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High Dietary Magnesium Intake is Significantly and Independently Associated with Higher Insulin Sensitivity in a Mexican-Mestizo Population: A Brief Cross-Sectional Report

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ABSTRACT

Background: Magnesium acts as a cofactor in many intracellular reactions including phosphorylation of the insulin receptor; therefore, its imbalance can potentially cause insulin resistance. Low serum magnesium concentration has been associated with the development of metabolic syndrome and type 2 diabetes mellitus. **Objective:** To study the association between the daily dietary magnesium intake and insulin resistance estimated by the homeostatic model assessment of insulin resistance and homeostatic model assessment 2, as well as insulin sensitivity estimated by the Matsuda index. **Methods:** In a university affiliated medical center, 32 participants (22 women, 10 men) that had an indication for testing for type 2 diabetes mellitus with an oral glucose tolerance test were enrolled in this cross-sectional, comparative study. Clinical and biochemical evaluations were carried out including an oral glucose tolerance test. Hepatic insulin resistance index, homeostatic model assessment 2, homeostatic model assessment of insulin resistance, and Matsuda insulin sensitivity were calculated for each participant. They were asked to recall their food ingestion (24 hours) of three days of the past week, including a weekend day; magnesium intake was calculated according to the food nutritional information. **Results:** The low dietary magnesium intake group (< 4.5 mg/kg/day) had a higher two-hour insulin concentration after an oral glucose tolerance test compared to those with high dietary magnesium (119.5 [73.0-190.6] vs. 63.5 [25.4-114.2]; p = 0.008), and insulin sensitivity assessed by the Matsuda index was higher in the high dietary magnesium intake group (4.3 ± 3.1 vs. 2.4 ± 1.5; p = 0.042). In multiple linear regression analysis a higher dietary magnesium intake was independently associated (β = 4.93; p = 0.05) with a better insulin sensitivity estimated by the Matsuda index. **Conclusions:** Our results suggest that higher magnesium intake is independently associated with better insulin sensitivity in patients at risk for type 2 diabetes mellitus. (REV INVES CLIN. 2017;69:40-6)

Key words: Dietary magnesium. Insulin resistance. Insulin sensitivity.

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INTRODUCTION

In 2015, 415 million people worldwide were living with type 2 diabetes mellitus (T2DM) and this number is expected to rise to 642 million by 2040. Moreover, 318 million adults have impaired glucose tolerance, meaning that they are at risk of developing the disease in the future[1]. In Mexico, the prevalence of T2DM in 2012 was 9.17% of the total population (6,400,000)[2]; by 2015, this number increased to 11,500,000 persons living with diabetes[1].

Magnesium (Mg) is the second most abundant cation in the body and plays an important physiological role in over 300 enzymatic reactions[3,4]. A normal plasma Mg concentration is 1.8-2.3 mg/dl. There are three states of Mg in the body: ionized (60%), protein bound (30%), and coupled with serum anions (10%)[4].

Magnesium is a significant cofactor for the function of important enzymes, such as those related to the transfer of phosphate groups, and all the steps involving replication and transcription of DNA and translation of mRNA. This cation is used for cellular energy metabolism, membrane stabilization, nerve conduction, ion transport, and calcium channel activity[5], and is an essential cofactor in all adenosine triphosphate transfer reactions; this implies that Mg concentration is critical in the phosphorylation of the insulin receptor. It has been postulated that the activation of tyrosine kinase in the insulin receptor is an important step in transmembrane signaling for insulin action[6].

The average daily intake of Mg is 300-325 mg, from which 120 mg is eliminated (100 mg in urine, and 20 mg from the gastrointestinal tract), leaving a net absorption of 100 mg per day[4]. The recommended daily Mg intake is 350 mg[7]. Foods rich in Mg are mainly grains, cereals, green vegetables, nuts, and seafood[8].

