

The role of magnesium in type 2 diabetes: A brief based-clinical review

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Abstract. A growing body of evidence from experimental studies that shows the essential role that magnesium exerts on glucose metabolism has been developed in last years, strongly suggesting that magnesium could plays an important roles in the reduction of the risk of developing type 2 diabetes. In the clinical setting, large epidemiological studies show that low dietary magnesium intake is associated with the increased risk of developing type 2 diabetes; however, results from randomized controlled clinical trials that have evaluated the beneficial effects of magnesium supplementation on glucose metabolism and insulin sensitivity are controversial. In this article we searched (in the electronic databases of Medline, Embase, and the Cochrane Controlled Trials Register up to June 2011) the evidence derived from epidemiological studies and clinical trials, about the relationship between magnesium and type 2 diabetes. The body of evidence from epidemiological studies consistently shows a strong inverse relationship between dietary magnesium intake and the risk of developing T2D; however, results from clinical trials are scarce and controversial.

Key words: magnesium, type 2 diabetes, randomized controlled clinical trials, epidemiological studies

Introduction

Although hypomagnesemia is a common feature in patients with type 2 diabetes (T2D), the hypomagnesemia also has been proposed as a risk factor of developing T2D.

Magnesium, the most abundant intracellular divalent cation [1, 2], is involved as an essential cofactor in the enzymatic process of high-energy phosphate, energetic metabolism [3, 4], and glucose metabolic pathways [4-7]. Furthermore, clinical studies show that serum magnesium concentration is inversely associated with serum levels of C reactive protein (CRP) [8, 9], suggesting that hypomagnesemia is related with the triggering of low-grade chronic inflammatory syndrome, which is associated with the decrease of insulin

sensitivity [10-17]. So, through impairment of enzymatic pathways involved in glucose transport and phosphorylation as well as by the triggering of low-grade chronic inflammation, magnesium deficiency is implicated in the decrease of insulin action [18].

In addition, it has been reported that among individuals with serum magnesium deficiency, the decrease in insulin sensitivity is not appropriately compensated by the increase of beta-cell function [19, 20] and, that oral magnesium supplementation improves the ability of pancreatic β -cells to compensate the decreases in insulin sensitivity in non-diabetic subjects with significant hypomagnesemia [21]. These data strongly suggests that magnesium deficiency also is implicated in the decrease of insulin secretion.

Given that normal glucose tolerance is maintained by the balance between insulin secretion and insulin action, it is rationale to state that hypomagnesemia could play an important role in the development of glucose metabolic disorders and T2D.

In this article we searched (in the electronic databases of medline, embase, and the Cochrane Controlled Trials Register up to June 2011) the evidence derived from epidemiological studies and clinical trials, about the relationship between magnesium and type 2 diabetes.

The Based-population studies that tested the role of magnesium dietary intake were criteria for identifying the epidemiological studies; on the other hand, the randomized-controlled clinical trials using inorganic or organic magnesium salts, with duration of at least 12 weeks, were criteria for identifying the clinical trials.

Epidemiological studies

Magnesium is an important component of unprocessed foods such as whole grains, nuts, and green leafy vegetables; however the adoption of westernized diets has contributed to the reduction of magnesium intake in the vast majority of countries. On this regards, epidemiological studies have measured the association between magnesium intake and the risk of developing T2D.

Involving a total of 394,877 individuals enrolled in 9 follow-up studies (with 366,502 subjects and mean follow-up of 10.3 years), 7 cross-sectional studies (with 28,040 individuals), and 1 interventional life study (with 335 individuals), the role of magnesium intake in the customary diet, on glucose metabolism disorders and T2D has been tested in different age, sex, and ethnicity [9, 11, 16, 17, 22-34] (*table 1*).

Results of 15 (88.2%) of these studies consistently show that magnesium dietary intake play an independent role in ameliorating metabolic, inflammatory, and oxidative markers; benefits that have been documented in different age, sex, and ethnias [9, 11, 17, 22-31, 33, 34].

A total of 9 (52.9%) studies show that magnesium intake is positively related with reduction of the risk for developing T2D; 3 (17.6%) with the beneficial effect on inflammation and oxidative markers; 2 (11.8%) with the reduction of preva-

lence of metabolic syndrome; and 1 (5.9%) with the improvement on insulin sensitivity. These results strongly supports the benefits of dietary magnesium intake on blood glucose metabolic disorders and T2D (*table 1*).

On the other hand, 2 (11.8%) studies [16, 32] show that dietary magnesium intake is not appreciably associated neither reduction of the risk of T2D nor glucose levels and inflammation markers (*table 1*). These findings suggest that magnesium dietary intake by itself might be inadequate to modification the health status of subjects in high risk of developing T2D.

The discrepancy between studies could be related with additional nutrients involved in the diet, which vary according ethnicity and/or with the control of involved confounders. Furthermore, is necessary to take into account that usually epidemiological studies do not report magnesium status of participants at basal and final conditions; so, in these studies the magnesium status of participants is unknown. On this regard, is important to keep in mind that magnesium-induced changes on insulin sensitivity, insulin secretion, and glucose levels are inversely related with basal magnesium level; so, magnesium intake is likely more beneficial among individuals with magnesium deficiency.

