Changes in Plasma, Erythrocyte, and Platelet Magnesium Levels in Normotensive and Hypertensive Obese Subjects During Oral Glucose Tolerance Test

Francesco Corica, Alessandro Allegra, Riccardo Ientile, Michele Buemi, Andrea Corsonello, Salvatore Bonanzinga, Salvatore Macaione, and Domenico Ceruso

We evaluated the 75-g oral glucose tolerance test (OGTT)-induced modifications in glucose, insulin, and norepinephrine plasma concentrations, and in plasma, erythrocyte, and platelet magnesium levels in two groups of obese subjects (normotensive obese, NT-Ob, N = 19; hypertensive obese, HT-Ob, N = 15), and in a group of healthy control subjects (N = 12). During OGTT we detected a reduction in plasma magnesium concentrations and an increase in erythrocyte and platelet magnesium levels in the controls, whereas in both normotensive and hypertensive obese subjects, there was a reduction in plasma, erythrocyte, and platelet magnesium levels. Furthermore, no statistically significant difference was detected among the groups studied as regards Δ-plasma magnesium. On the other hand, Δ-erythrocyte magnesium and Δ-platelet magnesium were negative in the NT-Ob (Δ-erythrocyte magnesium: −0.24 ± 0.08 mmol/L; Δ-platelet magnesium: −0.49 ± 0.09 μmol/10^8 cells) and HT-Ob (Δ-erythrocyte magnesium: −0.20 ± 0.10 mmol/L; Δ-platelet magnesium: −0.50 ± 0.11 μmol/10^8 cells) groups, and positive in control subjects (Δ-erythrocyte magnesium: 0.40 ± 0.08 μmol/L; Δ-platelet magnesium: 0.47 ± 0.09 mmol/10^8 cells). Finally, a direct correlation was found between Δ-norepinephrine and Δ-erythrocyte magnesium (r = 0.80, P < .01) in the control group, and a negative correlation was detected between Δ-norepinephrine and Δ-platelet magnesium (r = −0.58, P < .05) in the HT-Ob group. Our results seem to indicate that the insulin resistance status, the hyperglycemia, and the disregulation of the adrenergic system in obese subjects could be involved in the pathogenesis of the magnesium homeostasis impairment observed in the obese subjects. Am J Hypertens 1999;12:128–136 © 1999 American Journal of Hypertension, Ltd.

KEY WORDS: Platelet magnesium, oral glucose tolerance test, norepinephrine, obesity.
Although numerous epidemiologic and clinical studies have confirmed the frequent association between obesity and hypertension,\(^1\) the mechanisms underlying the onset of hypertension in obese subjects are not well understood. As well as the genetic aspect,\(^2\) other factors considered to be of pathogenic relevance are an increased renin-angiotensin-aldosterone system activity,\(^3\) the dis-regulation of the sympathetic nervous system,\(^4\) and, above all, hyperinsulinemia and insulin resistance, which are present in both obese\(^5\) and non-obese hypertensive subjects.\(^6\) In fact, insulin can stimulate the sympathetic nervous system, with an increase in catecholamine plasma concentrations,\(^7\) and can influence the renal sodium reabsorption, with an antinatriuretic effect,\(^8\) determining the so-called natriuretic handicap in obese subjects.\(^9\)

More recently, however, it has been claimed that an alteration in the ionic metabolism may be involved in the onset of hypertension in obese individuals. In fact, in these subjects, an alteration in calcium homeostasis has been found,\(^10\) as well as modifications in magnesium status, with a reduction in erythrocyte magnesium levels.\(^11\) Furthermore, Resnick and colleagues have formulated the so-called ionic hypothesis, which attempts to link the pathogenesis of apparently different diseases, such as hypertension, obesity, diabetes mellitus, left ventricular hypertrophy, and atherosclerosis. They suggested, in fact, that an impairment in ionic metabolism may lead to an increase of intracellular calcium and a reduction in intracellular magnesium, with a consequent alteration of sodium balance; this would be followed by hyperinsulinemia, insulin resistance, and renal and systemic vasoconstriction that are considered to be responsible in the onset of the diseases mentioned.\(^12\) On this subject, we elsewhere demonstrated a common reduction in plasma, erythrocyte, and platelet magnesium concentrations in hypertensive and normotensive diabetics.\(^13\) The aim of the present study was therefore to evaluate plasma, erythrocyte, and platelet magnesium concentrations during the oral glucose tolerance test (OGTT), and the relationships between insulinemia, plasma norepinephrine concentrations, and magnesium homeostasis.

