Disturbances of Phosphate Metabolism: Another Feature of Metabolic Syndrome

Rigas Kalaitzidis, MD, Vasilis Tsimihodimos, MD, Eleni Bairaktari, PhD, Kostantinos C. Siamopoulos, MD, and Moses Elisaf, MD

Background: Despite important recent advances in the understanding of the consequences of metabolic syndrome, its pathophysiological characteristics remain unclear. It has been proposed that disturbances in phosphate metabolism may contribute to the development of this constellation of cardiovascular risk factors. However, there have been insufficient clinical data supporting this hypothesis to date. The aim of our study is to confirm the presence of hypophosphatemia in patients with metabolic syndrome, as well as investigate mechanisms that may underlie the disturbances in phosphate metabolism in this patient group.

Methods: Two hundred fifty-five individuals were enrolled. The diagnosis of metabolic syndrome was based on Adult Treatment Panel III guidelines. Subjects with fewer than 3 criteria served as controls.

Results: Patients with metabolic syndrome showed significantly lower phosphate and magnesium levels compared with controls. Because fractional excretion of phosphate was similar in both groups, we assume that hypophosphatemia in patients with metabolic syndrome can be attributed to decreased dietary intake, as well as internal redistribution of this element. Lower magnesium values in the patient group may result from the same mechanisms as lower phosphate levels. In addition, hyperinsulinemia-induced renal magnesium wasting also may be a contributory factor.

Conclusion: Patients with metabolic syndrome show significantly lower phosphate and magnesium levels compared with healthy individuals. 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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INDEX WORDS: Metabolic syndrome; phosphate; magnesium.

METABOLIC SYNDROME represents a cluster of cardiovascular risk factors that recently has become a public health problem of epidemic proportions. Individuals with metabolic syndrome are at increased risk for cardiovascular events, and the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) stresses the importance of targeting prevention strategies for this population. According to the Adult Treatment Panel III guidelines, the definition of this syndrome is based on the presence of 3 or more of the following characteristics: hypertension, impaired glucose tolerance, abdominal obesity, and dyslipidemia characterized by hypertriglycerideremia and decreased high-density lipoprotein (HDL) cholesterol values. However, despite recent advances in the understanding of the consequences of metabolic syndrome, its pathogenesis remains uncertain. More specifically, 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.

It recently was proposed that disturbances in phosphate metabolism may represent a key feature of metabolic syndrome. Because phosphate is involved directly in carbohydrate metabolism, hypophosphatemia can result in impaired utilization of glucose, insulin resistance, and hyperinsulinemia. In addition, according to this model, reduced phosphate levels may contribute directly to the development of the obesity, hypertension, and dyslipidemia that characterize metabolic syndrome. However, there are insufficient clinical data supporting the presence of hypophosphatemia in patients with metabolic syndrome, as well as its potential pathophysiological implication in the pathogenesis of this cluster of cardiovascular risk factors. Thus, we undertook the present study to investigate the relationship between phosphate levels and the presence of the characteristics of metabolic syndrome, as well as the mechanisms that may be responsible for

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reduced phosphate levels in patients with this syndrome.

METHODS

Patients

Two hundred fifty-five consecutive healthy individuals receiving a regular annual medical checkup at our hospital were included in the study. All individuals receiving a checkup at outpatient medical clinics of our hospital (a large university hospital located in the northwestern part of Greece) from January to December 2001 (n = 380) were evaluated for inclusion in the study. To avoid the potential confounder effect of antihypertensive and hypolipidemic medications on our results, only incident cases of hypertension and dyslipidemia were included. No study participant had diabetes (fasting glucose level > 126 mg/dL (>7 mmol/L)) or clinical or electrocardiographic evidence of coronary heart disease. Patients with known preexisting liver or kidney diseases (defined as a positive medical history or 3-fold increase in serum aminotransferase level and serum creatinine level > 1.6 mg/dL (>141 μmol/L), respectively), as well as patients with thyroid dysfunction (thyroid-stimulating hormone level > 5 mIU/L), were excluded from the study. In addition, patients administered drugs that may interfere with glucose or lipid metabolism (β-blockers, corticosteroids, hormonal replacement therapy, selective estrogen receptor modulators) or affecting serum concentrations of electrolytes (inhaled β2-adrenergic agonists, biphosphonates, antacids, diuretics, angiotensin-converting enzyme inhibitors, β-blockers, angiotensin II receptor blockers, non-steroidal anti-inflammatory drugs, recent use of such antibiotics as aminoglycosides or amphotericin B) were excluded. Individuals consuming more than 30 g/wk of alcohol also were excluded from the study.

