Oral Magnesium Supplementation and Metabolic Syndrome: A Randomized Double-Blind Placebo-Controlled Clinical Trial

Martha Rodríguez-Morán, Luis E. Simental-Mendia, Claudia I. Gamboa-Gómez, and Fernando Guerrero-Romero

The objective of the study was to evaluate the efficacy of oral magnesium supplementation in the improvement of metabolic syndrome (MetS) and its components. This is a randomized double-blind, placebo-controlled clinical trial that enrolled 198 individuals with MetS and hypomagnesemia who were randomly allocated to receive either 30 mL of magnesium chloride 5% solution, equivalent to 382 mg of elemental magnesium (n = 100), or placebo solution (n = 98), daily for 16 weeks. Serum magnesium levels <1.8 mg/dL defined hypomagnesemia. At final conditions, a total of 48 (48%) and 76 (77.5%) individuals had MetS in the magnesium and placebo groups (P = 0.01), respectively. At baseline, percent of individuals with 3, 4, and 5 criteria of MetS in the magnesium group were 60.0%, 37.0%, and 3.0%, respectively, and in the control group 55.1%, 35.7%, and 9.2%, respectively. Between basal and final conditions, changes in the components of MetS were significantly higher in the magnesium than placebo groups: −3.6 ± 3.3 mmHg, P = 0.001 for systolic blood pressure; −5.5 ± 1.7 mmHg, P = 0.005 for diastolic blood pressure; −12.4 ± 3.6 mg/dL, P < 0.005 for fasting glucose; −61.2 ± 24 mg/dL, P = 0.003 for triglycerides; and 0.9 ± 0.4 mg/dL, P = 0.06 for high-density lipoprotein cholesterol. Magnesium supplementation improves MetS by reducing blood pressure, hyperglycemia, and hypertriglyceridemia.

INTRODUCTION

The metabolic syndrome (MetS), a cluster of cardiovascular risk factors that includes obesity, hyperglycemia, hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-c) levels, and high blood pressure (HBP), is related to the increased risk of developing cardiovascular disease. Given the worldwide rising of MetS, the strategies that focused on its prevention and management emerge as a public health priority.

Magnesium, the most abundant intracellular divalent cation, is involved in more than 300 enzymatic reactions including glycogen breakdown, adenosine triphosphate (ATP) synthesis, and activity of tyrosine kinase at insulin receptors, as well as in the metabolism of lecithin (ATP) synthesis, and activity of tyrosine kinase at insulin including glycogen breakdown, adenosine triphosphate (HDL-c) levels, and high blood pressure (HBP), is related to the increased risk of developing cardiovascular disease. Therefore, the objective of this study was to evaluate the efficacy of oral magnesium supplementation in the improvement of MetS and its components.

MATERIALS AND METHODS

With the approval of the protocol by the Mexican Social Security Institute Research Committee (R-2013-785-023), and after obtaining the subject’s informed consent, a randomized double-blind, placebo-controlled clinical trial was conducted.

Sampling strategy was based on a public call to apparently healthy Mexican men and nonpregnant women, aged 30 to 60 years, who were inhabitants of Durango, a city in northern Mexico. Newly diagnosed hypomagnesemia and MetS were the eligibility criteria to participate, criteria that were verified by detailed medical history and laboratory tests.

The exclusion criteria were alcohol intake equal or greater than 30 g/d for men and 20 g/d for women, smoking, chronic diarrhea, use of hypoglycemic and/or antihypertensive drugs, intake of magnesium supplementation in the previous 3 months, or impairment of renal function.

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Key Words: Magnesium, Metabolic syndrome, High blood pressure, Hyperglycemia, Hypertriglyceridemia
Using a list of computer-generated random numbers, eligible individuals were randomly allocated to receive either 30 mL of magnesium chloride (MgCl₂) solution (50 g of MgCl₂ by 1,000 mL of solution—5% solution), equivalent to 382 mg of elemental magnesium, or placebo solution daily for 16 weeks. Patients and personnel were blinded to group assignment for randomization and allocation using identical and sealed containers. Adherence to supplementation was performed by monthly quantification of the remnant magnesium and placebo solutions each month.

Participants in both groups received 1-hour sessions per month for diet and exercise advice, which was provided by trained personnel. Total caloric intake was calculated based on 30 kcal per kg per day of ideal body weight. The recommendations for exercise were walking, dancing, cycling, or swimming half an hour per day, at least 5 days per week. Diaries of both diet and exercise were completed by participants and reviewed at each visit for assessing adherence to diet and exercise.