**PLATELET Mg DURING OGTT IN THE OBESE**

**MATERIALS AND METHODS**

**Subjects** The study was conducted with three groups of subjects who gave informed consent. These groups consisted of 19 normotensive obese subjects (NT-Ob), 15 hypertensive obese subjects (HT-Ob), and 12 healthy controls (Table 1), and were strictly matched for age and gender. All obese subjects were recruited from the obese population attending our Outpatient’s Service for Prevention and Treatment of Obesity. Exclusion criteria included severe hypertension, cardiovascular disease, left ventricular hypertrophy, renal disease, and renal failure (serum creatinine > 1.4 mg/dL), diabetes mellitus, electrolyte imbalance, smoking habit, and alcoholism or psychiatric problems. Subjects who were receiving treatment with drugs known to modify magnesium metabolism or sympathetic nervous system activity were also excluded; in particular, none of them was in treatment with angiotensin-converting enzyme (ACE) inhibitors, \(\beta\)-blockers, or diuretics. Hypertensive status in the HT-Ob group had been recently diagnosed, and enrolled hypertensive obese subjects participated in the study before they started any antihypertensive therapy.

The subjects were defined as obese according to Garrow’s criteria (body mass index [BMI] > 30 kg/m\(^2\)).\(^14\) Subjects were considered lean when body mass index (BMI) values were \(<25\) kg/m\(^2\). Body height was measured without shoes to the nearest 0.5 cm; body weight was measured without clothes to the nearest 0.1 kg; body mass index was measured as weight/(height)\(^2\) (kg/m\(^2\)); waist circumference was measured midway between the lower rib margin and the iliac crest; hip circumference was determined as the widest circumference measured over the great trochanters. The waist-to-hip ratio (WHR) was then calculated.\(^15\)

Hypertension was defined as a supine reading >140/90 mm Hg on at least three separate measurements at 1-week intervals according to the indications of JNC-V.\(^16\)

**Measurements** In all subjects, after overnight fasting, an OGTT was performed. Venous blood samples were obtained in the supine position 30 min before and every 30 min for 3 h after ingestion of 75 g/200 mL oral glucose solution, from the cubital vein of the arm using a cannula that had been placed at ~30 min, and maintained by slow infusion of saline solution (10 gtt/min). Blood samples for the assay of glycemia (AutoAnalyzer, Beckman, Milan, Italy), insulinemia (IRI, RIA kit, Insulin Solid Phase, Diagnostic Products Corporation, Los Angeles, CA), and norepinephrine (HPLC, Diaman DM Bio-Rad, Segrate, Milan, Italy), were collected under EDTA (10% acid citrate-dextrose, ACD) and were centrifuged at 4°C within 1 h. Plasma was then transferred into capped polystyrene round-bottom tubes and frozen at ~70°C until the assay. Heparinized venous blood samples were collected at 0, 30, 60, 90, 120, 150, and 180 min for the evaluation of plasma, erythrocyte, and platelet magnesium levels (direct current plasma spectrometer SpectraSpan IV, Beckman, Milan, Italy).

Arterial blood pressure was measured with a Riva-Rocci sphygmomanometer (Zenith, Rome, Italy) with an appropriate large cuff in obese subjects. The first measurement was excluded and the average of the
following three measurements, taken at 3-min intervals, was considered. Mean blood pressure was calculated by the sum of diastolic blood pressure plus one-third of pulse pressure.

Preparation of Platelet Pellets and Magnesium Assay

Platelets were isolated as previously reported by Touyz and Milne.17 Polypropylene plasticware was used for platelet handling. Fifteen milliliters of heparinized venous blood, obtained by aspiration (through vacuum needle extraction), were collected in a conical polypropylene tube containing 20 mmol/L EDTA and citrate anticoagulant (75 mmol/L trisodium citrate, 42 mmol/L citric acid H2O). The citrate blood was gently inverted for 3 min. Essentially, platelet-rich plasma was obtained from the blood samples by centrifugation at 600 g for 10 min. The pellet was then suspended in 1 mL of buffer, was corrected according to the formula: erythrocyte magnesium levels were recorded magnesium mEq/L = recorded magnesium × 100/PCV.

