The Role of Disturbances of Phosphate Metabolism in Metabolic Syndrome

Marilena STOIAN\textsuperscript{a,b}; Victor STOICA\textsuperscript{a,b}

\textsuperscript{a}“Dr. Ion Cantacuzino” Hospital, Bucharest, Romania
\textsuperscript{b}“Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT

Background: Metabolic syndrome represents a cluster of cardiovascular risk factors that has become a public health problem of epidemic proportions. It was proposed that disturbances in phosphate metabolism may represent a key feature of metabolic syndrome, with a high contribution of cardiovascular risk factors.

Objectives: The aim of the study is to investigate the relationship between phosphate levels and the presence of the characteristics of metabolic syndrome, as well as the mechanisms that may responsible for reduced phosphate levels in patients with metabolic syndrome.

Methods: One hundred fifty five subjects are enrolled in the study: 64 with metabolic syndrome and 91 without this syndrome. Biochemical parameters of the metabolic syndrome study populations were compared with healthy population study.

Results: Patients with metabolic syndrome showed significantly lower phosphate (46\%) and magnesium levels compared with controls (22.7\%) (p<0.001). Because fractional excretion of phosphate was similar in both groups, we think that hypophosphatemia in patients with metabolic syndrome can be attributed to decreased dietary intake, as well as internal redistribution of this element. Lower magnesium hyperinsulimemia-induced renal magnesium wasting also may be a contributory factor.

Conclusions: Patients with metabolic syndrome show significantly lower phosphate and magnesium concentrations compared with individuals who do not fulfill criteria for 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.

Keywords: metabolic syndrome, phosphate concentration, magnesium concentration

Address for correspondence:
Marilena Stoian, „Dr. Ion Cantacuzino” Clinical Hospital, 5-7 Ion Movila Street, 2\textsuperscript{nd} District, Bucharest, Romania.
E-mail: marilenastoian@yahoo.com

Article received on the 27\textsuperscript{th} of February 2013. Article accepted on the 24\textsuperscript{th} of September 2014.
**INTRODUCTION**

Metabolic syndrome is a multiplex risk factor that arises from insulin resistance accompanying abnormal adipose deposition and function (1). 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 current guidelines 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 when a patient has at least 3 of the following 5:

- 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

Abundant 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 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 diagnostic criteria for metabolic syndrome (6). Metabolic syndrome is a burgeoning global problem. 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 developing East Asian countries, including China, Japan, and Korea. The prevalence of metabolic syndrome in East Asia may range from 8-13% in men and from 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 (10). Metabolic syndrome has been recognized as a highly prevalent problem in many other countries worldwide (11-16). The pathogenesis of metabolic syndrome remains uncertain: 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 key feature of metabolic syndrome? This is the question that needs an answer in our review. Recent studies (17, 18) shows that the 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 Cantaucuzino 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 excluded. For our study were excluded: patients with known preexisting liver or kidney diseases, patients with thyroid dysfunction, individuals consuming more than 30g/wk 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 (biphosphonates, antacids, diuretics, beta-blockers, non-steroidal anti-inflam-
THE ROLE OF DISTURBANCES OF PHOSPHATE METABOLISM IN METABOLIC SYNDROME

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. 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 (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 acid uric values and an adverse lipid profile, characterized by elevated concentrations of total cholesterol, LDL choles-

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. 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.

<table>
<thead>
<tr>
<th>Metabolic Syndrome</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>64</td>
<td>91</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>40/24</td>
<td>46/41</td>
</tr>
<tr>
<td>Smokers/nonsmokers</td>
<td>26/38</td>
<td>30/61</td>
</tr>
<tr>
<td>Age (y)</td>
<td>48.8</td>
<td>48.7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.6</td>
<td>24.7</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>100.1</td>
<td>88.8</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Metabolic Syndrome</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dL)</td>
<td>107±17</td>
<td>92 ± 9</td>
</tr>
<tr>
<td>Insulin (U/mL)</td>
<td>13.3 ± 6.1</td>
<td>8.8 ± 5.1</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>157.9±17.8</td>
<td>133.3±23.9</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>95.0±10.1</td>
<td>83.1 ± 14.1</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>77.8 ± 9.49</td>
<td>73.5 ± 8.78</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>242 ± 45</td>
<td>226 ± 41</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>177 ± 77</td>
<td>107 ± 52</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>38 ± 8</td>
<td>51 ± 12</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>169 ± 42</td>
<td>154 ± 36</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.91 ± 0.13</td>
<td>0.92 ± 0.13</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>5.3 ± 1.6</td>
<td>4.6 ± 1.6</td>
</tr>
</tbody>
</table>

TABLE 2. Biochemical Characteristics of the Study Population.
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. Serum phosphate concentrations correlated negatively with blood pressure, triglyceride, and glucose values, as well as waist circumference; HDL cholesterol level correlated positively with serum phosphate level. Negative correlations between serum phosphate levels and HOMA index values and insulin and acid uric concentrations also were observed. In the group of patients with metabolic syndrome systolic blood pressure and insulin level were the most important determinants of serum phosphate values. 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).

**DISCUSSION**

The previous studies have shown that obese and hypertensive subjects had significantly lower phosphate levels compared with healthy individuals (21,22). In our study we provide additional clinical data for phosphate metabolism abnormalities in patients with metabolic syndrome; our patients showed significantly greater blood pressure values (both systolic and diastolic) and increased heart rate. Finally, patients in the metabolic-syndrome group had greater acid uric 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.

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 (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 acid uric 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>
<thead>
<tr>
<th>Normal Value</th>
<th>Metabolic Syndrome</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>K (mEq/L)</td>
<td>3.5-5.3</td>
<td>4.5 ± 0.3</td>
<td>4.4 ± 0.4</td>
</tr>
<tr>
<td>Ca (mg/dL)</td>
<td>8.2-10.6</td>
<td>9.5 ± 0.4</td>
<td>9.5 ± 0.4</td>
</tr>
<tr>
<td>Na (mEq/L)</td>
<td>135-145</td>
<td>142.1 ± 1.8</td>
<td>142.1 ± 1.8</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>
</tr>
<tr>
<td>Phosphate (mg/dL)</td>
<td>3-4.5</td>
<td>3.0 ± 0.5</td>
<td>3.3 ± 0.5</td>
</tr>
<tr>
<td>Fractional excretion phosphate (%)</td>
<td>10.1± 10.2</td>
<td>13.1 ± 9.9</td>
<td>Not significant</td>
</tr>
<tr>
<td>Fractional excretion magnesium (%)</td>
<td>3.1 ± 1.6</td>
<td>2.8 ± 1.3</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

TABLE 3. Electrolytes Concentrations and Fractional Excretion in Study Groups.
creased 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. 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 (23,24). The activation of sympathetic nervous system observed in patients with metabolic syndrome and the resulting increment in serum catecholamine levels also contribute to the intracellular shift of phosphate (25-27).

Both insulin and catecholamine 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; serum phosphate concentrations may decrease rapidly (28).

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 significantly greater fractional excretion of magnesium is consistent 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; there is a vicious circle that may contribute to the pathogenesis of 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 assess phosphate and magnesium intake.

Our result may represent the basis for future research concerning the causal relationship between reduced phosphate and magnesium levels and the incidence of metabolic syndrome.

Conflict of interests: none declared.
Financial support: none declared.

References


