



Oral magnesium supplementation: An adjuvant alternative to facing the worldwide challenge of type 2 diabetes?

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ABSTRACT

Background: In the search for answers that contribute to the metabolic control of patients with diabetes and the primary prevention of the disease, we performed a review of the evidence from cohort studies on the relationship between serum and/or magnesium intake with the risk of developing type 2 diabetes as well as of clinical trials on the efficacy of oral magnesium salts on reducing glycemia.

Methods: An electronic search using the databases MEDLINE, EMBASE, and Cochrane Controlled Trials Register, updated to September 30, 2013, was performed.

Results: A total of seven cohort studies (24,388 persons/year) show unequivocally that magnesium intake is associated with decreased risk of developing type 2 diabetes. Two studies (13,076 persons/year) indicate that low magnesium intake is not associated with the risk of diabetes; one study (8,735 persons/year) shows that hypomagnesemia is associated with the development of impaired glucose metabolism. A total of 11 randomized controlled trials were identified; five studies showed the effectiveness of oral magnesium salts in reducing glycemia in high-risk subjects and six studies carried out in patients with type 2 diabetes show inconsistent results.

Conclusions: Magnesium intake in the usual diet of subjects from the general population and high-risk groups and/or oral magnesium supplementation is recommended for the prevention of diabetes. The efficacy of oral magnesium supplementation in the reduction of glucose levels in type 2 diabetic patients is inconsistent.

Key words: Cohort, clinical trial, magnesium, diabetes, glycemia.

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BACKGROUND

According to estimates of the International Diabetes Federation (IDF), there are 189,831,890 men and 181,497,210 women between 20 and 79 years of age with diabetes worldwide. Of these subjects, 236,722,820 live in urban communities and 134,606,280 in rural communities.¹ According to this source, it is estimated that 280,353,530 persons worldwide suffer from glucose intolerance and, for that reason, are at risk of developing type 2 diabetes. It is estimated that by the year 2030 there will be 558,590,050 persons worldwide with diabetes.

The impact of diabetes on the health and economy of countries is such that 4,593,109 persons die each year from complications related to this disease, and the average annual expenditure on healthcare per person diagnosed with diabetes is \$1,274 USD, which represents a global health care expenditure of > \$471 million USD per year related to this health problem.

In Mexico, the prevalence of diabetes has increased from 8.2%² in 1993 to 9.17% in 2012³ according to data from the National Health Surveys. From 2000, diabetes has ranked third as a cause of mortality, with 59,912 deaths in 2003, indicating a rate of 56.8/100,000 inhabitants and causing more deaths than those generated by ischemic heart disease.

In 2004, diabetes ranked second with 62,243 deaths with a mortality rate of 59.1/100,000 inhabitants. In Mexico, in the year 2010, the annual expenditure on direct health care costs in patients with T2DM was \$452,064,988 USD, an average annual cost per patient of \$3193.75 USD,⁴ higher than that reported by the IDF internationally. Therefore, the magnitude of health problems related to diabetes and its complications is an enormous challenge that requires immediate attention aimed, ideally, at prevention.

In this context, large multicenter studies conducted for the purpose of preventing T2DM show that changes in lifestyle aimed at changing dietary and exercise habits effectively reduce the risk of diabetes,⁵⁻⁷ with higher percentages of lowering the risk compared with drugs such as metformin,⁷ alpha-glucosidase inhibitors,⁸ troglitazone,⁹ or orlistat.¹⁰

However, in Mexico, the overall increase in incidence and prevalence of diabetes is a reflection of the failure to adopt healthy lifestyles. Blood glucose values recorded on admission of hospitalized diabetic patients were, on average, 264 mg/dL. Among the most frequent diagnoses was necrobiosis (10.1%), a major acute complication of diabetes and hyperosmolarity (9.1%). The main discharge diagnosis in patients hospitalized for diabetes was corrected decompensation (28.05%).¹¹ Despite the development of novel drugs with different mechanisms of action to reduce glucose concentrations, it is clear that we are not only losing the glycemic battle but the war against diabetes. In the search for answers that promote metabolic control in patients with diabetes and primary prevention of the disease in high-risk subjects, one of the lines of research of the Biomedical Research Unit of IMSS in Durango has focused on the role of magnesium on glucose metabolism and the potential benefit for oral consumption of magnesium salts in prevention and treatment of T2DM.

Magnesium, the most abundant intracellular divalent cation,¹² is an essential cofactor in enzymatic processes involving high-energy phosphate bonds, implicating different pathways of glucose metabolism.¹³

Furthermore, numerous studies consistently show that hypomagnesemia may be one of the triggers of the acute phase response and the chronic inflammatory syndrome associated with decreased insulin sensitivity.¹⁴⁻¹⁷ Therefore, there is a framework of biological plausibility support-

ing the hypothesis that oral supplementation of magnesium salts may be useful in the treatment and prevention of diabetes.

