Oral magnesium supplementation decreases alanine aminotransferase levels in obese women

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Abstract. To evaluate the effect of oral supplementation with magnesium chloride on the systemic and hepatic inflammation, 38 non-hypertensive obese women aged 30 to 65 years were allocated into groups with and without hypomagnesemia. Hypomagnesemic women drank 50 mL of 5% solution of MgCl2 equivalent to 450 mg of elemental magnesium. Low-carbohydrate diets and physical activity were indicated for women in both groups. Chronic diarrhea, alcohol intake, use of diuretics, previous oral magnesium supplementation, hepatic disease, and renal damage were exclusion criteria. Hypomagnesemia is defined by serum magnesium concentrations ≤ 1.8 mg/dL, hepatic inflammation by serum alanine aminotransferase (ALT) levels ≥ 40 U/L, and systemic inflammation by serum high-sensitivity C reactive protein (hs-CRP) concentration ≥ 3 mg/L. At baseline (p = 0.06) and final of follow-up (p = 0.80), there were no significant differences by body mass index between the groups in the study. In the same way, at baseline ALT (48.1 ± 25.5 and 34.6 ± 24.1 U/L, p = 0.14) and hs-CRP (9.4 ± 6.0 and 7.9 ± 5.9 mg/dL, p = 0.47) levels were similar in the supplemented and non-supplemented women. In the magnesium group, ALT (24.3 ± 10.3 and 34.8 ± 13.6 U/L, p = 0.02) levels, but not hs-CRP (5.2 ± 1.9 and 8.0 ± 5.6 mg/L, p = 0.08) reached significantly lower levels, in the fourth month of treatment, than in women in the control group. The adjusted odds ratios between the improvement in serum magnesium and reduction in ALT and hs-CRP levels were 0.56 (95% CI: 0.3-0.9) and 0.93 (95% CI: 0.6-29.9), respectively. Results of this study show that in hypomagnesemic obese women, oral supplementation with magnesium chloride reduces plasma ALT levels; hs-CRP levels only show a reduction trend.

Key words: systemic inflammation, hepatic inflammation, hs-CRP, ALT, magnesium, magnesium chloride

Obesity is a worldwide public health problem characterized by chronic systemic low-grade inflammation and fatty infiltration of liver [1]; thus, obese subjects frequently exhibited metabolic disturbances and elevated inflammatory markers, such as the C reactive protein (CRP) and alanine aminotransferase (ALT); markers associated with an increase of cardiovascular disease and liver damage [2, 3].

Magnesium deficiency is related to the triggering of inflammatory response, mitochondrial dysfunction, profibrogenic response [4], decrease of the antioxidant system activity [5], and stimulation of aldosterone [6], which stimulate lipid peroxidation and cytokine induction, well-known pathways for the development of steatohepatitis and hepatic fibrosis [7, 8].
Given that both obesity and magnesium deficiency are related with systemic and hepatic inflammation, and that magnesium supplementation attenuates blood levels of CRP in heart failure patients [9], in this study we evaluated the effect of oral supplementation with magnesium chloride on systemic and hepatic inflammation of obese women.

**Materials and methods**

With protocol approval from the Mexican Social Security Institute Research Committee and after obtaining subject informed consent, a clinical trial was carried out from July 2009 to January 2010.

Participants were recruited from the general population of Durango, a city in northern Mexico. Non-hypertensive obese women aged 30 to 65 years were candidates for inclusion in the study. Chronic diarrhea, alcohol intake (equal to or more than 30 g/day), use of diuretics, previous oral magnesium supplementation, hepatic disease, or renal damage were exclusion criteria. All women were clinically evaluated and laboratory tested to verify the absence of exclusion criteria.

The primary trial endpoint was a reduction in ALT and high-sensitivity C reactive protein (hs-CRP) concentrations to levels lower than 40 U/L and 3 mg/dL, respectively.

Sample size estimation was based on a statistical power of 80% with a 0.05 alpha value and expected ALT level decreases of 75% and 25% for the women receiving magnesium supplementation and in the control group, respectively. The required sample size to detect a treatment effect was 15 subjects per group.