Definitions
According to the definition by the National Cholesterol Education Program-Adult Treatment Panel III, MetS was defined by the presence of 3 or more of the following components: waist circumference ≥90 cm in men and ≥80 cm in women; SBP ≥130 mmHg and/or DBP ≥85 mmHg; fasting plasma glucose (FPG) ≥100 mg/dL; serum triglycerides ≥150 mg/dL; and HDL-c <40 mg/dL in men and <50 mg/dL in women. Serum magnesium levels <1.8 mg/dL defined the presence of hypomagnesemia.

Measurements
Weight and height were measured with the subjects in light clothing and without shoes, using a fixed scale with stadiometer (Tanita TBF-2015, Tokyo, Japan). The increments of weight and height measurements were 0.1 kg and 1 cm. The waist circumference was measured around the abdomen horizontally at the midpoint of the costal margin and the iliac crest on the midaxillary line. The body mass index was calculated as weight (kg) divided by height (m) squared.

The technique of using a baumanometer (Microlife AG, Heerbrugg, Switzerland) and stethoscope (3M Littmann Classic II, Neuss, Germany) with the appropriate sized cuff, which was placed on the left arm (right arm for left-handed individuals) for the measurement of BP was recommended by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. The BP was recommended by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. The BP was the average of 3 readings separated by 2 minutes. The standardization of techniques and personnel training was performed before the start of the study to reduce the interobserver variation to less than 0.05.

Assays
After 8- to 10-hour overnight fasting, whole-blood samples were obtained from the antecubital vein. Serum magnesium levels were measured using the Xylidyl Blue method (Biosystems S.A., Barcelona, Spain); its intra-assay and interassay coefficients of variation (CVs) were 5.1 and 5.5, respectively. Serum glucose was measured using the glucose oxidase method; its intra-assay and interassay CVs were 1.3% and 1.7%, respectively. Triglyceride levels were enzymatically measured by spectrophotometric methods, and the HDL-c fraction was obtained after precipitation by the phosphotungstic reagent. The intra-assay and interassay CVs were 1.6% and 3.0% for triglycerides and 1.4% and 2.7% for HDL-c, respectively. All measurements were performed in an automated spectrophotometer A15 (Biosystems S.A., Barcelona, Spain).

Sample Size
Taking into account the alpha and beta values of 0.05 and 0.20, and a difference of 0.15 in the increase of HDL between the groups receiving oral magnesium supplementation and placebo, the estimated sample size was 95 individuals per group.

Statistical Analysis
Analysis was performed on patients who satisfactorily completed the follow-up. The improvement of MetS and its components was performed in all randomly allocated participants.

Differences between the groups were assessed using the unpaired Student t test or Mann-Whitney U test (for quantitative variables) and the chi-square test or Fisher’s exact test (for qualitative variables). Spearman correlation was used to evaluate the correlation between serum magnesium levels and number of MetS criteria.

All data were processed and analyzed using the statistical package SPSS for Windows, version 15.0 (SPSS, Chicago, IL); P-value < 0.05 defined the level of statistical significance.

RESULTS
A total of 320 individuals were screened; of them, 108 (33.7%) did not fulfill the inclusion criteria or exhibited exclusion criteria; finally, 212 (66.3%) individuals were enrolled and randomly allocated into the groups to receive either MgCl₂ (n = 109) solution or placebo (n = 103), Figure 1.

There were 14 who dropped out; of them, 8 patients with adverse events (mild abdominal pain or mild diarrhea),
5 lost to follow-up, and 1 withdrawn consent; thus, 100 subjects in the MgCl₂ group and 98 in the placebo group, successfully completed the 4-month follow-up, Figure 1.

Adherence to treatment, equal to or greater than 90%, was achieved in 95 (87.2%) and 96 (93.2%) subjects in the MgCl₂ and placebo groups, respectively.

There were no significant differences in sex (34 vs 35 women and 66 vs 65 men, \( P = 0.087 \)) or age (39.4 ± 9.8 and 40.4 ± 10.6 years, \( P = 0.50 \)) between the individuals in the MgCl₂ and placebo groups, respectively.