Magnesium deficiency is linked to several diseases and conditions including endothelial cell dysfunction, hypertension, inflammation, and oxidative stress, with a consequent higher risk for atherosclerosis, dyslipidemias[9-12], heart disease, and stroke[9,13]. Furthermore, low Mg serum concentration is linked to the development of insulin resistance (IR), characterized by a subnormal biologic response to a given concentration of insulin in target tissues[14], metabolic syndrome, and T2DM[15-17]. Several prospective studies where Mg was supplemented and found to exert an improvement in IR[15,18,19] have confirmed these associations. Nevertheless, there are few studies associating dietary Mg intake to IR[20-22], so the aim of this study was to determine the association between the average dietary Mg intake and IR estimated by the homeostasis model assessment of insulin resistance (HOMA-IR) and HOMA 2, as well as insulin sensitivity (IS), estimated by the Matsuda IS index and the Hepatic Insulin Resistance Index (HIRI).

MATERIALS AND METHODS

Study population

A total of 32 subjects who fulfilled the selection criteria and signed an informed consent form were enrolled in this cross-sectional study. Participants were subjects from the Internal Medicine and Endocrinology outpatient clinics of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ), a non-profit, university affiliated medical center. We recruited subjects between March 2009 and July 2010. The inclusion criteria were: both gender subjects, aged 18 - 65 years, that were at risk for T2DM and had an indication for testing with a two-hour oral glucose tolerance test (OGTT) with 75 g intake and at least two risk factors for T2DM according to the American Diabetes Association (ADA)[23], including: physical inactivity, a first-degree relative with T2DM, high-risk race/ethnicity, women who delivered a baby weighing > 4 kg or were diagnosed with gestational diabetes mellitus, hypertension (blood pressure ≥ 140/90 mmHg) or on hypertension therapy, high-density lipoprotein cholesterol (HDL-C) concentration < 35 mg/dl and/or a triglyceride concentration > 250 mg/dl, women with polycystic ovary syndrome, A1C ≥ 5.7%, impaired glucose tolerance (IGT), or impaired fasting glucose (IFG) on previous testing, other clinical conditions associated with IR (i.e. severe obesity, acanthosis nigricans), or a history of cardiovascular disease.

We excluded subjects who weighed >150 kg, or who were taking medications that could influence glucose

and insulin values during the OGTT such as steroids, oral glucose-lowering drugs, insulin, and thyroid hormones. We also excluded subjects who had any pathology that modified glucose or insulin concentrations (i.e. dysthyroidism, hypercortisolism), subjects whose laboratory tests denoted any situation that interfered with IR, or individuals who had other chronic diseases (including infections like HIV or hepatitis C), autoimmune diseases, seizures, major depression, use of hepatotoxic drugs (i.e. acetaminophen, antibiotics, chemotherapy), who were hospitalized in the past six months, had active cancer or were under treatment for cancer, and pregnant women.

Subjects who did not sign the informed consent form or who could not remember the food ingested one week before the OGTT were also excluded from the study. This study is a *post hoc* analysis of the information obtained in a previous study approved by our Ethics board (REF: 1650).

Definitions

Impaired fasting glucose was defined as a fasting glucose between 100 and 125 mg/dl; IGT as a two-hour glucose value in the OGTT between 140 and 199 mg/dl; and T2DM as a fasting glucose concentration ≥ 126 mg/dl on two occasions, or glucose ≥ 200 mg/dl at the second hour of the OGTT, according to the ADA criteria[23].

The HOMA-IR, HOMA 2, HIRI, and Matsuda indexes were calculated using the glucose and insulin values obtained every 30 minutes during the OGTT. Insulin resistance was estimated using the HOMA 2-IR calculator provided on the web page[24]; results ≥ 2.5 were considered as IR[25,26]. Insulin sensitivity was estimated with the IS Matsuda index with the formula: 10,000/√(glucose 0' × insulin 0') × (mean glucose × mean insulin); values lower than 1.5 indicated IR[26]. To obtain HIRI, we used the formula described by Abdul-Ghani: √(glucose 0-30 [AUC in mg/dl/hr] × insulin 0-30 [AUC in μU/ml/hr])[27].