Given that MgCl₂ solution shows good bioavailability [10], MgCl₂ solution [50 g of MgCl₂ by 1,000 mL of solution (5% solution)] was the magnesium supplement used. Under fasting conditions, women in the magnesium group drank 50 mL of 5% solution of MgCl₂ to receive 2.5 g of MgCl₂ daily, equivalent to 450 mg of elemental magnesium, that corresponds to approximately 7% in excess (to compensate the hypomagnesemia) of the recommended dietary allowance for women (420 mg) [11, 12].

Based on serum magnesium levels, women were allocated into the intervention group, who received oral magnesium supplementation (hypomagnesemic women) or into the control group (normomagnesemic women). They remained in the same allocation through the period of intervention.

According to the age and physical condition of each participant, all the women were advised to perform mild to moderate physical activity with a goal of 30 minutes of physical activity at least three times per week. In the same way, all the women underwent diet advice to follow a low-carbohydrate diet based on the following percentage of total caloric intake per nutrient: 27% protein, 28% fat, and 45% carbohydrate [13]. The total caloric intake was calculated based on 30 kcal/kg per day of ideal body weight.

At baseline and after 4 months of follow-up, anthropometric measurements, fasting plasma glucose, lipid profile, ALT, hs-CRP, and magnesium levels were measured.

Adherence to magnesium supplementation and lifestyle intervention were assessed every month by personal interview and measurement of remaining solution.

**Definitions**

Based on previous results from healthy subjects of our population [8] low serum magnesium levels were defined by magnesium concentrations ≤ 1.8 mg/dL.

Elevated ALT levels were defined by serum ALT levels equal to or higher than 40 U/L [14].

A serum hs-CRP concentration equal to or higher than 3 mg/L defined the elevated hs-CRP levels [15].

**Measurements**

Height and weight were taken using standard protocols with the subjects in light clothing and without shoes. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. Waist circumference was measured to the nearest centimeter with a flexible steel tape while the subjects were in standing position. The anatomical landmarks used to determine tape placement were midway between the lowest portion of the rib cage and the superior border of the iliac crest (laterally). Overall adiposity was measured by impedance using a body composition analyzer (Tanita TBF-215, Tokyo, Japan) with 0.1% increments.

**Assays**

Serum magnesium concentrations were measured by colorimetric method; the intra- and inter-assay variations were 1.0% and 2.5%, respectively. ALT levels were determined by UV kinetic methods.
(Erlic, Tlalnepantla, Estado de Mexico, Mexico); the intra- and inter-assay variations were 1.5% and 2.0%, respectively. Hs-CRP was determined by automated microparticle enzyme immunoassay (IMx, Abbot Laboratories, USA). The detection limit of CRP was 0.05 mg/dl, with an intra- inter-assay coefficient of variation of 4.1% and 5.8%, respectively.

Serum glucose was measured by the glucose-oxidase method; the intra- and inter-assay variations were 2.5% and 4.0%, respectively. Triglycerides were measured enzymatically; the intra- and inter-assay coefficients of variation were 1.7% and 3.1%.

**Statistical analysis**

The preplanned intention-to-treat analysis of the primary study endpoint was performed on all women who satisfactorily completed the follow-up (**figure 1**). For comparison of normally distributed variables, we used a two-tailed, unpaired, Student t test (or Mann-Whitney U test for skewed data). The Chi-squared test with continuity correction (or Fisher's exact test) was used for testing differences between categorical variables.

The relationship between variations of serum magnesium levels (independent variable) and ALT and hs-CRP levels (dependent variables) was established by calculating the odds ratio (OR) using multivariate logistic regression analysis. Decrease of ALT and hs-CRP levels to values lower than 40 U/L and 3 mg/dL, respectively, was the expected outcome. The model was adjusted by BMI, and WC.

A 95% confidence interval (CI95%) was considered, and p-value < 0.05 defined the level of statistical significance. Data analysis was performed using the SPSS for windows version 15.0 (SPSS Inc., Chicago, IL).

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**Figure 1.** Flow diagram of enrollment, follow-up, and analysis.