In this framework, recent results from the National Health Survey linked to the prevalence of deficiency of some trace elements, including the prevalence of hypomagnesemia, were published. The survey indicates that 36% of women and 31% of men suffer from magnesium deficiency, which represents a high proportion of subjects at risk.¹⁸ Thus, the aim of this study was to conduct a thorough review of the evidence from cohort studies and randomized clinical trials with the most robust study designs of the relationship between serum concentrations and magnesium intake with the risk of T2DM, as well as the efficacy of oral magnesium supplements in reducing blood glucose in patients with diabetes and high-risk subjects. For this purpose, a search was conducted in the electronic databases of MEDLINE, EMBASE, and Cochrane Controlled Trials Register, updated on September 30, 2013 using the following search keywords: magnesium, glucose, hyperglycemia, diabetes, IGT, impaired fasting glucose, metabolic monitoring, prevention, population-based studies and randomized-controlled clinical trials.

RESULTS

Cohort Studies

Ten cohort studies were identified^{16,19-27} with a mean follow-up of 10.5 years, which incorporated 305,903 patients from different ethnic backgrounds including Caucasians from the U.S. and Europe, mestizos from northern Mexico, Asians from Japan, and native Hawaiian Polynesians (Table 1).^{16,19-27}

In nine of these studies, the effect of the dietary intake of magnesium and risk of type 2 diabetes^{16,19-26} were analyzed. Of these, seven studies,^{16,20-23,25,26} involving 292,653 subjects

with an average follow-up of 12 years (24,388 person-years) show unequivocally that magnesium intake is associated with a decreased risk of T2DM, maintaining a significant inverse relationship between magnesium intake and risk of T2DM.

Two studies^{19,24} in which 71,919 subjects participated with a mean follow-up of 5.5 years (13,076 persons/year) indicate that although a low effect cannot be excluded, low intake of magnesium in the diet does not appear to be associated with risk of T2DM.

Finally, the study in the Mexican population that included 8,735 persons/year (at baseline, 3,351 persons/year had normal glucose tolerance and 5,384 persons/year had some imbalance of glucose metabolism fasting glucose, impaired glucose tolerance, or both) showed that at the conclusion of hypomagnesemia monitoring, serum magnesium ≤ 1.8 mg/dL is associated with T2DM (incidence rate of 105/10,000 person-years in the group with hypomagnesemia and 29/10,000 person-years in the unexposed group, $p < 0.001$) and alterations in glucose metabolism (incidence rate of 815/10,000 persons/year in the group with hypomagnesemia and 558/10,000 persons/year in the unexposed group, $p < 0.001$).

Clinical Trials

Eleven randomized placebo-controlled clinical trials were identified in which the effectiveness of oral supplementation of magnesium salts in the reduction of plasma glucose concentrations was evaluated. Of these, in five studies the target population was represented by individuals at high risk of T2DM,²⁸⁻³² and in six studies the target population was comprised of patients with T2DM³³⁻³⁸ (Table 2).²⁸⁻³⁸ In high-risk subjects, studies show the effectiveness of magnesium salts in lowering plasma glucose concentrations and therefore a possible reduction in the incidence of T2DM. In the study by Mooren et al.,²⁹ the



Table 1. Cohort studies of the relation between magnesium intake and serum concentrations with risk of metabolic alterations of glucose.

	<i>n</i>	Population	Beneficial effect*
Kim et al. ¹⁶	4,497	Caucasians	Yes
Kao et al. ¹⁹	12,128	Caucasians and Afroamericans	No
Rumawas et al. ²⁰	2,708	Caucasians and Afroamericans	Yes
Hopping et al. ²¹	75,512	Japanese-Americans, natives of Hawaii	Yes
Lopez-Ridaura et al. ²²	127,932	Caucasians and Afroamericans	Yes
Kirii et al. ²³	17,592	Asians (Japan)	Yes
Nanri et al. ²⁴	59,791	Asians (Japan)	No
Song et al. ²⁵	39,345	Caucasian and Afroamerican females	Yes
Schulze et al. ²⁶	25,067	Europe	Yes
Guerrero-Romero et al. ²⁷	1,122	Northern Mexico	Yes

*In the reduction of risk of type 2 diabetes.