These indexes were used because of their strong correlation with IS in the hyperinsulinemic-euglycemic clamp technique, being reliable indices for assessing our objective[26,28].

Anthropometric and biochemical measurements

Anthropometric measurements were taken with participants barefoot and without their upper clothes. A mechanical beam scale (HealthOMeter Inc, Bridgeview, IL) with daily calibration was used to measure body weight. Body fat was measured with Quantum Desktop-BIA Analyzer (RJL Systems, Michigan, USA). Height was obtained using the floor scale's stadiometer to the nearest 0.5 cm. Waist circumference was measured to the nearest 0.1 cm at the level of the greatest frontal extension of the abdomen between the bottom of the rib cage and the top of the iliac crest. Body mass index (BMI) was calculated using weight (kg) divided by squared height (m^2). Sitting blood pressure was measured after a rest of at least five minutes.

The central laboratory of the INCMNSZ performed all biochemical laboratory measurements with commercially available standardized methods. Synchron CX® analyzer (Beckman Systems, Fullerton CA) was used to measure glucose, total cholesterol, HDL-C, and triglycerides. Plasma insulin concentrations were estimated using a radioimmunoassay method (MEIA, Abbott Laboratories).

The daily average Mg intake, as well as the intake of carbohydrates, lipids, and proteins, was estimated with the food nutritional content[29] according to a 24-hour food ingestion register that all 32 participants were asked to complete with the ingested food information for three days of the previous week, including a weekend day. The Mg intake was classified as low (< 350 mg/day or < 4.5 mg/kg/day) or high (≥ 350 mg/day or ≥ 4.5 mg/kg/day); this arbitrary division was made considering the median Mg intake in the subjects studied. We also considered the recommended daily Mg intake of 350 mg[7]; thus, for an average person weighing 70 kg it would be 4.5-5.0 mg/kg.

Statistical analysis

Normal variables are described with mean ± standard deviation as assessed by the Kolmogorov-Smirnov test, whereas variables with a skewed distribution are reported as medians (interquartile range). Parametric Pearson correlation test or Spearman correlation test

Table 1. Multiple linear regression analysis of variables associated with the Matsuda index

Variable	β	Standardized β	T	p value
Gender (male)	–1.965	–0.358	–2.249	0.03
Age (years)	–0.047	–0.215	–1.354	0.18
Logarithm of dietary Mg/kg	4.938	0.323	2.028	0.05

Parameters of model: Constant: 5.413, F = 0.226; r^2 = 0.321; p = 0.017
Mg: magnesium.

were used to determine the relationship between Mg intake, taken as quantitative continuous variables, and other clinical and biochemical measurements, also expressed as continuous quantitative variables. Student's *t* parametric or Mann-Whitney *U* tests were used to evaluate the differences between Mg intake, taken as a dichotomous qualitative variable, and other clinical and biochemical measures, expressed as quantitative continuous variables. To adjust for confounding factors, multiple linear regression analyses were made using, as dependent variables, the different indexes studied and, as independent variables, factors that influence insulin resistance (e.g. age[30] and sex[31]). Data were analyzed in Statistical Package for the Social Sciences (SPSS) v20.

RESULTS

We enrolled 36 patients that met the inclusion criteria; four of them were excluded, three due to the presence of hypothyroidism and another one for being unable to complete the food register. Clinical and biochemical characteristics of the 32 eligible patients are shown in table S1. The mean age was 43.9 years, 68.75% were women, and the mean BMI was 30.22 ± 7.8 kg/m^2. The mean serum Mg was normal (2.1 ± 0.7), and the median HOMA-2 IR was 1.8 (1.0-3.0). The median daily Mg intake was 360.65 (302.52-476.40) mg/day (Supplementary Information [SI], Table 1).