With this method, there was no detectable magnesium in the final wash for both erythrocytes and platelets. The DC plasma emission spectrometer was set up as reported by Roberts et al,18 using an argon (high purity grade) flow of 2 L/min across the tungsten and carbon electrodes. The samples were nebulized with argon carrier gas at 7 L/min. The magnesium emission lines were chosen to maximize sensitivity and minimize spectral and matrix interference. Calibration, carried out between low and high standards of spectroscopy grade solutions (BDH Italia, Milan, Italy) in appropriate diluents, was linear throughout the range. The intra- and interassay variation for plasma magnesium method are 0.7% at 2.2 mmol/L and 1.8% at 2.2 mmol/L, respectively. The intra- and interassay variation for plasma magnesium method are 1.1% at 0.9 mmol/L and 0.9% at 0.89 mmol/L, respectively. The intra- and interassay variation for platelet magnesium method are 0.7% at 2.2 μmol/10⁸ cells and 0.9% at 2.5 μmol/10⁸ cells, respectively.17

### TABLE 1. GENERAL CHARACTERISTICS OF THE SUBJECTS STUDIED

<table>
<thead>
<tr>
<th></th>
<th>Controls (N = 12)</th>
<th>NT-Ob (N = 19)</th>
<th>HT-Ob (N = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>34.3 ± 1.4</td>
<td>39.2 ± 2.4</td>
<td>38.3 ± 1.3</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>8/4</td>
<td>13/6</td>
<td>8/7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.1 ± 0.73</td>
<td>36.0 ± 1.5*</td>
<td>38.8 ± 1.8*</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>74.6 ± 3.72</td>
<td>107.5 ± 3.5*</td>
<td>113.6 ± 4.0*</td>
</tr>
<tr>
<td>WHR</td>
<td>0.79 ± 0.02</td>
<td>0.89 ± 0.02</td>
<td>0.97 ± 0.02†</td>
</tr>
<tr>
<td>Total plasma cholesterol (mg/dL)</td>
<td>167.5 ± 5.4</td>
<td>195.0 ± 7.1†</td>
<td>197.6 ± 5.1†</td>
</tr>
<tr>
<td>HDL cholesterol (%)</td>
<td>47.5 ± 2.4</td>
<td>42.0 ± 2.7</td>
<td>40.3 ± 2.6</td>
</tr>
<tr>
<td>Plasma triglycerides (mg/dL)</td>
<td>54.7 ± 7.8</td>
<td>87.3 ± 5.6†</td>
<td>87.4 ± 6.0†</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>120.0 ± 1.2</td>
<td>123.9 ± 2.1</td>
<td>159.7 ± 4.8‡</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>77.5 ± 1.0</td>
<td>77.9 ± 2.0</td>
<td>94.7 ± 2.7‡</td>
</tr>
<tr>
<td>MBP (mm Hg)</td>
<td>91.7 ± 0.9</td>
<td>93.2 ± 1.8</td>
<td>116.3 ± 3.0‡</td>
</tr>
</tbody>
</table>

NT-Ob, normotensive obese subjects; HT-Ob, hypertensive obese subjects; BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure.

Data are means ± SE.

* P < .001, † P < .01 v controls; ‡ P < .01 v NT-Ob (ANOVA one-way test with Scheffé post-hoc test for multiple comparisons).
**RESULTS**

We found no statistically significant variations in the basal plasma, erythrocyte, and platelet magnesium concentrations of normotensive or hypertensive obese subjects with respect to those of controls, whereas insulin and norepinephrine plasma levels at time 0 were higher in both the NT-Ob and HT-Ob groups when compared with controls (Table 2).

The oral administration of glucose caused an increase in glycemia, insulinemia, and plasma norepinephrine concentrations in all the groups studied (Figure 1, Table 2). Moreover, the oral glucose tolerance test caused a reduction in plasma magnesium concentrations and an increase in erythrocyte and platelet magnesium levels in the control subjects. In normotensive and hypertensive obese subjects, on the other hand, a reduction was found in plasma, erythrocyte, and platelet magnesium concentrations (Figure 1, Table 2).

