Variations in Magnesium and Zinc in Hypertensive Patients Receiving Different Treatments
M. Angustias Rubio-Luengo, Antonia Maldonado-Martín, Blas Gil-Extremera, Luis González-Gómez, and Juan de Dios Luna del Castillo

We studied the influence of captopril, atenolol, and verapamil on serum and intraerythrocyte concentrations of magnesium and zinc in 30 normotensive control subjects (12 men and 18 women, aged 30 to 65 years, mean ± SD 45.76 ± 12.15 years) and 30 patients with untreated mild or moderate essential hypertension (14 men and 16 women, aged 30 to 65 years, mean ± SD 49.50 ± 13.58 years). Ten each of the hypertensive patients were treated with captopril, atenolol, or verapamil. Physical examination and biochemical analyses (serum Mg and Zn) were done in all participants at baseline, and in patients after 3 and 6 months of treatment. The results were compared according to a nested design with Neumann-Keuls test. We found no significant differences between controls and patients in serum and intraerythrocyte concentrations of Zn at the start of the study, although there was a significant decrease in serum Zn in patients after 3 (P < .01) and 6 months (P < .001) of treatment, regardless of the drug used. This decrease was thought to be attributable to the zincuric effect of captopril or to dietary measures, or both. Intraerythrocyte Zn was not significantly affected by antihypertensive treatment. Serum and intraerythrocyte concentrations of Mg were significantly lower (P < .001) in hypertensive than in normotensive subjects, and serum Mg in patients treated with verapamil was significantly lower (P < .05) than after treatment with captopril or atenolol. Serum Mg concentration was related directly with serum concentrations of high density lipoprotein cholesterol (r = 0.4043, P < .05). We conclude that supplementation with Mg may benefit patients with hypertension. Am J Hypertens 1995;8:689–695

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In addition to hypercholesterolemia and smoking, hypertension, a chronic disease with many cardiovascular complications, is one of the major risk factors for cardiac ischemia, and is the main risk factor for cerebrovascular disease. These reasons justify the need to control hypertension with methods based on multiple approaches. Although some of the functions of magnesium (Mg) and zinc (Zn) have been known for some time, recent studies have shown that these elements are involved in the pathogenesis of certain cardiovascular...
diseases—particularly hypertension—and in lipid metabolism.\textsuperscript{2,5}

Magnesium, a divalent element found mainly in the inner surface of the cell membrane, is involved in membrane permeability to sodium and calcium. Supplementation with Mg salts for an appropriate period can reduce blood pressure.\textsuperscript{6} In connection with this finding, many studies have suggested a relation between Mg deficit and physiopathology of hypertension.\textsuperscript{7} Magnesium behaves as a physiologic calcium antagonist (CaA), although it is only one-third to one-fifth as potent as organic calcium channel blockers.\textsuperscript{8} Experimental Mg deficit results in damage to the arterial wall, which in turn is involved in the development of the lesions that characterize arteriosclerosis.\textsuperscript{9}

Zinc, a trace element with important functions in the human organism,\textsuperscript{10–12} is the only metal present in the molecular structure of angiotensin converting enzyme (ACE), which converts angiotensin I to angiotensin III.\textsuperscript{13} Serum Zn is correlated directly with plasma ACE activity.\textsuperscript{13–15} The role of Zn in the cardiovascular system has always been controversial. According to Saltman,\textsuperscript{9} Zn deficit causes hypoguesia, which leads to increased salt intake, and consequently, increased blood pressure and hypertension. Plasma Zn was reportedly lower in patients with hypertension than in healthy controls; this alteration was inversely correlated with blood pressure and plasma Zn concentration.\textsuperscript{16} In contrast, other studies have related increased serum Zn with hypertension.\textsuperscript{17–19}

Of the antihypertensive drugs currently in use (including diuretics, β-blockers, calcium antagonists [CaA], and ACE inhibitors), some can modify the patient's biochemical and lipid profile, and change serum and intraerythrocyte concentrations of Zn and Mg.\textsuperscript{20–24} Thiazide diuretics increase urinary excretion of Mg and reduce serum levels of this element.\textsuperscript{21,25,26} Few studies have investigated the effects of β-blockers, ACE inhibitors, or CaA on circulating levels of Mg and Zn.\textsuperscript{22,27,28}

The purpose of this study was to evaluate the influence of the antihypertensive drugs captopril, atenolol, and verapamil on blood pressure and serum and intraerythrocyte concentrations of Zn and Mg. We also searched for correlations between changes after 6 months in biochemical and lipid parameters, and in serum Mg and Zn levels.