160 patients screened

No randomized, did not fulfilled inclusion criteria = 122
No randomized, refused participate = 0

38 randomized

Magnesium group = 20

Control group = 18

Not included in intent to treat
Lost of follow-up = 3
Withdrew consent = 2
Adverse effects = 1
Treatment failure = 0

Completed 4-months included in the analysis = 15

Not included in intent to treat
Lost of follow-up = 3
Withdrew consent = 0
Adverse effects = 0
Treatment failure = 0

Completed 4-months included in the analysis = 15
Results

A total of 160 obese women with average age of 48.0 ± 9.8 years were screened between July and September 2009; of these, 122 women did not satisfactorily fulfill the inclusion criteria. Twenty women with hypomagnesemia received MgCl₂ solution and were compared with 18 normomagnesemic women in the control group. Six women (3.6%) were lost follow-up (three in each group). One woman in the magnesium group showed vomiting that required suspension of the magnesium solution; two women in the magnesium group withdrew consent because they got jobs and were unable to attend programmed visits of the protocol, Figure 1. There were no protocol deviations. A total of 15 women in the magnesium and 15 in the placebo group, who satisfactorily completed the follow-up, were included in the analysis of data.

Women in both groups achieved appropriate adherence to diet and exercise intervention (80% versus 73.4% of women in the magnesium and placebo groups, p = 0.99); the adherence to magnesium supplementation reach 100%.

A total of 7 women with previously diagnosed diabetes were included (4 in the magnesium group and 3 in the control group). The diabetic treatment was similar in the women of both groups (combined therapy with glibenclamide and metformin) and remained without change during the period of study.

There were no significant differences in age between the groups in study (49.1 ± 9.8 and 46.9 ± 10.0 years, p = 0.54; for the women in the magnesium and control group, respectively). A total of 20 (66.6%) women had passed the menopause, 10 in each group. There were no significant statistical differences for magnesium levels between menopausal and non-menopausal women, neither in the hypomagnesemic (1.70 ± 0.3 and 1.86 ± 0.05, p = 0.10) nor normomagnesemic (1.88 ± 0.2 and 1.91 ± 0.1, p = 0.77) groups.

General characteristics of the enrolled women are shown in Table 1. At baseline, women in the magnesium group were more obese and at final follow-up exhibited similar reduction of BMI, waist circumference, and adiposity. Serum magnesium concentration gradually increased in the supplemented women; at the end of follow-up women in both groups exhibited similar levels. In the magnesium group, ALT levels, but not hs-CRP, reached significantly lower levels in the fourth month of treatment as compared with women in the control group. Other variables showed no significant differences, at baseline or end follow-up, between women in the magnesium and placebo groups.

At baseline, the proportion of women with elevated hs-CRP (93.3 and 100%, p = 0.045) and ALT (30 and 16.7%, p = 0.45) levels was similar in both groups. At the end of follow-up, the proportion of elevated ALT in the magnesium supplemented

<table>
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<tr>
<th>Table 1. Anthropometric and laboratory characteristics of obese women with (MgCl₂) and without oral magnesium supplementation.</th>
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<tbody>
<tr>
<td><strong>Baseline</strong></td>
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<tr>
<td>Body Mass index, kg/m²</td>
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<tr>
<td>Waist circumference, cm</td>
</tr>
<tr>
<td>Total body fat, %</td>
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<tr>
<td>Systolic blood pressure, mmHg</td>
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<tr>
<td>Diastolic blood pressure, mmHg</td>
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<td>Fasting glucose, mg/dL</td>
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<td>Total cholesterol, mg/dL</td>
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<tr>
<td>Triglycerides, mg/dL</td>
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<tr>
<td>Serum magnesium, mg/dL</td>
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<tr>
<td>ALT, U/L</td>
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<tr>
<td>hs-CRP, mg/dL</td>
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</tbody>
</table>

* p < 0.05 between baseline and end follow-up in the women within the same group.
women was significantly lower (6.7 and 40%, p = 0.04) than in non supplemented women; on the other hand, the proportion of elevated hs-CRP levels decreased in the women who received oral magnesium supplementation, but not in control women (60 and 86.7%, p = 0.21) (figure 2).

The adjusted OR that computes the relationship between the improvement in serum magnesium levels and reduction in hs-CRP and ALT levels was 0.56 (95% CI: 0.3-0.9) and 0.93 (95% CI: 0.6-29.9), respectively.

Discussion

This study shows that oral magnesium supplementation significantly reduces the plasma ALT, but not CRP, levels in hypomagnesemic obese women.