However, on the basis that 88.2% of the analyzed studies show a beneficial effect of magnesium intake on glucose metabolism and reduction in the risk of developing T2D, it should be rationale that physicians and dietitians encourage to those individuals in high risk to the consumption of foods with elevated content of magnesium.

Clinical trials

Nonetheless the evidence from epidemiological studies showing the essential role of dietary magnesium intake on insulin-mediated glucose uptake, insulin sensitivity, and markers of chronic inflammation, randomized double blind controlled clinical trials regarding magnesium supplementation are scarce and have yielded inconsistent results.

A total of 12 randomized controlled studies that have enrolled 244 non-diabetic subjects and 345 type 2 diabetic patients have tested the efficacy of oral magnesium supplementation on insulin sensitivity and glucose levels [21, 35-45].

Table 1. Epidemiological studies.

Author	Design	N	Population	Conclusions
Song <i>et al.</i> [9]	Cross-sectional	657	Nurses' Health Study cohort	Magnesium intake from diet is modestly and inversely associated with some but not all markers of systematic inflammation and endothelial dysfunction
Kim <i>et al.</i> [11]	20-y follow-up study	4,497	Non-diabetic Americans	Magnesium intake was inversely associated with incidence of diabetes in young American adults
Kao <i>et al.</i> [16]	6-y follow-up cohort of nondiabetic adults	12,128	Atherosclerosis Risk in Communities Study	Low dietary magnesium intake does not confer risk for type 2 diabetes
Rumawas <i>et al.</i> [17]	Cross-sectional	2,708	Framingham Offspring cohort	Improved insulin sensitivity may be one mechanism by which higher dietary magnesium intake may reduce the risk of developing type 2 diabetes.
Ma <i>et al.</i> [22]	Cross-sectional	15,248	Atherosclerosis Risk in Communities	Low serum and dietary Magnesium may be related to the etiologies of diabetes.
Bo <i>et al.</i> [23]	Lifestyle intervention trial	335	Dysmetabolic adults	Magnesium intake might play an independent role in ameliorating some metabolic, inflammatory, and oxidative markers
Hopping <i>et al.</i> [24]	14-y follow-up Multiethnic Cohort	75,512	Caucasian, Japanese American, and Native Hawaiian	Protection against diabetes can be achieved through food choices.
Shi <i>et al.</i> [25]	Cross-sectional	2,849	General population from Jiangsu Province of China	Magnesium:iron intake ratio is an independent risk marker for diabetes
McKeown <i>et al.</i> [26]	Cross-sectional	535	Elderly adults from USA	Magnesium intake is inversely associated with prevalence of the MS in older adults
Ma <i>et al.</i> [27]	Cross-sectional	1,036	Insulin Resistance Atherosclerosis Study	Magnesium and calcium intake specifically is associated with insulin sensitivity
Lopez-Ridaura <i>et al.</i> [28]	18-y follow-up in women and 12-y in men	127,932	Women and men from US	Significant inverse association between magnesium intake and diabetes risk
He <i>et al.</i> [29]	15-y follow-up study	4,637	Young Americans	Young adults with higher magnesium intake have lower risk of development of metabolic syndrome
Kirii <i>et al.</i> [30]	5-y follow-up study	17,592	Japanese individuals	Dietary intake of magnesium is associated with a reduced risk of type 2 diabetes in Japanese populations
Schulze <i>et al.</i> [31]	Prospective study and Review from 8 cohort studies	25,067	General European population	Higher cereal fiber and magnesium intakes may decrease diabetes risk.
Nanri <i>et al.</i> [32]	5-y Follow-up study	59,791	Japan Public Health Center-based Prospective Study	Although a small effect cannot be excluded in men, magnesium intake may not be appreciably associated with risk of type II diabetes for Japanese adults
King <i>et al.</i> [33]	Cross-sectional	5,007	National Health and Nutrition Examination Survey	Children with intakes below the RDA are more likely to have elevated CRP levels
Song <i>et al.</i> [34]	5-y follow-up study	39,345	Women's Health Study cohort	Protective role of higher intake of magnesium in reducing the risk of developing type 2 diabetes, especially in overweight women

Table 2. Randomized double blind controlled clinical trials.