MATERIAL AND METHODS

Subjects  We studied a total of 60 individuals in two groups. The control group comprised 30 normotensive persons (12 men, 18 women) aged 45.67 ± 12.15 years (mean ± SD), with a mean body mass index (BMI) of 25.86 ± 3.41 kg/m\textsuperscript{2}. The patient group consisted 30 subjects (14 men, 16 women) aged 49.5 ± 13.58 years, with a mean BMI of 28.86 ± 4.56 kg/m\textsuperscript{2}. All patients had essential hypertension and were not receiving treatment of any kind at the start of the study. Patients with hypertension were randomly assigned to receive monotherapy with one of the following: captopril 50 to 150 mg/day (2 men, 8 women; mean age, 54.9 ± 13.3 years; mean BMI, 30.24 ± 5.72 kg/m\textsuperscript{2}), atenolol 50 to 150 mg/day (4 men, 6 women; mean age, 45.4 ± 16.49 years; mean BMI, 28.53 ± 3.91 kg/m\textsuperscript{2}) or verapamil 240 mg/day (8 men, 2 women; mean age, 48.2 ± 9.6 years; mean BMI, 27.81 ± 3.95 kg/m\textsuperscript{2}). There were no significant differences in BMI between the treatment subgroups.

Inclusion And Exclusion Criteria  Members of the control group were healthy men and women aged 30 to 65 years, with a mean systolic blood pressure ≤140 mm Hg, and a mean diastolic blood pressure (DBP) ≤90 mm Hg. All laboratory values (blood count, biochemical tests, and circulating lipids) were within normal limits. We excluded from study those healthy subjects who had normal laboratory results, but had suffered any infectious process during the 3 months before the study or who habitually consumed toxic substances (alcohol or drugs). The patients were men and women aged 30 to 65 years, with slight (DBP, 95 to 104 mm Hg) or moderate essential hypertension (DBP, 105 to 114 mm Hg). A pharmacologic washout period of at least 20 days was allowed. Patients with any of the following were excluded from study: severe hypertension (DBP ≥115 mm Hg); malignant, complicated, refractory, or secondary hypertension; grade III or IV retinopathy according to the Keith-Wegener-Barker classification; known intolerance to β-blockers, CaA, or ACE inhibitors; pregnancy, lactation, or treatment with oral contraceptives; history of acute myocardial infarction or cerebrovascular disease, chronic alcoholism, drug addiction, or other status associated with inadequate compliance; treatment with carbamazepine, sodium bicarbonate, corticosteroids, insulin, oral antidiabetic agents, or medication to correct hypercholesterolemia or hypertriglyceridemia; renal insufficiency (serum creatinine >1.5 mg/dL), type I or type II diabetes mellitus; hyperkalemia (>5.0 mEq/L), or proteinuria (>150 mg/day).

Methods  All subjects were questioned about their past medical history and underwent a complete physical examination including body weight, height, and blood pressure recordings. After a 12-h fast, a blood sample was obtained for blood count, biochemical and lipid analyses including total cholesterol, high density (HDL-chol), low density, and very low density lipoprotein cholesterol, phospholipids, triglycerides, free fatty acids, apolipoproteins A-1 and B, serum and intraerythrocyte concentrations of Mg and Zn.
Patients were followed for 6 months; blood pressure and the results of biochemical analyses were recorded at the start of the study and after 3 and 6 months of antihypertensive treatment.

To determine Mg and Zn, 10 mL of whole blood was placed in an Mg-and Zn-free glass test tube with 2 drops of Zn-free heparin sodium, and another 10 mL of blood was placed in a test tube without anticoagulant to obtain serum. Samples in the first group were washed several times with physiologic saline solution (0.9% NaCl) to obtain cells; the plasma was discarded. Any serum sample that showed signs of hemolysis was discarded.

Serum and intraerythrocyte Mg and Zn were measured with a Perkin-Elmer (Norwalk, CT) 560 atomic absorption spectrophotometer equipped with a flame ionization detector and hollow cathode lamp, according to a previously developed technique.28-33

Biochemical and lipid analyses were done at the Biochemical Service of our hospital. The technique of Lopes et al34 was used to measure HDL-chol, and the formula of Friedewald et al35 to measure low density lipoprotein cholesterol as total cholesterol. Circulating concentrations of phospholipids were found with the technique of Takayama et al.36

Statistical Methods We used one-way analysis of variance (ANOVA) to compare the results for each of the different variables between controls and hypertensive patients. Significant differences were subjected to pair-wise comparison with Neumann-Keuls test. To compare the differences between groups, we used a nested design. The group factor (fixed effect) comprised three levels (captopril, atenolol, and verapamil). The individual factor (random effect) comprised 10 levels and was nested within the group factor. The time factor (fixed effect) comprised three levels (0, 3, and 6 months) and was crossed with the treatment factor. Significant results were further analyzed with Neumann-Keuls test using an appropriate estimator of variance. Finally, to explain as much of the variation as possible in the values at different times, we calculated Pearson’s correlation coefficient for the increases in values that yielded significant results in the nested design.