Blood pressure and heart rate were measured in duplicate, with patients in a sitting position, after 5 minutes of rest, and mean values were used in statistical analysis. Waist circumference was measured midway between the last rib and iliac crest by an experienced nurse. Blood and urine samples were obtained after a 12-hour overnight fast while study participants followed their regular diet. 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.4 Otherwise healthy individuals with fewer than 3 criteria for the diagnosis of metabolic syndrome served as controls. All study participants gave their written informed consent before enrollment in the study. The study protocol was approved by the Scientific Committee of the University Hospital of Ioanna.

Methods

Blood samples were obtained in the morning after an overnight fast. Serum was isolated by centrifugation at 1500g for 15 minutes. Serum parameters were measured on an Olympus AU600 Clinical Chemistry analyzer (Olympus Diagnostica, Hamburg, Germany). Concentrations of total cholesterol and triglycerides were determined enzymatically, and HDL cholesterol was determined by means of a direct assay (Olympus Diagnostica). Phosphate concentrations were determined by means of a photometric method with molybdate in acid medium (Olympus Diagnostica). Our laboratory currently is participating in the Bio-Rad Clinical Chemistry Quality Assessment Program. Imprecision (coefficient of variation) for phosphate in this program in the past 2 years (4 cycles) has ranged between 2.08% and 2.47%, and mean bias, between −0.19% and −0.35%. In cases of hypoalbuminemia, the corrected serum calcium level was calculated by adding 0.8 mg/dL (0.2 mmol/L) to the total serum calcium concentration for every 1-g/dL (10-g/L) decrement in serum albumin level from normal (assumed to be 4 g/dL [40 g/L]). In these cases, serum magnesium concentrations were corrected for hypoalbuminemia according to the proposed formula of Kroll and Elin9:

\[
\text{Corrected serum magnesium (mmol/L)} = \frac{\text{measured total serum magnesium (mmol/L)} + 0.005}{40 - \text{serum albumin (g/L)}}
\]

Serum low-density lipoprotein (LDL) cholesterol level was calculated using the Friedewald formula, providing that triglyceride concentration was less than 400 mg/dL (<4.52 mmol/L). In patients with serum triglyceride values greater than 400 mg/dL (>4.52 mmol/L), LDL cholesterol concentrations were not determined. Insulin levels were determined by means of a Microparticle Enzyme Immunoassay on an AXSYM analyzer (Abbott GmbH Diagnostika, Wiesbaden-Delkenheim, Germany). We assessed insulin sensitivity by using the homeostasis model assessment (HOMA) index as a surrogate marker of insulin resistance. Use of this index has been validated previously in various populations,10,11 and a recently published comparative study of individuals without diabetes confirmed that the HOMA index does not differ significantly from other surrogate markers used for the quantification of insulin sensitivity.12 The HOMA index was calculated using the following formula:

\[
\text{Serum insulin (mU/mL)} \times \text{plasma glucose (mmol/L)} / 22.5
\]

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 comparisons between study groups, whereas differences in proportions were assessed by using chi-square test. Correlations between phosphate concentrations and metabolic parameters were estimated by using linear regression analysis, whereas multiple regression analysis was used for the multivariate assessment of correlations between phosphate concentrations and those variables.
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. The similar age in both study groups probably is related to the characteristics of individuals attending the outpatient clinics for medical checkups, ie, middle-aged otherwise healthy subjects. In addition, inclusion in the control group of people with 1 or 2 components of metabolic syndrome may, at least in part, explain the absence of differences in age distribution.

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 index values. 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.

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 study groups. Conversely, patients with metabolic syndrome had significantly lower serum magnesium and phosphate concentrations compared with controls. When study participants were divided according to sex, women showed significantly
greater serum phosphate levels than men (3.32 ± 0.47 mg/dL [1.07 ± 0.15 mmol/L] versus 3.18 ± 0.49 mg/dL [1.03 ± 0.16 mmol/L]; P < 0.03). Conversely, serum magnesium levels did not differ significantly between men and women. To exclude that the (not statistically significant) 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 ± 0.45 mg/dL [0.33 ± 0.15 mmol/L] versus 3.22 ± 0.49 mg/dL [1.04 ± 0.16 mmol/L] for men with and without metabolic syndrome, respectively; P < 0.01; 3.16 ± 0.42 mg/dL [1.02 ± 0.14 mmol/L] versus 3.38 ± 0.43 mg/dL [1.09 ± 0.14 mmol/L] for women with and without metabolic syndrome, respectively; P < 0.05). In the metabolic-syndrome group, 46% of patients had abnormally low phosphate concentrations (<3 mg/dL [<0.97 mmol/L]) 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. As shown, there was a strong linear decrease in phosphate values as the number of components of meta-