These results were also confirmed when Δs were considered. In fact, no statistically significant difference was detected among the groups studied as regards Δ-plasma magnesium. On the other hand, Δ-erythrocyte magnesium and Δ-platelet magnesium were negative in the NT-Ob (Δ-erythrocyte magnesium: −0.24 ± 0.08 mmol/L; Δ-platelet magnesium: −0.49 ± 0.09 μmol/10^8 cells) and HT-Ob (Δ-erythrocyte magnesium: −0.20 ± 0.10 mmol/L; Δ-platelet magnesium: −0.50 ± 0.11 μmol/10^8 cells) groups, and positive in control subjects (Δ-erythrocyte magnesium: 0.40 ± 0.08 mmol/L; Δ-platelet magnesium: 0.47 ± 0.09 μmol/10^8 cells) (Figure 2). Furthermore, a positive correlation between Δ-norepinephrine and Δ-erythrocyte magnesium was detected in control subjects (Figure 3), and a negative correlation was found between Δ-norepinephrine and Δ-platelet magnesium (Figure 4) in the HT-Ob group. No statistically significant correlation was found between Δ-norepinephrine and Δ-platelet magnesium (r = 0.19, P = ns) in controls, and between Δ-norepinephrine and Δ-erythrocyte magnesium (r = 0.22, P = ns) in the HT-Ob group. Finally, when we considered the whole group of obese subjects (N = 34), the negative relationship between Δ-norepinephrine and Δ-platelet magnesium was still present but not statistically significant (r = −0.29, P = ns).

**DISCUSSION**

Although no difference was found among the groups studied as regards the basal values of plasma, erythrocyte, and platelet magnesium, the dynamic responses to the OGTT were clearly different. In agreement with other authors, 19 we found a reduction in plasma magnesium concentrations and an increase in erythrocyte magnesium levels in healthy subjects during OGTT. This probably follows the hyperinsulinemia due to the administration of glucose, and this effect may have been mediated by the dose-correlated effect of insulin on the Na^+ /K^+ -ATPase, independently from glucose uptake. 20 The finding of increased platelet magnesium concentrations in the control group seems to be in accordance with the hypothesis that insulin can cause an intraplatelet magnesium increase probably by activating the platelet insulin receptors, 21 as has been demonstrated in vitro after blocking this action using monoclonal antibodies against the platelet insulin receptor.

In both the NT-Ob and HT-Ob groups, on the other hand, OGTT caused a reduction in plasma, erythrocyte, and platelet magnesium concentrations. A possible explanation for this finding is that insulin resistance, frequently occurring in obese subjects and increasing parallel with the body mass index, 22 can alter the ionophoretic action of insulin in platelets. 23 An impairment in the ionophoretic action of insulin has been observed in erythrocytes from hypertensive, obese, and diabetic patients 11 and, in red blood cells from hypertensive subjects, a suppression of insulin-induced magnesium influx has been demonstrated. 24 Moreover, insulin resistance can influence platelet aggregation, as demonstrated by the finding of a reduced insulin-induced antiaggregating activity in obese subjects. 25 However, together with insulin resistance, other factors could contribute to the altered magnesium compartmentalization during OGTT in obese subjects. Among these factors, there is the effect of catecholamines on magnesium flow through the cell membranes, as suggested by our finding of a negative correlation between Δ-norepinephrine and Δ-platelet magnesium in hypertensive obese subjects (Figure 4), where a rise in adrenergic activity has been found. In fact, plasma norepinephrine increased in all subjects after glucose administration. In particular, obese subjects showed higher plasma norepinephrine levels than control subjects. Moreover, in the HT-Ob group...
### Table 2. Data Values for Glucose, Insulin, and Norepinephrine Plasma Concentrations and Plasma, Erythrocyte, and Platelet Magnesium Levels During 75-G Oral Glucose Tolerance Test in the Groups Studied