RESULTS

Table 1 summarizes mean blood pressures in healthy controls and patients with hypertension. As expected, blood pressure at the start of the study was significantly higher in patients (P < .01). In patients, blood pressure decreased after 3 and 6 months, with no significant differences between treatment subgroups (Table 2).

Mean concentrations of Mg and Zn in controls and patients are given in Table 3. Serum and intraerythrocyte Mg were significantly lower (both P < .01) in patients in comparison to controls. We found no significant differences between serum or intraerythrocyte levels of Zn between patients and normotensive controls.

As shown in Table 4, serum Zn was significantly lower after 3 (P < .01) and 6 months (P < .001) in all three treatment subgroups. In patients who took captopril, serum Mg increased after 3 months (P < .01), but decreased somewhat after 6 months (P < .05). In patients treated with verapamil, mean serum Mg decreased after 3 (P < .05) and 6 months (P < .01) with respect to basal levels. We found no significant differences between the treatment subgroups, or values after 3 and 6 months of treatment, in intraerythrocyte concentrations of Zn or Mg.

Variations in serum Zn and HDL-chol were inversely correlated (r = −0.4779, P < .05) (Figure 1). Serum Mg correlated directly with HDL-chol (r = 0.4043, P < .05) (Figure 2) and phospholipids (r = 0.4670, P < .05) (Figure 3).

DISCUSSION

The three antihypertensive drugs compared in this study were equally effective in controlling blood pressure. Serum and intraerythrocyte concentrations of Zn were similar in normotensive controls and hypertensive patients. Frithz and Ronquist37 found that plasma determinations yielded similar results in normotensives and hypertensives, although values in erythrocytes differed between the two groups. In their subjects, intraerythrocyte Zn was higher in patients with hypertension. In our subjects, serum Zn decreased in hypertension, with no significant differences between treatment subgroups. We know of no other studies of the effects of CaA on serum Zn levels, although there are reports of the effects on this trace element of ACE inhibitors and β-blockers.

O’Connor et al22 found no effect of serum Zn concentration in patients with essential hypertension after oral monotherapy with captopril or propanolol. Golik et al38 found that captopril and enalapril increased urinary Zn excretion, the former also depleting intraerythrocyte Zn. In the present study we also found
TABLE 2. EVOLUTION OF BLOOD PRESSURE IN PATIENTS TREATED WITH THREE DIFFERENT ANTIHYPERTENSIVE DRUGS

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>3 Months</th>
<th>6 Months</th>
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</thead>
<tbody>
<tr>
<td><strong>SBP (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>154.00 ± 17.13</td>
<td>150.50 ± 16.41*</td>
<td>149.50 ± 16.06*</td>
</tr>
<tr>
<td>Atenolol</td>
<td>161.00 ± 17.92</td>
<td>148.00 ± 10.59*</td>
<td>149.00 ± 12.20*</td>
</tr>
<tr>
<td>Verapamil</td>
<td>168.00 ± 30.48</td>
<td>140.00 ± 18.86*</td>
<td>147.00 ± 17.51*</td>
</tr>
<tr>
<td><strong>DBP (mm Hg)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Captopril</td>
<td>95.50 ± 4.38</td>
<td>92.50 ± 8.58*</td>
<td>91.50 ± 5.30*</td>
</tr>
<tr>
<td>Atenolol</td>
<td>94.00 ± 10.75</td>
<td>89.00 ± 7.75*</td>
<td>88.00 ± 6.75*</td>
</tr>
<tr>
<td>Verapamil</td>
<td>97.50 ± 15.14</td>
<td>82.50 ± 11.36*</td>
<td>86.50 ± 7.09*</td>
</tr>
</tbody>
</table>

*P < .001 v basal.

SBP, systolic blood pressure; DBP, diastolic blood pressure.