### Table 3. Electrolyte Concentrations and Fractional Excretion in Both Study Groups

<table>
<thead>
<tr>
<th></th>
<th>Normal Values</th>
<th>Metabolic Syndrome (n = 64)</th>
<th>Controls (n = 191)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mEq/L)</td>
<td>135-145</td>
<td>142.1 ± 1.8</td>
<td>141.6 ± 1.9</td>
<td>Not significant</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>3.5-5.3</td>
<td>4.5 ± 0.3</td>
<td>4.4 ± 0.4</td>
<td>Not significant</td>
</tr>
<tr>
<td>Magnesium (mEq/L)</td>
<td>1.3-2.1</td>
<td>1.6 ± 0.1</td>
<td>1.7 ± 0.1</td>
<td>&lt;0.050</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>8.2-10.6</td>
<td>9.5 ± 0.4</td>
<td>9.5 ± 0.4</td>
<td>Not significant</td>
</tr>
<tr>
<td>Phosphate (mg/dL)</td>
<td>3-4.5</td>
<td>3.0 ± 0.5</td>
<td>3.3 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fractional excretion phosphate (%)</td>
<td>10.1 ± 10.2</td>
<td>13.1 ± 9.9</td>
<td>Not significant</td>
<td></td>
</tr>
<tr>
<td>Fractional excretion magnesium (%)</td>
<td>3.1 ± 1.6</td>
<td>2.8 ± 1.3</td>
<td>Not significant</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Values expressed as mean ± SD. Unpaired t-test was used for comparisons between groups, and P < 0.05 is considered significant. To convert sodium and potassium in mEq/L to mmol/L, multiply by 1; magnesium in mEq/L to mmol/L, multiply by 0.5; calcium in mg/dL to mmol/L, multiply by 0.2495; phosphate in mg/dL to mmol/L, multiply by 0.3229.
Table 4. Multivariate Assessment of the Relationship Between Phosphate Concentrations and Metabolic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$\beta$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference</td>
<td>-0.26</td>
<td>0.055</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>-0.29</td>
<td>&lt;0.045</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>-0.04</td>
<td>0.407</td>
</tr>
<tr>
<td>Glucose</td>
<td>-0.08</td>
<td>0.363</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-0.10</td>
<td>0.302</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.20</td>
<td>0.055</td>
</tr>
<tr>
<td>Uric acid</td>
<td>-0.04</td>
<td>0.554</td>
</tr>
<tr>
<td>Heart rate</td>
<td>-0.20</td>
<td>0.058</td>
</tr>
<tr>
<td>Insulin</td>
<td>-0.28</td>
<td>&lt;0.050</td>
</tr>
</tbody>
</table>

Metabolic syndrome increased ($P < 0.001$). The same significant trend was observed after adjustment for potential confounders, such as BMI, age, and sex (data not shown). Unadjusted linear regression analysis shows that serum phosphate concentrations correlated negatively with blood pressure (both systolic and diastolic), triglyceride, and glucose values, as well as waist circumference. In addition, HDL cholesterol level correlated positively with serum phosphate level. Finally, negative correlations between serum phosphate levels and HOMA index values and insulin and uric acid concentrations also were observed. Multiple regression analysis including all 5 components of metabolic syndrome (as well as some other potential confounders, such as age, sex, BMI, and uric acid level) in the group of patients with metabolic syndrome showed that systolic blood pressure and insulin level were the most important determinants of serum phosphate values (Table 4).

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. Finally, when insulin concentrations in all study participants were divided into quartiles, individuals in the higher quartiles showed significantly greater fractional excretion of magnesium compared with those in the lower quartiles after adjustment for such potential confounders as age, sex, and BMI (Fig 2).

**DISCUSSION**

Metabolic syndrome represents an important cluster of risk factors for the development of cardiovascular disease, and its prevalence has increased dramatically in recent years. Despite advances in clinical and experimental research, metabolic disturbances that underlie the development of this syndrome remain ill defined. To our knowledge, there are only sparse clinical data on
the association between serum phosphate levels and characteristics of metabolic syndrome. Thus, previous studies have shown that obese and hypertensive subjects had significantly lower phosphate levels compared with healthy individuals.\textsuperscript{13,14} 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 total 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 argues against increased renal losses as an important mechanism for phosphate depletion in these patients. It has been proposed that insulin sensitivity correlates inversely with plasma intact parathyroid hormone levels.\textsuperscript{15} However, parathyroid hormone reduces phosphate concentration mainly by enhancing its renal excretion. Although in the present study, intact parathyroid hormone levels were not determined in all participants, it seems unlikely that the reduction in phosphate levels in patients with metabolic syndrome may be caused by greater parathyroid hormone levels because these patients showed lower fractional excretion of phosphate compared with controls. Recently published studies showed a positive correlation between insulin sensitivity and vitamin D concentration.\textsuperscript{16} However, if lower phosphate values in patients with metabolic syndrome were caused by vitamin D deficiency, greater fractional excretion of phosphate would have been observed in this group, and this was not the case in our study.