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Baseline</th>
<th>30 Min</th>
<th>60 Min</th>
<th>90 Min</th>
<th>120 Min</th>
<th>150 Min</th>
<th>180 Min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose (mg/dL)</td>
<td>Controls</td>
<td>72.5 ± 2.9</td>
<td>122.4 ± 7.1*</td>
<td>109.8 ± 9.2**</td>
<td>100.5 ± 8.6**</td>
<td>83.8 ± 9.3</td>
<td>80.4 ± 10.8</td>
<td>74.0 ± 8.0</td>
</tr>
<tr>
<td></td>
<td>NT-Ob</td>
<td>82.8 ± 3.5</td>
<td>146.8 ± 6.7*</td>
<td>163.8 ± 11.6***</td>
<td>147.5 ± 12.3**</td>
<td>143.4 ± 11.3***</td>
<td>119.7 ± 8.6</td>
<td>110.4 ± 7.3**</td>
</tr>
<tr>
<td></td>
<td>HT-Ob</td>
<td>88.2 ± 3.0***</td>
<td>154.9 ± 8.0***</td>
<td>172.2 ± 12.2***</td>
<td>167.3 ± 16.0***</td>
<td>150.7 ± 14.9***</td>
<td>130.7 ± 14.7***</td>
<td>110.1 ± 13.8***</td>
</tr>
<tr>
<td>Plasma insulin (μU/mL)</td>
<td>Controls</td>
<td>7.8 ± 0.6</td>
<td>38.9 ± 3.6*</td>
<td>38.8 ± 4.5*</td>
<td>34.4 ± 3.4*</td>
<td>25.6 ± 2.9*</td>
<td>19.6 ± 3.3*</td>
<td>9.9 ± 1.6</td>
</tr>
<tr>
<td></td>
<td>NT-Ob</td>
<td>16.5 ± 1.2†</td>
<td>69.6 ± 6.3*</td>
<td>82.5 ± 9.9***</td>
<td>71.6 ± 7.8***</td>
<td>72.9 ± 10.0***</td>
<td>51.6 ± 8.2***</td>
<td>35.0 ± 6.8***</td>
</tr>
<tr>
<td></td>
<td>HT-Ob</td>
<td>18.7 ± 2.5†</td>
<td>60.3 ± 13.4**</td>
<td>82.4 ± 12.8***</td>
<td>80.9 ± 11.2**</td>
<td>69.4 ± 10.6**</td>
<td>54.3 ± 9.1***</td>
<td>39.6 ± 9.4******</td>
</tr>
<tr>
<td>Plasma norepinephrine (pg/mL)</td>
<td>Controls</td>
<td>87.6 ± 2.0</td>
<td>110.4 ± 2.6*</td>
<td>132.2 ± 6.2*</td>
<td>168.1 ± 7.5*</td>
<td>154.7 ± 5.6*</td>
<td>132.3 ± 9.9**</td>
<td>105.2 ± 4.8**</td>
</tr>
<tr>
<td></td>
<td>NT-Ob</td>
<td>214.3 ± 13.5†</td>
<td>258.1 ± 15.0†</td>
<td>270.3 ± 16.7**</td>
<td>278.1 ± 15.9**</td>
<td>263.8 ± 14.9**</td>
<td>245.6 ± 13.8**</td>
<td>222.6 ± 14.4†</td>
</tr>
<tr>
<td></td>
<td>HT-Ob</td>
<td>246.7 ± 12.7†</td>
<td>301.2 ± 14.4**</td>
<td>331.3 ± 11.9***</td>