Intraerythrocyte Zn to be decreased by antihypertensive treatment, although the change was not significant. The possible increase in urinary Zn excretion by captopril may decrease indirectly ACE activity, as this metalloenzyme is Zn dependent. This suggests that oral supplementation with Zn sulfate in patients with hypertension may increase ACE activity, although some investigators have found the opposite to occur. After Zn administration to patients with hypertension, aldosterone and plasma renin activity decrease significantly, as did DBP. Although ACE is activated by Zn, hypertensive patients show evidence of saturation of the enzyme by its cofactor. The significant decrease in mean serum Zn in our patients after treatment with captopril for 3 and 6 months may reflect increased urinary excretion of this element. The decrease in zincemia in all three treatment subgroups may also be related with dietary measures designed to restrict the intake of foods rich in cholesterol, saturated fats, and uric acid.

Patients with hypertension, especially those treated with captopril, should ensure an adequate intake of dietary Zn to avoid the undesirable effects of hypozincemia (eg, dysgeusia, hyposmia, and eczema). An adequate intake of Zn would also increase the antihypertensive effectiveness of captopril by enhancing the blockade of ACE; in fact, this measure may also reduce the effective therapeutic dose of captopril. We know of no reports of the effects of CaA or β-blockers on zincuria; however, because β-blockers can act by inhibiting renin secretion dietary zinc supplementation in patients treated with these drugs may effectively potentiate the effects of β-blockers due to the saturation of ACE.

The concentrations of Mg were significantly lower in patients with hypertension than in controls. This finding is in agreement with those of Resnick et al and Altura et al. Magnesium ions play an important role in the regulation of Na and K transport across the cell membrane by activating the Na/K ATPase pump. By allowing the influx of excess Ca and the consequent decrease in the potency of vasodilators, a reduction in extracellular Mg may lead to hypertension, vasospasm, and potentiation of vasoconstrictors. Therefore, an increase in blood pressure may be inversely related with intracellular and plasma levels of Mg ions.

Serum and intraerythrocyte levels of Mg did not change significantly after treatment with atenolol. This finding is in consonance with results reported by Cocco et al. In patients with ischemic heart disease, alprenolol (a noncardioselective β-blocker) did not change serum Mg, which remained within normal limits.

Treatment for 3 months with captopril significantly raised serum Mg in our patients with respect to basal levels. After 6 months, serum Mg had decreased significantly in comparison with the 3-month level. Mean intraerythrocyte concentrations of Mg did not change significantly throughout the study period. These results for serum concentration appear to be fortuitous, as no previous studies found evidence that captopril altered plasma concentrations of Mg in patients with hypertension.

In patients who took verapamil, serum Mg decreased. On the other hand, intraerythrocyte Mg increased, although these changes were not significant. Our findings support the hypothesis of Singh that

TABLE 3. SERUM AND INTRAERYTHROCYTE CONCENTRATIONS OF ZINC AND MAGNESIUM IN NORMOTENSIVE CONTROLS AND HYPERTENSIVE PATIENTS

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 30)</th>
<th>Hypertensive Patients (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serum Zn (µg/dL)</strong></td>
<td>107.11 ± 20.88</td>
<td>113.17 ± 23.98</td>
</tr>
<tr>
<td><strong>Serum Mg (mg/dL)</strong></td>
<td>3.29 ± 0.22</td>
<td>2.54 ± 0.26*</td>
</tr>
<tr>
<td><strong>IE Zn (µg/dL)</strong></td>
<td>950.24 ± 127.11</td>
<td>956.31 ± 152.62</td>
</tr>
<tr>
<td><strong>IE Mg (mg/dL)</strong></td>
<td>4.51 ± 0.38</td>
<td>3.58 ± 0.50*</td>
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</table>

*P < .01 v controls.

IE, intraerythrocyte.
TABLE 4. EVOLUTION OF SERUM AND INTRAERYTHROCYTE CONCENTRATIONS OF ZINC AND MAGNESIUM IN PATIENTS TREATED WITH THREE DIFFERENT ANTIHYPERTENSIVE DRUGS