We made correlation analyses to associate Mg intake with clinical and laboratory variables (SI, Table 2). Since the dietary Mg was correlated with the weight (r = 0.45; p = 0.010), we decided to divide the daily Mg intake by the weight. The weight-adjusted Mg intake was correlated with insulin two hours after OGTT (r = –0.46; p = 0.007. Fig. 1), serum Mg (r = 0.50; p = 0.027), and HOMA-2 (%B, percentage of beta cell function; r = –0.42; p = 0.017).

We then divided the population by the median weight-adjusted Mg intake (< 4.5 mg/kg/day [low Mg intake] and ≥ 4.5 mg/kg/day [high Mg intake]), and found that the low Mg intake group had higher insulin two hours post OGTT: 119.5 (73-190.6) vs. 63.5 (25.4-114.2), p = 0.008, a lower serum Mg (p = 0.037), a lower Matsuda index (2.4 ± 1.5 vs. 4.3 ± 3.1; p = 0.042), and higher HOMA-2 (%B) (p = 0.037) than those patients who consumed ≥ 4.5 mg/kg/day (SI, Table S3).

To adjust for confounding factors, a multiple linear regression analysis was made using as the dependent variable the Matsuda index, and as independent variables, gender (male), age, and the logarithm of dietary Mg intake (mg/kg). Male gender was negatively associated with insulin sensitivity (β = –1.965; p = 0.03), and the logarithm of dietary Mg/kg was positively associated with insulin sensitivity (β = 4.938; p = 0.05) (Table 1).

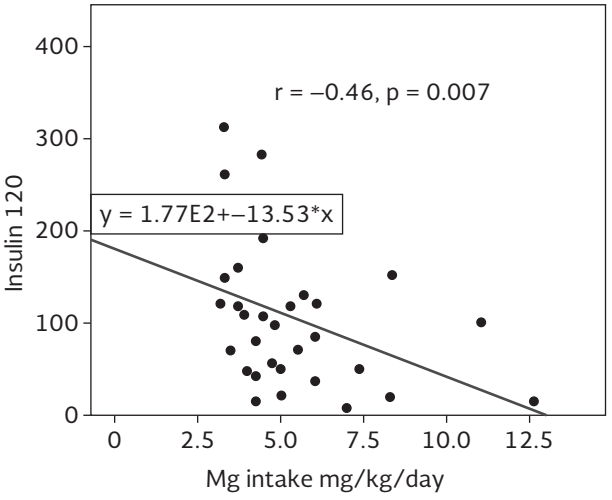
In SI, table 4 depicts the multiple linear regression analysis of variables associated with two hours post OGTT insulin. Dietary Mg intake below the recommended intake was independently associated with two hours post OGTT insulin.

In the last regression model, using HOMA-2 %S (percentage of insulin sensitivity) as a dependent variable with the same independents variables we used before, gender (male) was independently associated with HOMA-2 %S according to the regression analysis (SI, Table 5).

DISCUSSION

The association between serum Mg concentration, IR, and IS has been extensively studied[11,18,20,32]. However, only a few studies have assessed the relationship between these insulin parameters and Mg intake[20-22]. The aim of this study was to evaluate the

Figure 1. Association between weight-adjusted daily magnesium intake and insulin 120', after oral glucose tolerance test.
Mg: magnesium.



association between dietary Mg intake and IS in a Mexican-Mestizo population.

In this study, we found a significant and independent association between high weight-adjusted Mg intake and IS, assessed with the Matsuda index. Although no significant differences were found in fasting serum insulin concentration, subjects with a lower Mg intake had a higher two-hour post-OGTT insulin concentration compared to the higher Mg intake group (119.5 [73.0-190.6] vs. 63.5 [25.4-114.2]; p = 0.008). Moreover, both IS assessed by Matsuda index and HOMA-2 %B were higher in the high Mg intake group.