Table 2. Randomized, controlled clinical trials concerning the efficacy of oral magnesium salts in reducing serum glucose

	Salt	<i>n</i>	Population	Beneficial effect*
Guerrero-Romero et al. ²⁸	Chloride	106	Without diabetes	Yes
Mooren et al. ²⁹	Aspartate	52	Without diabetes	Yes
Guerrero-Romero et al. ³⁰	Chloride	60	Without diabetes	Yes
Chacko et al. ³¹	Citrate	14	Without diabetes	Yes
Paolisso et al. ³²	Pidolate	12	Without diabetes	Yes
Rodríguez-Morán et al. ³³	Chloride	63	T2DM	Yes
Purvis et al. ³⁴	Chloride	28	T2DM	Mild
de Lordes Lima et al. ³⁵	Oxide	128	T2DM	Yes [†]
Johnsen et al. ³⁶	Oxide	11*	T2DM**	No
de Valk et al. ³⁷	Aspartate	50	T2DM	No
Gullestad et al. ³⁸	Citrate	56	T2DM	No

*With regard to glycemia.

**Controls.

[†]Elevated doses.

T2DM, type 2 diabetes mellitus.

efficacy of oral magnesium salts in lowering blood glucose was shown in high-risk patients with normomagnesemia.

With regard to clinical trials conducted in patients with T2DM, results are inconsistent with studies showing the efficacy of oral magnesium salts in reducing blood glucose levels,³³⁻³⁵ whereas other studies do not show beneficial results.³⁶⁻³⁸

DISCUSSION

The systematic review of evidence-based articles with the strongest methodological design used in this study shows that the recommended daily intake of magnesium is a protective factor against disturbances of glucose metabolism. Evidence from clinical trials shows, unequivocally, the effectiveness of magnesium salts administered orally in the improvement of glucose concentrations in subjects

at high risk for developing T2DM; however, results of the efficacy of magnesium salts in reducing glycemia in T2DM patients is inconsistent.

Magnesium is an important component of unprocessed foods, particularly found in whole grains, nuts, dried fruit, seafood and green leafy vegetables;³⁹ however, changes in lifestyles characterized by the adoption of "Westernized diets" has contributed to decreased magnesium intake in the diet, favoring hypomagnesemia. In addition, it must also be considered that lack of crop rotation and indiscriminate use of fertilizers along with increasing environmental pollution have contributed to the acidification of agricultural soils, resulting in a loss of contents of magnesium, which is an alkaline earth mineral.⁴⁰

All these conditions are key to the recommended daily intake of magnesium (450 mg for men and 360 mg for women)⁴¹ and is barely reached, contributing to the increased prevalence of hypomagnesemia in Mexico that, according to the report of the National Health and Nutrition Survey 2006 was 36.3% and 31.0% in women and men, respectively.¹⁸

Based on findings from cohort studies that consistently show the protective role of the recommended daily intake of magnesium for diabetes,^{16,20-23,25-27} it is advisable to promote and encourage the intake of foods rich in magnesium or the consumption of oral magnesium salts as part of the strategies aimed at the primary prevention of T2DM. Regarding the use of oral supplements of magnesium salts in high-risk subjects, results from all clinical trials show efficacy in lowering blood glucose.²⁸⁻³² This finding should encourage the consumption of magnesium salts as an adjunct lifestyle intervention to reduce the incidence of T2DM. Given the high prevalence of hypomagnesemia in Mexico, this inexpensive alternative intervention with virtually no side events (mild diarrhea reported in < 5% of users, sometimes accompanied by mild

abdominal pain) may be useful as a prevention strategy. It is important to note that in Mexico there are only two magnesium salts available for oral consumption: chloride and lactate, both with excellent bioavailability. According to the international panel of experts who met at the XIII International Symposium on Magnesium in Merida, Yucatan (October 2012), routine use of oral supplementation with magnesium salts in high-risk subjects was recommended to reduce the occurrence of disorders of glucose and lipid metabolism, thus contributing to the decrease in the incidence of diabetes. The efficacy results of supplemental magnesium in patients with T2DM are inconsistent.³³⁻³⁸ The variability in metabolic conditions, which depend on multiple factors such as age, disease evolution, pancreatic reserve, hypoglycemic therapy, chronic complications, chronic inflammatory state and oxidation, and the status of hypomagnesemia, among others, are factors that contribute to modifying the response of magnesium salts in patients with diabetes. Considering that the prevalence of hypomagnesemia in patients with diabetes is 55%⁴² and that foods rich in magnesium as the only natural source of salt are not part of the regular diet or have low concentrations of salts due to soil degradation, these are reasons why routine measurement of serum magnesium in patients with diabetes would be advisable and, in cases of deficiency, supplementation with oral magnesium salts would be recommended.

In conclusion, evidence available from cohort studies and clinical trials strongly suggests the benefits of diets rich in magnesium or consumption of oral magnesium salts in subjects from the general population and in high-risk groups. Although there is no solid evidence for the use of oral magnesium salts in patients with T2DM, based on its low cost, low frequency of significant adverse effects, and potential benefits, routine monitoring of serum magnesium concentrations and, in case of deficiencies, replacement with oral salts is recommended.



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