Oral Magnesium supplementation improves insulin sensitivity in non-diabetic subjects with insulin resistance. A double-blind placebo-controlled randomized trial

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Summary
Objective: Although hypomagnesemia reduces insulin sensitivity, benefits of magnesium supplementation to non-diabetic insulin resistant subjects has not been established. Our purpose was to determine whether oral magnesium supplementation with magnesium chloride (MgCl2) 2.5 g daily modify insulin sensitivity in non-diabetic subjects.

Material and Methods: This study was a 3 months randomized double-blind placebo-controlled trial. Apparently healthy subjects were eligible to participate if they had insulin resistance (HOMA-IR index equal or greater than 3.0) and hypomagnesemia (Serum magnesium levels equal or lower than 0.74 mmol/l). Subjects were randomized to receive either, MgCl2 2.5 g daily or placebo by 3-months.

Results: At baseline there were not significant anthropometric or laboratory differences between both groups. At ending of the study, magnesium-supplemented subjects significantly increased their serum magnesium levels (0.61 ± 0.08 to 0.81 ± 0.08 mmol/l, p < 0.0001) and reduced HOMA-IR index (4.6 ± 2.8 to 2.6 ± 1.1, p < 0.0001), whereas control subjects did not (0.62 ± 0.08 to 0.61 ± 0.08 mmol/l, p = 0.083 and 5.2 ± 1.9 to 5.3 ± 2.9, p = 0.087).

Conclusions: Oral magnesium supplementation improves insulin sensitivity in hypomagnesemic non-diabetic subjects. Clinical implications of this finding have to be established.

Key-words: Magnesium supplementation - Magnesium Chloride - Insulin sensitivity - Hypomagnesemia - Insulin resistance.

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Insulin resistance, characterized by the impairment of insulin action and decreased glucose-uptake in target tissues [1, 2] precedes the development of type 2 diabetes [3-6]. Hypomagnesemia reduces tyrosine-kinase activity and autophosphorylation at the insulin receptor level [7] decreasing insulin sensitivity [8-11], findings that support the hypothesis that magnesium supplementation could be useful for improving insulin resistance in non-diabetic subjects [12].

In this regard, although glucose disposal after an intravenous glucose tolerance test is directly related to fasting plasma magnesium concentrations [13] and that has been reported a decreased insulin mediated glucose disposal in healthy subjects with low plasma magnesium levels [14], to the best of our knowledge there are not previous randomized studies showing the benefits of magnesium supplementation in apparently healthy subjects with insulin resistance. Recently, the findings in the Nurses’ Healthy Study and Health Professionals’ Follow-up study [15] as well as in the Women’s Health Study [16, 17] support a protective role of higher magnesium diet intake in reducing the risk of developing type 2 diabetes.

In this study we determine whether oral magnesium supplementation with magnesium chloride (MgCl₂) 2.5 g daily modify insulin sensitivity in non-diabetic subjects with decreased serum magnesium levels.

Material and methods

With the approval of protocol by the Mexican Social Security Institute (MSSI) Research Committee, and after obtaining the subject informed consent, a randomized double-blind placebo-controlled trial was carried out.

Design and Setting

Apparently healthy subjects were eligible to participate if they had both decreased serum magnesium levels and insulin resistance. Based on previous results on healthy subjects from Durango, community in the northern of Mexico, decreased serum magnesium levels were defined by magnesium concentration equal or lower than 0.74 mmol/l [18, 19], and insulin resistance by the homeostasis model analysis for insulin resistance (HOMA-IR) index value equal or greater than 3.0.

The most frequent causes of magnesium depletion linked to a metabolic dysregulation as chronic diarrhea, alcohol intake (equal or more than 30 g per day), smoking, diabetes, high blood pressure, surgical stress, chronic diseases, diuretic therapy, and reduced renal function were exclusion criteria. In addition, subjects who received magnesium supplementation previous to randomization were not included.

Although all the subjects included in this study had low serum magnesium levels and insulin resistance, none of them showed clinical symptoms or signs related to their electrolytic deficit or metabolic status.

The primary trial end point was the change in HOMA-IR index. Sample size was determined based on a statistical power of 80%, alpha value 0.05, and allowing non-improve in the serum insulin level of 40 and 80% for the subjects who received magnesium supplementation and placebo [20], respectively. The required sample size to detect a treatment effect was of 26 subjects in each group [21].

Sixty eligible subjects were enrolled and randomly allocated to daily receive either MgCl₂ 2.5 g (that represents approximately 300 mg/day) or placebo by 12-weeks. Magnesium chloride solution (50 gr of MgCl₂ by 1000 ml of solution) was the magnesium supplement used. In fasting conditions, subjects in the MgCl₂ group drank 50 ml of the 5% solution thus, they received 2.5 gr of MgCl₂ daily.

Computer-generated random numbers were used to assign participants to oral magnesium supplementation or placebo groups. The final distribution is showed in the Figure 1.