Table 1 shows the anthropometric and biochemical characteristics of participants; at basal conditions, there were no significant differences between the groups. At

### Table 1. Anthropometric and Biochemical Characteristics of Participants in the Study

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>Final</th>
<th>Change</th>
<th>Basal*</th>
<th>Final</th>
<th>Change</th>
<th>Difference in Change</th>
<th>( P ) Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>100</td>
<td>100</td>
<td></td>
<td>98</td>
<td>98</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.7 ± 6.5</td>
<td>28.8 ± 6.1</td>
<td>−0.8 ± 0.5</td>
<td>30.5 ± 5.9</td>
<td>30.0 ± 5.5</td>
<td>−0.4 ± 1.4</td>
<td>−0.4 ± 0.8</td>
<td>0.36</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>100.8 ± 13.3</td>
<td>99.3 ± 14.4</td>
<td>−1.4 ± 1.0</td>
<td>101.1 ± 13.8</td>
<td>100.8 ± 12.2</td>
<td>−0.8 ± 0.6</td>
<td>−0.7 ± 1.1</td>
<td>0.43</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>119.4 ± 17.2</td>
<td>115.5 ± 17.4</td>
<td>−2.1 ± 2.3</td>
<td>117.9 ± 16.0</td>
<td>119.7 ± 17.0</td>
<td>1.7 ± 2.1</td>
<td>−3.6 ± 3.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>75.1 ± 10.9</td>
<td>72.7 ± 10.2</td>
<td>−2.6 ± 1.1</td>
<td>73.1 ± 9.6</td>
<td>76.5 ± 10.0</td>
<td>3.4 ± 1.1</td>
<td>−5.5 ± 1.7</td>
<td>0.005</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>111.3 ± 15.1</td>
<td>96.7 ± 20.2</td>
<td>−14.5 ± 2.5†</td>
<td>106.4 ± 15.6*</td>
<td>108.8 ± 19.9</td>
<td>2.3 ± 2.0</td>
<td>−12.4 ± 3.6</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>253.5 ± 187.1</td>
<td>186.6 ± 128.0</td>
<td>−66.9 ± 15.8</td>
<td>214.3 ± 108.3</td>
<td>220.1 ± 106.4</td>
<td>5.8 ± 12.0</td>
<td>−61.2 ± 24.0</td>
<td>0.003</td>
</tr>
<tr>
<td>HDL-c, mg/dL</td>
<td>36.9 ± 13.5</td>
<td>38.5 ± 10.1</td>
<td>1.6 ± 1.4</td>
<td>36.7 ± 13.0</td>
<td>35.9 ± 9.9</td>
<td>−0.8 ± 1.5</td>
<td>0.9 ± 0.4</td>
<td>0.06</td>
</tr>
<tr>
<td>Serum magnesium, mg/dL</td>
<td>1.5 ± 0.3</td>
<td>1.9 ± 0.2</td>
<td>0.5 ± 0.03</td>
<td>1.5 ± 0.3</td>
<td>1.6 ± 0.4</td>
<td>0.1 ± 0.04</td>
<td>0.3 ± 0.05</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± standard deviation.

Abbreviations: HDL-c, high-density lipoprotein cholesterol.

*There were no statistically significant differences between the magnesium and placebo groups at baseline.

†\( P \) value of difference between groups.

‡\( P \) value < 0.05 between baseline and final condition within group.

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**Figure 1.** Flow diagram of the individuals in the study.
the final follow-up, individuals who received MgCl₂ showed a significant reduction in the SBP, DBP, FPG, and triglyceride levels and a significant increase in the serum magnesium levels.

Individuals in the magnesium group, as compared with the control group, had significantly reduced SBP, DBP, FPG, and triglyceride levels and increased serum magnesium levels.

At baseline, a total of 161 (81.3%), 53 (26.8%), 175 (88.4%), 148 (74.7%), and 153 (77.3%) individuals exhibited central obesity, HBP, hyperglycemia, hypertriglyceridemia, and low HDL-c, respectively, without significant differences between the groups, Table 2. At the final follow-up, the number of individuals with HBP, hyperglycemia, and hypertriglyceridemia was significantly lower in the magnesium group compared with the control group, Table 2.

Serum magnesium levels, in the overall population, showed a normal distribution and a significant inverse correlation with the number of MetS criteria ($r = 0.471$, $P < 0.0001$).