Lower phosphate concentrations in patients with metabolic syndrome compared with the control population may result, at least in part, from reduced dietary intake.\textsuperscript{5} It has been 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.\textsuperscript{5}

Finally, 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.\textsuperscript{17,18} This assumption is supported indirectly by results of multivariate analysis showing that insulin levels correlated negatively with phosphate concentrations. In addition, the activation of the sympathetic nervous system observed in patients with metabolic syndrome and the resulting increment in serum catecholamine levels\textsuperscript{19,20} also may contribute to the intracellular shift of phosphate.\textsuperscript{21} In this context, the increased heart rate in patients with metabolic syndrome compared with controls may just reflect the altered autonomic function in this patient group, a finding supported by the important, although insignificant, negative correlation between heart rate and phosphate concentration. Both insulin and catecholamines stimulate glycolysis, thus increasing the intracellular formation of phosphorylated carbohydrate compounds in the liver and skeletal muscles. The source of this phosphate is the inorganic phosphate of the extracellular fluid, and, as a result, serum phosphate concentrations may decrease rapidly.\textsuperscript{22}

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.\textsuperscript{23} Additionally, the hyperinsulinemia-induced renal magnesium wasting also may have a contributory role.\textsuperscript{24} Our finding that patients with high insulin levels showed significantly greater fractional excretion of magnesium is consistent with this hypothesis.

On the basis of our results, it could be assumed that improvement in insulin sensitivity would be followed by a decrease in serum insulin levels and, consequently, an increase in serum phosphate and magnesium concentrations. However, studies that tested the effects of insulin sensitizers on serum electrolyte values showed contradictory results. For example, McBain et al\textsuperscript{25} showed that the administration of metformin to patients with poorly controlled type 2 diabetes reduced renal magnesium wasting, a finding in line with our results. Neverthe-
less, this reduction was not accompanied by an increase in serum magnesium levels. Magnesium concentrations were significantly reduced after metformin administration. In contrast to these results are those recently reported by Guerrero-Romero and Rodríguez-Moran showing that pioglitazone administration significantly increased serum magnesium concentrations in glucose-intolerant subjects. Thus, it is evident that additional studies are needed to delineate the effect of the improvement in insulin sensitivity on serum electrolyte values.

To date, it is not known whether low phosphate concentrations in patients with metabolic syndrome represent a consequence of the clustering of multiple metabolic abnormalities or are directly implicated in the pathogenesis of this syndrome. However, 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, thus leading to the development of a vicious circle that may contribute to the pathogenesis of metabolic syndrome. Of special relevance are results of the recently published Coronary Artery Risk Development in Young Adults study, which showed that overweight individuals with high consumption of dairy products (that contain large quantities of phosphate) had a significantly lower risk for metabolic syndrome compared with those with lower dairy consumption. In addition, other studies have shown that magnesium supplementation may significantly increase insulin sensitivity. In contrast to these data, recent studies have shown that increased consumption of soft drinks (which contain a large amount of phosphate) may increase the incidence of type 2 diabetes in young individuals. However, in this case, the large amounts of rapidly absorbable sugars contained in these products, as well as the weight gain that accompanies their increased consumption, may offset the beneficial effect of phosphate on insulin sensitivity. In addition, high concentrations of advanced glycation end products in cola-based soft drinks may be implicated directly in the pathogenesis of insulin resistance.

Differences in serum phosphate and magnesium concentrations between patients with metabolic syndrome and controls are relatively small, and their clinical relevance is not yet known. Although there are not sufficient data on phosphate concentrations in patients with metabolic syndrome, our results are consistent with those reported by Guerrero-Romero and Rodríguez-Moran showing that patients with metabolic syndrome had small, but significant, reductions in serum magnesium levels. In addition, prospective studies have shown that small increases in serum magnesium levels (after magnesium supplementation) significantly improved insulin sensitivity, thus indirectly supporting the hypothesis that even small changes in serum electrolyte concentrations may be of important clinical relevance. Finally, the presence of individuals with 1 or 2 components of metabolic syndrome in our control group may result in underestimation of the differences in phosphate and magnesium concentrations between patients with metabolic syndrome and healthy individuals.

Our study expands the current knowledge on disturbances in phosphate and magnesium metabolism in patients with metabolic syndrome and raises important questions concerning their potential implication in the pathogenesis of insulin resistance. Our results may represent the basis for future research concerning the causal relationship between reduced phosphate and magnesium levels and the incidence of metabolic syndrome. In addition, more studies are needed to delineate whether phosphate and magnesium supplementation may prevent or reverse the development of this cluster of cardiovascular risk factors. 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 assess phosphate and magnesium intake.

In conclusion, patients with metabolic syndrome show significantly lower phosphate (and magnesium) concentrations 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.
REFERENCES