Adherence to magnesium supplementation was assessed every month by personal interview and measurement of residual solution of MgCl₂. All the participants and personnel assessing outcomes were blinded to group assignment.

Measurements

Height and weight were measured 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 taken as the minimum circumference at umbilicus level, and hip circumference at the level of greater than 3.0.

Completed

Week 12 = 30

Completed

Week 12 = 30
ference as the maximum circumference at symphysis of pubis level. Waist-to-Hip ratio (WHR) was estimated as waist circumference divided by hip circumference.

At baseline and end of study, anthropometric measurements, lipid profile, and insulin levels were measured. Fasting serum glucose and magnesium levels were measured every 4-weeks. Serum glucose was measured by glucose-oxidase method; its intra- and inter-assay variations were 2.5% and 4.0%. Insulin levels were measured by microparticle enzyme immunoassay, its intra- and inter-assay variation coefficients were 4.5 and 6.9, respectively. Serum magnesium concentrations were measured by colorimetric method, the intra- and inter-assay variations were 1.0% and 2.5%.

The HOMA-IR index (Fasting glucose (mmol/l) x Fasting insulin (µIU/ml)/22.5) was used for estimating insulin sensitivity [22].

Statistical analysis

The preplanned intention-to-treat analysis of the primary study end-point, was done for all the randomly allocated participants (Fig 1).

Two-tailed unpaired student t test was used for comparisons between normally distributed variables (Mann Whitney U test for skewed data), and chi-squared test for categoric variables. Two-tailed paired t test was used for comparisons before and after treatment within each group.

A multiple logistic regression analysis adjusted by age, gender, BMI, and WHR was done at baseline to convincingly demonstrate the baseline independent relationship between low serum magnesium levels and insulin resistance. In this regression model, HOMA-IR index value was the dependent variable and serum magnesium levels the independent variable.

A 95% Confidence interval (CI95%) was considered, and a p value < 0.05 defined the level of statistical significance. Data analysis was performed using the SPSS 10.0 statistical package (SPSS Inc., Illinois USA 1998).

Results

A total of 740 subjects were screened; of them 60 subjects who fulfilled the inclusion criteria were randomized to receive either MgCl2 2.5 g or placebo. There were not dropped nor serious adverse events or side effects due to MgCl2 or placebo. Four (13.3%) magnesium-supplemented subjects showed slight bone pain in the first month that not required specific treatment nor discontinuation of magnesium administration. All the randomized subjects satisfactorily completed the follow-up. Adherence to treatment was achieved for 28 (93.3%) subjects in the MgCl2 group and 29 (96.6%) subjects in the placebo group, p = 1.0.

There were not differences by age 43.0 ± 7.9 vs 42.2 ± 6.8 yr, p = 0.69, for the magnesium-supplemented and control subjects. At the beginning of the study, anthropometric and laboratory characteristics of the participants in both groups did not differ, Table I. Furthermore, in baseline conditions, there were a strong and independent relationship between

Table I
Baseline characteristics of subjects randomly allocated to receive either magnesium chloride 2.5 g daily (MgCl2) or placebo (Control group) by 12-weeks.

<table>
<thead>
<tr>
<th>MgCl2</th>
<th>Control group</th>
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<tbody>
<tr>
<td></td>
<td>n = 32</td>
</tr>
<tr>
<td></td>
<td>Baseline*</td>
</tr>
<tr>
<td>Body Mass Index, Kg/m²</td>
<td>29.3 ± 6.3</td>
</tr>
<tr>
<td>Waist-to-Hip ratio</td>
<td>0.93 ± 0.14</td>
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<tr>
<td>Systolic blood pressure, mmHg</td>
<td>110 ± 8.4</td>
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<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>73 ± 7.5</td>
</tr>
<tr>
<td>Fasting glucose, mmol/l</td>
<td>5.8 ± 0.9</td>
</tr>
<tr>
<td>Fasting insulin, mmol/l</td>
<td>103.2 ± 56.4</td>
</tr>
<tr>
<td>HOMA-IR index</td>
<td>4.6 ± 2.8</td>
</tr>
<tr>
<td>Total cholesterol mmol/l</td>
<td>5.6 ± 1.5</td>
</tr>
<tr>
<td>HDL-cholesterol, mmol/l</td>
<td>0.9 ± 0.4</td>
</tr>
<tr>
<td>LDL-cholesterol, mmol/l</td>
<td>3.4 ± 1.2</td>
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<tr>
<td>Triglycerides, mmol/l</td>
<td>2.8 ± 2.8</td>
</tr>
<tr>
<td>Magnesium, mmol/l</td>
<td>0.61 ± 0.08</td>
</tr>
</tbody>
</table>

* At baseline, there were not significant differences in any parameters between both groups; † p < 0.05 from baseline at ending, for magnesium-supplemented subjects; ‡ p < 0.01, at ending of the study between magnesium-supplemented and control subjects.
low serum magnesium levels and elevated HOMA-IR index (odds ratio 7.4, Confidence Interval 95% 2.1-10.2, p < 0.001).