Our results point in the same direction as interventional studies where Mg supplementation improves IS[11,18,20,33]. We observed a higher Matsuda index in the high Mg intake group, reflecting better IS. Supplementation of Mg in diabetic patients reduced HOMA-IR index, fasting serum glucose, and insulin concentration[32]. In the case of non-diabetic participants, Mg supplementation for three months also decreased fasting glucose, insulin, and HOMA-B index compared to placebo[34]. This is also in agreement with a study where Mg supplementation was associated with a higher Matsuda index compared to placebo[35]. Simental-Mendia, et al., in a meta-analysis, report that supplementation of Mg for ≥ 4 months significantly improves the HOMA-IR index and fasting glucose in both diabetic and non-diabetic subjects[36]. All of these findings, including ours, confirm the role of Mg as an important insulin secretion regulator, improving IS and also enhancing beta-cell function[6]. On the other hand, Kao, et al. did not find an association between dietary Mg intake and the risk for incident T2DM using serum Mg concentration and dietary Mg intake. However, they suggested that the dietary Mg measurements could not be precise because the food frequency questionnaire might not have been appropriate for their studied population[10]. Also, the dietary Mg intake was adjusted as Mg in mg/4.2 kJ daily energy intake. In addition, it has been shown that serum Mg concentration may not accurately reflect real body Mg content since it is mainly an intracellular cation[37,38].

We found a significant and positive correlation between daily Mg intake, weight, and BMI. Conversely, other studies demonstrated an inverse correlation between serum Mg concentration and BMI[39,40]. A possible explanation of these findings is that they used serum Mg instead of daily Mg dietary intake.

In our study, the high dietary Mg intake group had higher serum Mg concentration compared to the low Mg intake group (2.15 ± 0.17 vs. 2.0 ± 0.09; p = 0.037). This finding is supported by Paolisso, et al. who reported a positive association between Mg intake and blood Mg concentration[41].

Initially, we did not find a significant association between IS and IR parameters and total Mg intake, but we did find a positive correlation between weight and Mg intake. Because of this, we decided to adjust the Mg intake by body weight and, in doing so, we found significant results. This fact is interesting because most studies have assessed total Mg intake without adjusting it for body weight, and perhaps a weight-adjusted analysis, as was done in this case, could be more reliable and reduce the inconsistency of the results among the different studies.

Our study has some limitations. First, the average of our population was obese according to their BMI (30.22 ± 7.8) and had IR; therefore, the results should be interpreted with caution. Because of the small sample size, we could not make a sensitivity analysis excluding IR patients to evaluate whether we could still find an association between Mg intake and IR/IS. It would be interesting to determine if our results can be replicated across all the spectrum of IR/IS. Second,

we decided to adjust Mg intake to body weight because there was a correlation between Mg intake and weight, and between Mg intake and total calorie intake. However, we cannot rule out that we demonstrated a significant association between weight-adjusted Mg intake because we included the variable weight, which we assumed *a priori* as a non-confounder. A larger sample size would be necessary to assess if there is an interaction or confusion between IS, weight, and Mg intake. We think that, because the Matsuda IS index incorporates in its formula all the glucose and insulin values during the OGTT, there is a lack of agreement with other evaluated indices. Finally, the 24-hour recall, which was the method we used to calculate Mg intake, is considered to have similar accuracy to that of semi-quantitative food frequency questionnaires[42], but it has the disadvantage that the participants may have voluntary omissions and memory failures that may affect the results. However, there is no gold standard for assessing Mg intake, and people usually do not know which foods contain Mg, so it is unlikely that the mentioned disadvantages may have influenced the results.

In conclusion, we found that a higher Mg intake was independently associated with a better IS.

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SUPPLEMENTARY DATA

Supplementary data is available at Revista de Investigación Clínica online (www.clinicalandtranslationalinvestigation.com). These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsability of the authors.

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