In the overall population, at basal conditions, a total of 114 (57.6%), 72 (36.4%), and 12 (6.1%) individuals exhibited 3, 4, and 5 criteria of MetS, respectively. At the final follow-up, the total number of individuals with 0, 1, 2, 3, 4, and 5 criteria of MetS was 2 (1.0%), 20 (10.1%), 52 (26.3%), 73 (36.9%), 44 (22.2%), and 7 (3.5%), respectively; hence, 74 (37.4%) individuals were free of MetS (Table 3).

The reduction in the components of MetS was significantly higher in the individuals in the magnesium group than in the control group (Table 3).

**DISCUSSION**

Results of this randomized double-blind placebo-controlled clinical trial show that oral magnesium supplementation improves incident MetS with a significant reduction in the SBP, DBP, FPG, and triglyceride levels and increased serum magnesium levels.

Regarding the effect of magnesium supplementation on lipid profile, our findings showed a significant decrease in triglyceride levels in the individuals who received magnesium supplements; the results are inconsistent with the study by Cosaro and colleagues, who showed no beneficial effect of magnesium supplements on the lipid profile of healthy young men with a family history of MetS. This inconsistency maybe is related to the normal basal serum triglyceride ($79 \pm 45$ vs $82 \pm 40$ mg/dL) and magnesium levels ($1.97 \pm 0.12$ vs $2.0 \pm 0.06$ mg/dL) in both the magnesium and placebo groups in the study by Cosaro and colleagues.

Furthermore, a recent meta-analysis showed a significant reduction in triglyceride levels after magnesium treatment, in a subgroup of studies that included individuals with hypertriglyceridemia, suggesting a possible beneficial effect of magnesium supplementation on dyslipidemic disorders.

Recently, Lima de Souza and colleagues conducted a 12-week randomized double-blind study to evaluate the effect of magnesium replacement, using magnesium chelate, on insulin resistance and cardiovascular risk factors in women with MetS; the mean serum magnesium levels at baseline were $1.82 \pm 0.14$ mg/dL and $1.87 \pm 0.18$ mg/dL in the magnesium and placebo groups, with hypomagnesemia identified in 23.2% of women. At the end of study, a significant reduction of SBP and a tendency to decrease FPG was reported only in the women of the magnesium group. Basal magnesium status, duration of intervention, and bioavailability of the magnesium salts used, may explain the differences between the study.

**Table 2. Components of Metabolic Syndrome According to the Study Groups**

<table>
<thead>
<tr>
<th>Component</th>
<th>Magnesium Basal</th>
<th>Magnesium Final</th>
<th>Placebo Basal</th>
<th>Placebo Final</th>
<th>$P$ value $\dagger$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N$</td>
<td>100</td>
<td>100</td>
<td>98</td>
<td>98</td>
<td>0.12</td>
</tr>
<tr>
<td>Obesity</td>
<td>82 (82.0)</td>
<td>67 (67.0)</td>
<td>79 (80.6)</td>
<td>63 (64.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>27 (27.0)</td>
<td>23 (21.0)</td>
<td>26 (26.5)</td>
<td>25 (25.5)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>88 (88.0)</td>
<td>26 (26.0)</td>
<td>87 (88.8)</td>
<td>72 (73.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>70 (70.0)</td>
<td>57 (57.0)</td>
<td>78 (79.6)</td>
<td>73 (74.5)</td>
<td>0.09</td>
</tr>
<tr>
<td>Low HDL-c</td>
<td>83 (83.0)</td>
<td>78 (78.0)</td>
<td>70 (70.0)</td>
<td>70 (71.4)</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as $n$ (%).

Abbreviations: HDL-c, high-density lipoprotein cholesterol.

$\dagger$ There were no statistically significant differences between the magnesium and placebo groups at baseline.

$\ddagger$ Values between the groups at final conditions.

$P$ value $< 0.05$ between baseline and final condition within group.
Values are expressed as ‡. Values are expressed as †.

