± 1.3	Not significant

Electrolyte concentrations and their fractional excretion in both study groups are listed in Table 3. There were no differences in potassium, sodium and calcium concentrations between the study groups. Conversely, patients with metabolic syndrome had significantly lower serum magnesium and phosphates levels compared with controls. Women showed significantly greater serum phosphate levels than men (3.32 mg/dl versus 3.18 mg/dl) (p<0.03). Serum magnesium levels did no differ significantly between men and women. To exclude that the lower proportion of women in the metabolic syndrome group may account for the lower serum phosphate levels in this group, men and women were compared separately. Both men and women with metabolic syndrome showed significantly lower phosphate concentrations compared with their counterparts in the control group (2.92 mg/dl versus 3.22 mg/dl for men, p<0.01; 3.16mg/dl versus 3.38 mg/dl for women, p<0.05). In the metabolic syndrome group, 46% of patients had abnormally low phosphate concentrations (<3

mg/dl) compared with 22.7% of individuals in the control group ($p<0.001$).

Figure 1 shows the unadjusted distribution of phosphate levels after study participants were classified according to their total number of components of metabolic syndrome. There was a strong linear decrease in phosphate value as the number of components of metabolic syndrome increased ($p<0.01$). The same significant trend was observed after adjustment for potential confounders, such as BMI, age, and sex. In contrast to differences observed in phosphate and magnesium concentrations between patients with metabolic syndrome and controls, fractional excretion values of these elements were similar in both study groups. Patients with metabolic syndrome had higher magnesium and lower phosphate fractional excretion values; however, these differences did not achieve statistical significance (Table 3).

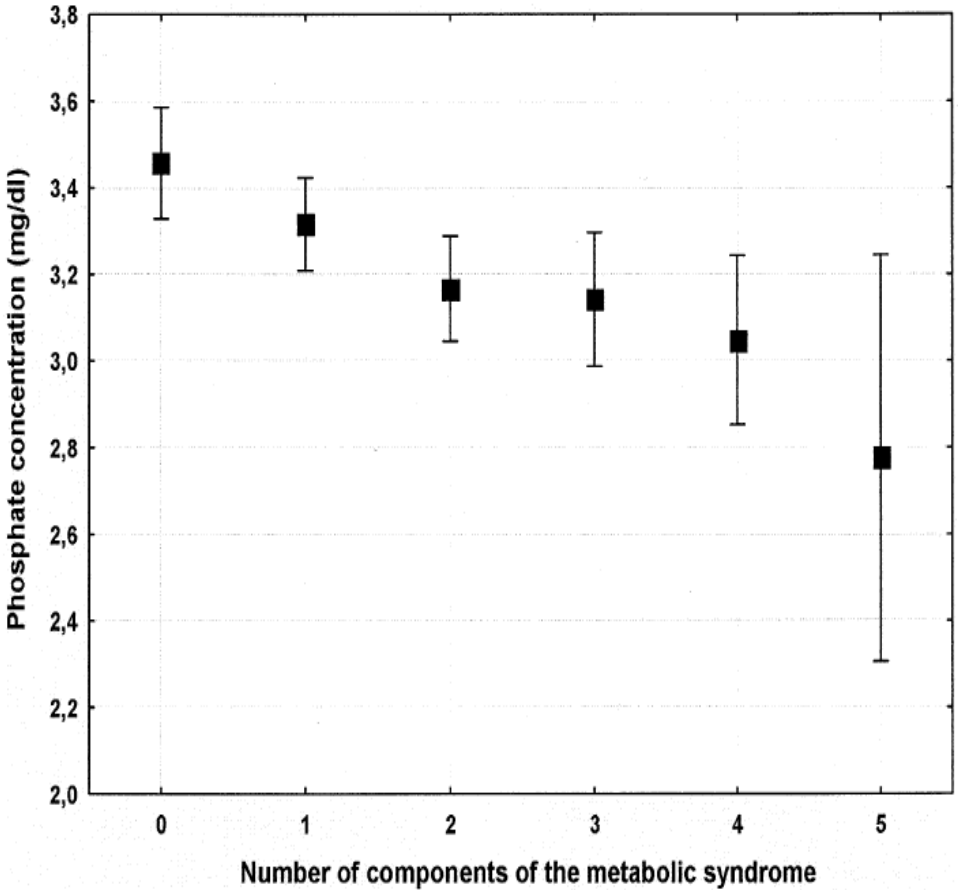

Figure 1. Distribution of phosphate concentrations in the study population according to the number of metabolic syndrome components.

Discussions

Previous studies have shown that obese and hypertensive subjects had significantly lower phosphate levels compared with healthy individuals [23,24]. In our study we provide additional clinical data for phosphate metabolism abnormalities in patients with metabolic syndrome. Our patients showed significantly lower phosphate concentrations compared with controls, and this reduction was proportional to the number of components of metabolic syndrome. This difference was not accompanied by differences in concentrations of other electrolytes (except magnesium), whereas fractional excretion of phosphate was similar in both study groups. Phosphate depletion may result from decreased dietary intake or reduced intestinal absorption, increased urinary excretion, and internal redistribution. The

observation that controls had relatively greater fractional excretion of phosphate compared with patients with metabolic syndrome invalidates increased renal losses as an important mechanism for phosphate depletion in these patients. Lower phosphate concentrations in patients with metabolic syndrome compared with the control population may result from reduced dietary intake [20].

In 2001, Haglin proposed 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 metabolic syndrome [20]. Reduced phosphate levels in the metabolic-syndrome group may represent the consequence of increased transfer of phosphate from the extracellular to the intracellular compartment. Increased insulin levels in patients with metabolic syndrome could be a major determinant of this process [25,26]. The activation of sympathetic nervous system observed in patients with metabolic syndrome and the resulting increment in serum catecholamine levels could also contribute to the intracellular shift of phosphate [27-29].

Lower magnesium concentrations in patients with metabolic syndrome compared with the control population can be attributed to the same mechanisms as lower serum phosphate levels. Our finding that patients with high insulin levels showed greater fractional excretion of magnesium but not achieve statistical significance with the hyperinsulinemia-induced renal magnesium wasting.

Because both phosphate and magnesium are vital to carbohydrate metabolism, it is possible that the reduced levels of these ions in patients with metabolic syndrome may decrease the peripheral utilization of glucose, thus leading to the development or exacerbation of insulin resistance. In this case, the resulting compensatory hyperinsulinemia can further decrease phosphate and magnesium concentrations inducing a vicious circle that may contribute to the pathogenesis of the metabolic syndrome.

Limitations of our study include the small sample size; use of single measurements, which did not permit assessment of reproducibility; and finally, the lack of dietary data to asses phosphate and magnesium intake. However, our result may represent the basis for future research concerning the causal relationship between reduced phosphate and magnesium levels and the incidence of the metabolic syndrome.

Conclusions

Significantly lower phosphate and magnesium concentrations were found in patients with metabolic syndrome compared with individuals who do not fulfill criteria for the diagnosis of this syndrome. This reduction is likely to be attributed to reduced dietary intake and internal redistribution of phosphate and is more pronounced as the number of components of metabolic syndrome increases. The clinical significance of these disturbances, as well as their importance as targets for preventive or therapeutic interventions, remains to be established.

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