Subjects who received magnesium chloride significantly increased their serum magnesium concentrations, that at the end of 3-month of supplementation were higher than 0.80 mmol/l (Tab I). In addition, at ending of the study, magnesium-supplemented subjects significantly reduced the fasting serum glucose, insulin levels, and HOMA-IR index, (Fig 2A), as well as improved their lipid profile decreasing serum triglycerides, total- and LDL-cholesterol, and increasing HDL-cholesterol levels, whereas control subjects did not, (Fig 2B).

Finally, in both groups, other parameters as BMI, WHR, and blood pressure did not show significant variations through the period of study.

Discussion

Recently, Rosolova et al. [23] demonstrates an inverse relationship between serum magnesium and fasting insulin concentrations in non-diabetic subjects. In addition, when normal volunteers received a low magnesium diet for 4 weeks, their insulin sensitivity decreased by 25% [9]; these data suggest that the association between plasma magnesium concentration and insulin resistance is also present in non-diabetic subjects [23]. In accordance with these findings [9, 23], in this study, magnesium-supplemented subjects reduced 32% and 43.5% the serum fasting insulin levels and HOMA-IR index, respectively. This reduction is the greatest reported in non-diabetic populations under pharmacological or non-pharmacological interventions [13-17, 19, 24], finding that could be related to the type of magnesium salt used as supplement, and support the benefits of oral magnesium supplementation in hypomagnesemic apparently healthy subjects in order to improve their glucose metabolic status. At baseline, both groups were similar in terms of anthropometric and laboratory characteristics, showing a strong and independent relationship between low serum magnesium and high HOMA-IR index. After 3-month of magnesium supplementation, whereas the main confounder variables did not change, subjects in the supplemented group significantly increased both their serum magnesium levels and peripheral insulin-mediated glucose uptake, finding that strongly support the relationship between serum magnesium changes and insulin/insulin sensitivity. Based on a randomized placebo controlled trial, this is the first demonstration of the beneficial effect of magnesium supplementation on insulin sensitivity in hypomagnesemic non-diabetic subjects.

Previous reports in type 2 diabetic subjects have shown a beneficial effect on insulin sensitivity by magnesium supplementation [21, 25] supporting that the impact of hypomagnesemia on insulin resistance is rather than an epiphenomen.

Some limitations of this study, deserves to be mentioned. First, we did not measure magnesium dietary intake so, based on the results of this study we can not explain the source of the low serum magnesium levels. However, because the studied population was eligible from the same community and were randomize allocated, the source of hy-

Figure 2
a) Percentage of variation in the serum fasting glucose (– 13.8% versus -1.8%), insulin levels (– 32.0% versus – 1.0%), and HOMA-IR index (– 43.5% versus 1.9%) for magnesium-supplemented subjects (white bar) and subjects in placebo group (dark bar), between baseline and end of the study.
b) Shows the percentage of variation in the lipid profile between baseline and end of the study for magnesium-supplemented subjects (white bar) and subjects in placebo group (dark bar).
Subjects who received magnesium supplementation significantly reduced the total-cholesterol (10.7%), LDL-cholesterol (11.8%), and triglycerides (39.3%) and increased the HDL-cholesterol (22.2%), whereas subjects in the placebo group increased triglycerides (28.6%), LDL-cholesterol (14.3%), and total-cholesterol (7.0%), and decreased HDL-cholesterol (1.0%).
pomagnesemia have not a significant role on the primary
trial end point of this study. Second, we estimated insulin
resistance by indirect method as HOMA-IR index is. How-
ever, given that HOMA-IR index is highly correlated with
euglycemic clamp [26, 27] we can assume that this potential
limitation tended to be slight and did not affect our conclu-

On the other hand, epidemiological data suggests that
hypomagnesemia could be involved in the pathogenesis of
cardiovascular disease in non-diabetic subjects altering the
blood lipid composition in a way that disposes to atheroscle-
rosis [24, 28, 29]. In this regard, previously we have reported
that low serum magnesium is associated with both decreased
HDL-cholesterol levels [30] and dyslipidemia of metabolic
syndrome [19]. In this study magnesium supplementation
significantly improved the lipid profile decreasing triglycer-
ides, total- and LDL-cholesterol, and increasing HDL-
cholesterol levels, supporting its beneficial effect on dyslipi-
demia.

Nonetheless, whether improve in lipid profile was a di-
rect consequence of the increased serum magnesium levels
or an indirect consequence of the improved insulin sensi-
tivity was not adequately established in this study, so fur-
ther research will be needed in this field.

In conclusion, our data show that oral magnesium
supplementation by MgCl₂ 2.5 g daily increase insulin sensi-
tivity in non-diabetic subjects with decreased serum magne-
sium levels. Clinical implications of this finding remained to
be established.

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