**Table 3. Criteria of Metabolic Syndrome According to the Study Groups**

<table>
<thead>
<tr>
<th>MetS Criteria</th>
<th>Magnesium</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>Final</td>
<td>Basal$^*$</td>
</tr>
<tr>
<td>0</td>
<td>—</td>
<td>2 (2.0)</td>
<td>—</td>
</tr>
<tr>
<td>1</td>
<td>—</td>
<td>18 (18.0)$^‡$</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>—</td>
<td>32 (32.0)$^‡$</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>60 (60.0)</td>
<td>30 (30.0)$^‡$</td>
<td>54 (55.1)</td>
</tr>
<tr>
<td>4</td>
<td>37 (37.0)</td>
<td>16 (16.0)$^‡$</td>
<td>35 (35.7)</td>
</tr>
<tr>
<td>5</td>
<td>3 (3.0)</td>
<td>2 (2.0)</td>
<td>9 (9.2)</td>
</tr>
<tr>
<td>MetS</td>
<td>100 (100)</td>
<td>48 (48.0)$^‡$</td>
<td>98 (100)</td>
</tr>
</tbody>
</table>

Values are expressed as n (%). Abbreviations: MetS, metabolic syndrome.

‡ P value < 0.05 between baseline and final condition within group.

by Lima de Souza and colleagues and our results. In this regard, it is important to note that although organic salts have a slightly higher bioavailability than inorganic salts, MgCl2 is among magnesium salts with the highest intestinal absorption and efficacy for restoring magnesium concentrations in plasma and blood cells.23

Furthermore, previous studies have observed a significant inverse association between dietary magnesium intake and the prevalence of MetS and its components;24,25 a finding that supports the statement that increasing dietary magnesium to meet the Recommended Dietary Allowance may have a protective effect.25 Although we did not measure dietary magnesium intake, our finding is in agreement with the results from dietary intervention studies.

Finally, our study adds to the field that oral magnesium supplementation significantly reduces the HBP, hyperglycemia, and hypertriglyceridemia, which are related to a reduction of 30% in the total cases of MetS as compared with the control group.

Taking into account the causal mechanisms linking alteration of magnesium homeostasis with components of MetS, our finding can be satisfactorily explained. In this regard, it is necessary to emphasize, on one hand, that life styles associated with obesity usually include low dietary magnesium intake, which might explain the hypomagnesemia related to obesity; hence, it is not expected that restoring magnesium stores, using oral magnesium salts, can produce changes in obesity. On the other hand, magnesium participates in the ATP synthesis and activity of tyrosine kinase at insulin receptors, the metabolism of lecithin cholesterol acyl transferase, HMG-CoA reductase, and lipoprotein lipase, in the inhibition of calcium flux, attenuation of Na-K ATPase, and endothelium-dependent vasodilation,8,10,14 which are involved in the metabolism of glucose, lipids, and BP. Hence, by correcting magnesium deficiency, it is plausible to expect an improvement in hyperglycemia, HBP, and dyslipidemia, components of MetS.

Thus, given that pharmacologic prevention and management of the MetS is difficult to attain, owing to numerous pharmacologic agents that must be used to control the cluster of cardiovascular disease risk factors, oral magnesium supplementation might eventually be implemented as an adjuvant therapy in the strategies focused at preventing and treatment of the MetS, particularly in those individuals with hypomagnesemia. In this regard, it is necessary to take into account that usually after 4 months of oral magnesium supplementation, the serum magnesium levels, and maybe the intracellular magnesium stores, restore to normal levels,26 hence, at fixed intervals, (e.g., twice a year) laboratory surveillance to verify the presence of normomagnesemia, rather than using oral magnesium salts during longer periods, should be suggested.

To the best of our knowledge, this is the first study to show the efficacy of oral magnesium supplementation in the improvement of MetS; previous reports has been focused on the efficacy of oral magnesium salts on the improvement of components of MetS as unconnected entities;14 studies with small sizes, short duration, and even focused on individuals with normomagnesemia, which might compromise their conclusions. Therefore, further studies are needed in the field.

Several limitations of our study deserve to be mentioned. First, we did not measure the intracellular Mg2+; however, given that all enrolled individuals exhibited hypomagnesemia and were randomly allocated into the study groups, the possibility of selection bias regarding this limitation is minimized because it is expected that individuals were similarly distributed in both groups. Second, we did not assess customary diet or physical activity in the target population; nevertheless, because all individuals received standard counseling about diet and exercise, this potential source of bias is reduced. Third, given that insulin levels were not determined, we could not estimate insulin sensitivity; however, taking into account the definition of MetS that we used, this limitation does not influence our conclusions.

In conclusion, our results show that oral magnesium supplementation significantly improves the MetS by reducing HBP, hyperglycemia, and hypertriglyceridemia.

**REFERENCES**

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