<td>344.2 ± 14.6***</td>
<td>307.0 ± 11.7***</td>
<td>278.8 ± 14.2††</td>
<td>281.2 ± 14.4††</td>
</tr>
<tr>
<td>Plasma magnesium (mmol/L)</td>
<td>Controls</td>
<td>1.23 ± 0.06</td>
<td>1.18 ± 0.06***</td>
<td>1.15 ± 0.07</td>
<td>1.10 ± 0.05*</td>
<td>1.09 ± 0.07**</td>
<td>1.12 ± 0.09</td>
<td>1.18 ± 0.08</td>
</tr>
<tr>
<td></td>
<td>NT-Ob</td>
<td>1.24 ± 0.04</td>
<td>1.17 ± 0.05***</td>
<td>1.16 ± 0.04**</td>
<td>1.13 ± 0.05**</td>
<td>1.10 ± 0.05**</td>
<td>1.13 ± 0.05**</td>
<td>1.12 ± 0.05**</td>
</tr>
<tr>
<td></td>
<td>HT-Ob</td>
<td>1.30 ± 0.06</td>
<td>1.22 ± 0.07</td>
<td>1.19 ± 0.08</td>
<td>1.21 ± 0.08</td>
<td>1.12 ± 0.06**</td>
<td>1.15 ± 0.06***</td>
<td>1.11 ± 0.09***</td>
</tr>
<tr>
<td>Erythrocyte magnesium (mmol/L)</td>
<td>Controls</td>
<td>2.23 ± 0.11</td>
<td>2.43 ± 0.09***</td>
<td>2.48 ± 0.13**</td>
<td>2.40 ± 0.08**</td>
<td>2.35 ± 0.10</td>
<td>2.38 ± 0.13</td>
<td>2.38 ± 0.12</td>
</tr>
<tr>
<td></td>
<td>NT-Ob</td>
<td>2.41 ± 0.07</td>
<td>2.35 ± 0.07</td>
<td>2.30 ± 0.08**</td>
<td>2.22 ± 0.08**</td>
<td>2.28 ± 0.07**</td>
<td>2.33 ± 0.08</td>
<td>2.31 ± 0.09</td>
</tr>
<tr>
<td></td>
<td>HT-Ob</td>
<td>2.38 ± 0.13</td>
<td>2.33 ± 0.13</td>
<td>2.26 ± 0.13</td>
<td>2.18 ± 0.10**</td>
<td>2.27 ± 0.10</td>
<td>2.27 ± 0.09</td>
<td>2.26 ± 0.11</td>
</tr>
<tr>
<td>Platelet magnesium (μmol/10⁸ cells)</td>
<td>Controls</td>
<td>2.54 ± 0.11</td>
<td>2.60 ± 0.11</td>
<td>2.91 ± 0.13*</td>
<td>2.86 ± 0.17***</td>
<td>2.80 ± 0.17</td>
<td>2.67 ± 0.13</td>
<td>2.70 ± 0.14</td>
</tr>
<tr>
<td></td>
<td>NT-Ob</td>
<td>2.48 ± 0.11</td>
<td>2.40 ± 0.11***</td>
<td>2.29 ± 0.10**†</td>
<td>2.19 ± 0.11†</td>
<td>2.23 ± 0.11*††</td>
<td>2.27 ± 0.10*** †††</td>
<td>2.24 ± 0.09*** †††</td>
</tr>
<tr>
<td></td>
<td>HT-Ob</td>
<td>2.47 ± 0.11</td>
<td>2.33 ± 0.11</td>
<td>2.20 ± 0.09**†</td>
<td>2.20 ± 0.09**†</td>
<td>2.18 ± 0.10***</td>
<td>2.14 ± 0.09***</td>
<td>2.21 ± 0.09***</td>
</tr>
</tbody>
</table>