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>3 Months</th>
<th>6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Zn (µg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>116.63 ± 13.05</td>
<td>102.40 ± 29.75*</td>
<td>101.52 ± 20.58†</td>
</tr>
<tr>
<td>Atenolol</td>
<td>114.76 ± 19.67</td>
<td>102.66 ± 29.22*</td>
<td>102.09 ± 21.95†</td>
</tr>
<tr>
<td>Verapamil</td>
<td>108.12 ± 35.37</td>
<td>103.31 ± 26.74*</td>
<td>94.43 ± 24.84†</td>
</tr>
<tr>
<td>Serum Mg (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>2.35 ± 0.14</td>
<td>2.53 ± 0.23*</td>
<td>2.40 ± 0.20‡</td>
</tr>
<tr>
<td>Atenolol</td>
<td>2.62 ± 0.22</td>
<td>2.67 ± 0.28</td>
<td>2.54 ± 0.28</td>
</tr>
<tr>
<td>Verapamil</td>
<td>2.64 ± 0.29</td>
<td>2.52 ± 0.16§</td>
<td>2.46 ± 0.18*</td>
</tr>
<tr>
<td>IE Zn (µg/dL)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Captopril</td>
<td>984.65 ± 203.35</td>
<td>960.47 ± 180.28</td>
<td>925.63 ± 200.88</td>
</tr>
<tr>
<td>Atenolol</td>
<td>947.02 ± 100.90</td>
<td>983.26 ± 131.35</td>
<td>915.82 ± 112.24</td>
</tr>
<tr>
<td>Verapamil</td>
<td>937.25 ± 148.76</td>
<td>997.27 ± 119.79</td>
<td>990.32 ± 115.57</td>
</tr>
<tr>
<td>IE Mg (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>3.57 ± 0.59</td>
<td>3.32 ± 0.39</td>
<td>3.44 ± 0.45</td>
</tr>
<tr>
<td>Atenolol</td>
<td>3.72 ± 0.52</td>
<td>3.69 ± 0.59</td>
<td>3.63 ± 0.58</td>
</tr>
<tr>
<td>Verapamil</td>
<td>3.46 ± 0.37</td>
<td>3.51 ± 0.40</td>
<td>3.55 ± 0.31</td>
</tr>
</tbody>
</table>

*P < .01 v basal; †P < .001 v basal; ‡P < .05 v 3 months; §P < .05 v basal.

IE, intraerythrocyte.

verapamil stimulates Mg transport and thus, increases the influx of Mg ions into the cell.

The decrease in serum Zn in our patients correlated weakly but significantly with increased HDL-chol after 6 months of antihypertensive treatment, regardless of the drug taken. Crouse et al\textsuperscript{44} found that high doses of Zn sulfate (≥440 mg/day) decreased HDL-chol, whereas low doses (<50 mg/day) did not have this effect. Black et al\textsuperscript{45} reported that high doses of zinc decreased HDL-chol in healthy subjects, and noted that the decrease was detectable sooner (after 6 weeks of treatment) with the higher dose assayed (75 mg/day). The lower dose (50 mg/day) also decreased HDL-chol, but the fall became detectable much later, after 12 weeks of treatment. Calero et al\textsuperscript{40} reported decreases in DBP in patients who took oral Zn supplements (300 mg ZnSO\(_4\)/day); doses this low would probably not alter the lipid profile, although further studies should be done to clarify this point.

In our patients with hypertension, changes in serum Mg were correlated directly with changes in HDL-chol after 6 months of treatment. Therefore, lower serum levels of Mg were associated with lower levels of HDL-chol, and a correspondingly higher risk of arteriosclerosis. This finding corroborates the results of experimental studies: severe Mg deficiency in rats led to marked hypertriglyceridemia and decreased the percentage of HDL-chol\textsuperscript{49}; oral supplementation with Mg salts in rabbits fed a cholesterol-rich diet decreased serum levels of cholesterol and triglycerides, and markedly reduced the process of atherosclerosis.\textsuperscript{46} In patients with ischemic heart disease and acute myocardial infarction, oral supplementation with Mg led to a 13% increase in the apolipoprotein A-I/B ratio, a 27% decrease in triglycer-
ides and very low density lipoprotein cholesterol, and tended to increase serum HDL-chol. These findings support the hypothesis that Mg deficiency participates in the pathogenesis of ischemic heart disease by altering the composition of circulating lipids in a way that predisposes the patient to atherosclerosis. Therefore, dietary supplementation with Mg may be an effective nonpharmacologic treatment for essential hypertension.

In conclusion, serum and intraerythrocyte concentrations of Zn were similar in healthy adults and hypertensive patients. Zincemia decreased after 6 months of antihypertensive treatment, probably because captopril increases the urinary excretion of Zn, and also in part, caused by dietary measures that accompanied pharmacologic treatment. On the other hand, serum and intraerythrocyte levels of Mg were lower in hypertensive patients than in normotensive controls, and verapamil reduced serum Mg in the former. Changes in serum Mg were accompanied by parallel modifications in HDL-chol and phospholipids, whereas serum Zn was inversely correlated with HDL-chol. Our findings support the hypothesis that dietary supplementation with Mg may benefit patients with essential hypertension.

ACKNOWLEDGMENTS

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