Plasma CRP is produced predominantly by hepatocytes [16] and is positively correlated with liver fat [17], whereas elevated concentrations of ALT are associated with liver damage and fatty infiltration [18], highlighting that CRP and ALT levels are associated with indices of adiposity in obese women and are useful markers of obesity-related systemic and hepatic inflammation [19]. In addition, it has been hypothesized that magnesium deficiency may trigger the development of a proinflammatory state and low-grade chronic inflammation [20, 21].

In this regard, King [22] recently reviewed data of cross-sectional and epidemiological studies highlighting that magnesium perhaps plays an important role in potentiating inflammatory processes. Thus, magnesium supplementation seems to be a rationale prescription in conditions associated with magnesium deficiency.

In this study, to evaluate the efficacy of oral magnesium supplementation for decreasing circulating markers of systemic and hepatic inflammation, obese women with and without hypomagnesemia received dietary and exercise advice in order to reduce body weight. In addition, hypomagnesemic women received oral magnesium supplementation. At end of a 4-month of follow-up, women in both groups showed similar serum magnesium levels and a similar reduction of body weight; however, women who received magnesium supplementation had significantly decreased ALT levels. To the best of our knowledge, there are no previous reports regarding the role of magnesium supplementation for decreasing markers of hepatic inflammation:

Previously, based on a cross-sectional study, we reported that low serum magnesium concentration is independently related to non-alcoholic steatohepatitis in obese subjects [7]. In this regard, it has been reported that a decrease of magnesium stimulates the induction of cytokine and Fas ligands [2, 23]; well-known pathways in the pathogenesis of the inflammatory infiltrate of hepatocytes and development of steatohepatitis [23]. The results of this study suggest that improving the magnesium status could improve hepatic inflammation and reduce the risk of progression of liver damage. Further research in this area is mandatory to corroborate our findings.

On the other hand, previous studies have showed that magnesium intake is inversely associated with systemic inflammation in apparently healthy subjects [24-27]; however, previous reports regarding the efficacy of oral magnesium supplementation for reducing CRP levels are scarce [9]. In this study, although there were no statistical significant

![Figure 2. HsCRP and ALT levels at baseline and end of follow-up for hypomagnesemic women who received oral magnesium chloride (black squares) and normomagnesemic women in the control group (white squares). At baseline, there were no significant differences between the groups; at the end of follow-up, ALT levels, but not hsCRP levels, were significantly decreased in the magnesium supplemented women. * p < 0.05.](image-url)
differences between the groups at the end of follow-up, women who received magnesium supplementation, but not the normomagnesemic women, decreased hs-CRP levels between baseline and end of follow-up. The absence of significant differences in hs-CRP between the groups at the end of follow-up could be related to the small sample size and the possibility of error type 2 in the interpretation of data. However, it is necessary to emphasize that in the magnesium supplemented group, but not in the non-supplemented group, the hs-CRP levels showed a significant reduction, suggesting that in addition to a reduction in body weight, magnesium supplementation had an additional role in the decrease of low-grade systemic inflammation.

Some limitations of the study deserve to be mentioned. First, we conducted a non-randomized non placebo controlled clinical trial; thus, our results should be taken into account as preliminary findings that require further research in order to confirm them. Second, the small sample size might have had an influence in the interpretation of data, particularly regarding differences of hs-CRP between the groups; however, the intragroup reduction of hs-CRP was statistically significant in the magnesium-supplemented, but not in the non-supplemented group; suggesting that magnesium supplementation exerted a role in the reduction of systemic low-grade inflammation. Further research, with a larger sample size, is required to draw conclusions about the role of magnesium supplementation on systemic inflammation.

The main strength of this study is that the initial and final body weight and adiposity was similar in the obese women in both groups, which allowed us to evaluate the role of magnesium supplementation in the reduction of markers of inflammation in a way independent of obesity. In conclusion, oral magnesium supplementation with magnesium chloride in hypomagnesemic obese women reduces plasma ALT levels, whereas hs-CRP levels show a reduction trend. Targeting the inflammatory cascade by magnesium supplementation in obese women might be a useful tool for decreasing hepatic inflammation and improving the prognosis of obesity-related comorbidities.

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None of the authors has any conflict of interest to disclose.

References