NT-Ob, normotensive obese subjects (N = 19); HT-Ob, hypertensive obese subjects (N = 15). Data are means ± SE.

* P < .001, ** P < .01, *** P < .05 v baseline (t test for paired data).
† P < .001, †† P < .01, ††† P < .05 v controls; ‡ P < .001 v Ni-Ob (ANOVA one-way test with Scheffé post-hoc test for multiple comparisons).
plasma norepinephrine concentrations were higher than in the NT-Ob group (Figure 1), in agreement with the findings reported by other authors.\textsuperscript{26,27} Furthermore, in the whole group of obese subjects the negative relationship between \( \Delta \)-norepinephrine and \( \Delta \)-platelet magnesium observed in the HT-Ob group was disrupted, thus suggesting that the presence of hypertension is necessary to elicit this correlation.

Hyperinsulinemia observed in obese patients, also confirmed by the increase in the \( \Delta \)-plasma insulin in both the NT-Ob and HT-Ob groups with respect to controls (Figure 2), may have contributed to the rise in plasma norepinephrine concentrations, given that hyperinsulinemia can activate the sympathetic nervous system, triggering an increase in catecholamine concentrations.\textsuperscript{28} Catecholaminergic stimulation could influence magnesium homeostasis during OGTT through indirect and direct mechanisms. It is in fact known that \( \beta \)-adrenergic stimulation can inhibit the entrance of magnesium into the cells.\textsuperscript{29} In platelets,
moreover, the activation of α-adrenoceptors by nor-
epinephrine can cause an increased entrance of cal-
cium ions, known to be associated with the loss of
intracellular magnesium.\textsuperscript{30} This may be of particular
importance in hypertensive obese subjects, whose
platelets show an increased sensitivity to cat-
echolamines.\textsuperscript{31} In hypertensive obese patients, the
greater adrenergic response with respect to controls
could increase insulin resistance, thus further compro-
mising the ionophoric action of insulin. In fact, a neg-

FIGURE 2. Changes from baseline to positive or negative peak (Δ) for glucose, insulin, and norepinephrine plasma concentrations, and plasma, erythrocyte, and platelet magnesium levels in the groups studied. NT-Ob, normotensive obese subjects; HT-Ob, hypertensive obese subjects. Data are means ± SE. *P < .05, **P < .01, ***P < .01 v controls (ANOVA one-way test with Scheffé post-hoc test for multiple comparisons).

FIGURE 3. Pearson’s correlation between Δ-erythrocyte magnesium and Δ-norepinephrine in control subjects (N = 12). Δ, changes from baseline to positive or negative peak.

FIGURE 4. Pearson’s correlation between Δ-platelet magnesium and Δ-norepinephrine in hypertensive obese subjects (HT-Ob, N = 15). Δ, changes from baseline to positive or negative peak.
ative correlation has been found between plasma catecholamines and sensitivity to insulin. On the other hand, the physiologic increase in catecholamines induced by OGTT triggers a further synthesis of insulin and therefore potentiates the insulin-induced entrance of magnesium. This could explain the finding of a positive correlation between Δ-norepinephrine and Δ-erythrocyte magnesium in healthy subjects (Figure 3). Interestingly, in obese subjects the reduced intracellular magnesium levels can also increase the insulin resistance, thus exacerbating ionic disregulation.

Finally, two other pathophysiologic explanations may be relevant to consider in the interpretation of our results. First, the rise in plasma norepinephrine could be secondary to the lower intracellular magnesium levels in hypertensive obese subjects, resulting in a negative correlation between Δ-norepinephrine and Δ-platelet magnesium. In fact, as it has been demonstrated that intracellular magnesium depletion reduces cellular responsiveness to insulin, it could be hypothesized that a reduction in intracellular magnesium concentrations could worsen the insulin sensitivity, thus leading to hyperinsulinemia and sympathetic system hyperactivity. Second, the opposite correlations between Δ-norepinephrine and Δ-intracellular magnesium observed in controls (positive) and in hypertensive obese subjects (negative) might also result from two different processes having opposite effects on intracellular magnesium concentrations, one predominant among normal subjects, the other among the obese. In controls, under normal insulin sensitivity conditions and with smaller rises in plasma glucose, the ionophoric action of insulin predominates and intracellular magnesium increases. As insulin also stimulates catecholamine secretion, the relation of Δ-erythrocyte magnesium and Δ-norepinephrine is positive (Figure 3). On the contrary, in hypertensive obese patients, in whom a greater excursion of plasma glucose and a lesser insulin action were observed, the negative effect of hyperglycemia on intracellular magnesium concentrations predominates. This decreased insulin action, as well as the effect of decreased intracellular magnesium itself to stimulate catecholamine secretion, would predict an inverse relation between Δ-platelet magnesium and Δ-norepinephrine, as was observed in the HT-Ob group (Figure 4).

In conclusion, our findings demonstrate the anomalous behavior of erythrocyte and platelet magnesium in normotensive and hypertensive obese subjects after OGTT with respect to healthy subjects. They further confirm the existence of a particular ionic status in normotensive and hypertensive obese subjects, as also regards the dynamic aspects of magnesium metabolism. Further studies should be undertaken in hypertensive nonobese subjects, as this could confirm the possible pathogenic link between the impairment of magnesium homeostasis and insulin resistance, hypertension, and obesity.

REFERENCES