Author	Magnesium salt	N	Population	Conclusions
Guerrero-Romero <i>et al.</i> [21]	Magnesium Chloride	106	Non-diabetic subjects	Improves insulin secretion for compensates variation in insulin sensitivity
Mooren <i>et al.</i> [35]	Magnesium aspartate	52	normomagnesemic, overweight, insulin resistant, non-diabetic subjects	Improves insulin sensitivity even in normomagnesemic, overweight, non-diabetic subjects
Guerrero-Romero <i>et al.</i> [36]	Magnesium chloride	60	Non-diabetic insulin resistant subjects	Improves insulin sensitivity in hypomagnesemic subjects
Chacko <i>et al.</i> [37]	Magnesium citrate	14	Healthy, overweight individuals	Favorable effects on several metabolic pathways
Paolisso <i>et al.</i> [38]	Magnesium pidolate	12	Elderly non-diabetic subjects	Increase insulin secretion and action. Improves glucose handling
Rodríguez-Morán <i>et al.</i> [39]	Magnesium chloride	63	Type 2 diabetic subjects	Improve insulin sensitivity and metabolic control in patients with decreased serum magnesium levels
Paolisso <i>et al.</i> [40]	Magnesium pidolate	9*	Elderly non-obese type 2 diabetic patients	Improves insulin sensitivity and glucose oxidation
Purvis <i>et al.</i> [41]	Magnesium chloride	28	Type 2 diabetic patients	Little impact on biochemical parameters related to diabetes
de Lordes Lima <i>et al.</i> [42]	Magnesium oxide	128	Type 2 diabetic patients	Prolonged use of magnesium in doses that are higher than usual is needed to improve control
Johnsen <i>et al.</i> [43]	Magnesium oxide	11*	Controlled Type 2 diabetic patients	No effect on diabetic control
de Valk <i>et al.</i> [44]	Magnesium aspartate	50	Type 2 diabetic patients	No effect on glycemic control or plasma lipid concentrations
Gullestad <i>et al.</i> [45]	Magnesium citrate	56	Type 2 diabetic patients	No effects on glucose and insulin

*crossover trials

Five studies (41.7%) [21, 35-38], conducted in non-diabetic subjects, show a beneficial role of magnesium supplementation on insulin sensitivity; of these, one (8.3%) study shows also that magnesium supplementation improves beta-cell function to compensate for variations in insulin sensitivity in non-diabetic individuals with significant hypomagnesemia [21]. These finding suggests that magnesium supplementation plays an important role not only in the improvement of insulin sensitivity but also in the beta-cell function of non-diabetic subjects (*table 2*).

Interestingly, in the study conducted by Paolisso *et al.* [38] it was reported that magnesium supplementation increases insulin secretion and action in elderly subjects. Because, in addition to inadequate nutrient intakes, decreased magnesium absorption, increased urinary magnesium loss,

elevated frequency of chronic illnesses, and/or multiple drug use, magnesium deficiency is more common in older persons than generally suspected [46]. Thus, the finding by Paolisso *et al.* [38], emphasizing the improves of glucose handling in the elderly, is of particular importance in the field. Unfortunately there are not more double blind studies that evaluate the effects of magnesium supplementation in geriatric populations.

Among non-diabetic subjects, magnesium aspartate (1 study), magnesium pidolate (1 study) magnesium citrate (1 study), and magnesium chloride (2 studies) were the magnesium supplements used.

On the other hand, results from 7 (58.3%) randomized double blind controlled clinical trials conducted in T2D subjects [39-45] are controversial with three (25.0%) studies showing that

magnesium supplementation improves insulin sensitivity and glucose metabolic control [39-41] and, three (25.0%) studies showing no effect on glycemic control [43-45]. Results from the last one (8.3%) study conclude that only the prolonged use of magnesium with doses higher than usual is required to improve metabolic control [42] (table 2).

The target population and magnesium salts used in these randomized controlled trials were: magnesium oxide (3 studies), magnesium chloride (2 studies), magnesium citrate (1 study), and magnesium pidolate (1 study). Unfavorable results in type 2 diabetic subjects were documented with the use of magnesium oxide, magnesium aspartate, and magnesium citrate (table 2).

The controversial results in diabetic individuals who received magnesium supplementation could be related with several powerful confounders such as magnesium status of participants, additional magnesium intake in the customary diet, bioavailability of salt used, appropriate statistical power, duration of magnesium supplementation, duration of T2D, and the presence of chronic complications of diabetes, particularly complications affecting renal and intestinal function.

Interestingly, all studies that include non-diabetic individuals consistently show a beneficial effect of magnesium supplementation on glucose levels and insulin sensitivity, finding that could be related with the lower urinary loss of magnesium, that non-diabetic subjects exhibit as compared with type 2 diabetic subjects, who usually exhibited high urinary loss of magnesium, particularly the non-controlled diabetic subjects. This statement strongly suggests that patients with T2D might require higher dose of magnesium than the required by non-diabetic individuals.

Nonetheless that the benefits of chronic administration of magnesium in subjects with T2D is controversial and remains to be adequately evaluated, the routine measure of serum magnesium in diabetic patients and subjects in the high risk groups is recommendable as well as the advice for the intake of foods rich on magnesium, and/or magnesium supplements, particularly in those individuals who show low serum magnesium levels.

Further research based on randomized controlled clinical trials that includes long-term periods of magnesium supplementation and

measurements of urinary magnesium levels is required.

Conclusions

The body of evidence from epidemiological studies consistently shows a strong inverse relationship between dietary magnesium intake and the risk of developing T2D.

Randomized controlled clinical trials that evaluate the benefits of magnesium supplementation on glucose levels in the individuals with T2D are scarce and controversial.

Among non-diabetic subjects, results of randomized controlled clinical trials are scarce but consistently show a beneficial effect of magnesium supplementation on insulin sensitivity and glucose levels.

Disclosure

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