

## Magnesium and type 2 diabetes

Mario Barbagallo, Ligia J Dominguez

Mario Barbagallo, Ligia J Dominguez, Geriatric Unit, Department of Internal Medicine and Medical Specialties, University of Palermo, 90127 Palermo, Italy

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**Correspondence to:** Mario Barbagallo, MD, PhD, Geriatric Unit, Department of Internal Medicine and Medical Specialties, University of Palermo, Via del Vespro 129, 90127 Palermo, Italy. [mario.barbagallo@unipa.it](mailto:mario.barbagallo@unipa.it)  
Telephone: +39-91-6552885  
Fax: +39-91-6552952

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### Abstract

Type 2 diabetes is frequently associated with both extracellular and intracellular magnesium (Mg) deficits. A chronic latent Mg deficit or an overt clinical hypomagnesemia is common in patients with type 2 diabetes, especially in those with poorly controlled glycemic profiles. Insulin

and glucose are important regulators of Mg metabolism. Intracellular Mg plays a key role in regulating insulin action, insulin-mediated-glucose-uptake and vascular tone. Reduced intracellular Mg concentrations result in a defective tyrosine-kinase activity, postreceptorial impairment in insulin action and worsening of insulin resistance in diabetic patients. A low Mg intake and an increased Mg urinary loss appear the most important mechanisms that may favor Mg depletion in patients with type 2 diabetes. Low dietary Mg intake has been related to the development of type 2 diabetes and metabolic syndrome. Benefits of Mg supplementation on metabolic profiles in diabetic patients have been found in most, but not all clinical studies and larger prospective studies are needed to support the potential role of dietary Mg supplementation as a possible public health strategy in diabetes risk. The aim of this review is to revise current evidence on the mechanisms of Mg deficiency in diabetes and on the possible role of Mg supplementation in the prevention and management of the disease.

**Key words:** Magnesium; Type 2 diabetes; Metabolic syndrome; Inflammation; Aging; Hypertension; Insulin resistance; Endothelium

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**Core tip:** Diabetes is frequently associated with Mg deficit. The fact that most but not all diabetic subjects have low magnesium (Mg) and that no large randomised controlled trial (RCT) has been specifically focused on subjects with Mg deficit, diagnosed with a reliable technique, may help explain discrepancies of the role of supplemental Mg on glycemic control, and the impact on diabetes risk in prospective epidemiological studies. Different baseline Mg, metabolic control, and age are other potential factors that may contribute. Future prospective RCTs are needed to support the potential role of dietary Mg supplementation as a possible public health strategy to reduce diabetes risk in the population.

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## INTRODUCTION

Magnesium (Mg) is an electrolyte of chief physiological importance in the body, being the *most abundant* divalent intracellular cation in the cells, the second most abundant cellular ion next to potassium and the fourth cation in general in the human body<sup>[1]</sup>.

Type 2 diabetes mellitus (DM2) is often accompanied by alteration of Mg status. An increased prevalence of Mg deficits have been identified in DM2 patients, especially in those with poorly controlled glycemic profiles, with longer duration of the disease and with the presence of micro- and macrovascular chronic complications<sup>[2-6]</sup>.

Laboratory tests with a high sensitivity and specificity and easy to perform to allow an accurate clinical assessment of Mg status are missing. Patients are considered frankly hypomagnesemic with serum Mg concentrations  $\leq 0.61$  mmol/L or 1.5 mg/dL<sup>[7-9]</sup>. Mg concentrations  $\leq 0.75$  mmol/L or 1.8 mg/dL may be considered as preclinical hypomagnesemia<sup>[10,11]</sup>.

Mg deficiency can be present without hypomagnesemia. However, hypomagnesemia, when present, is usually indicative of an important systemic Mg deficit. A depletion in intracellular and/or ionized plasma Mg can be found in individuals with normal total serum Mg<sup>[12]</sup>. However, most of the studies in the literature have measured total serum Mg instead of the free, ionized (bioactive) or the intracellular Mg concentrations, which make it a challenge to correlate Mg deficits to diseases.

We have recently confirmed that diabetic older patients are more prone to hypomagnesemia; this condition being closely related to metabolic control as measured by glycated hemoglobin even after adjustment for relevant confounders. Ionized Mg may help to identify diabetic older adults with low concentrations of blood Mg that are not evident with the only measurement of total Mg<sup>[12]</sup>.

Intracellular free Mg levels are consistently reduced in subjects with DM2, when compared with nondiabetic subjects<sup>[1,13,14]</sup>. Although the mechanism has not been fully elucidated, an alteration in the mechanism(s) of the Mg uptake in the cells, and/or a deficit of ATP, may help to understand the cellular Mg deficit observed in DM2<sup>[15]</sup>. The relationship between intracellular Mg and ATP concentration is rather complex. The decrease in cellular ATP might partially explain the decrease in cellular Mg. Otherwise, a decrease in cellular ATP leads to a decreased binding of Mg to ATP in the formation of MgATP, which might increase the intracellular Mg concentration.

The aim of this review is to revise current evidence

on the mechanisms of Mg deficiency in DM2. The evidence on the role of Mg supplementation in the management of DM2 will also be discussed.

## MECHANISMS OF MG DEFICIENCY IN DM2

Reduced Mg intake and/or augmented Mg urinary loss are among the most important causes of Mg deficits in DM2, while Mg absorption and retention seems to be maintained<sup>[16-18]</sup>.

A relationship between Mg levels in the plasma and the development of DM2 in the general population has been suggested<sup>[19]</sup>. DM2 is frequently accompanied by renal calcium and Mg loss<sup>[20,21]</sup>, but the mechanism(s) of this wasting is still not completely elucidated<sup>[22]</sup>.

Both hyperglycemia and hyperinsulinemia may increase urinary Mg excretion. Urinary Mg excretion and fasting blood glucose have been found to be inversely related to serum Mg levels. Thus, hyperglycemia decreases Mg tubular reabsorption<sup>[20]</sup>. A good metabolic control is associated with a reduction of the urinary Mg wasting<sup>[3]</sup>.

In streptozotocin-induced diabetic rats, Lee *et al.*<sup>[22]</sup> found an increase in renal Mg transporters. The alteration was corrected by insulin administration. Insulin resistance and hyperinsulinemia may also affect Mg transport<sup>[21]</sup>.

## MG AND INSULIN SENSITIVITY

Hypomagnesemia in DM2 is present only in severe (and generally long lasting) Mg deficits. A chronic latent Mg deficiency without alteration in serum total Mg is more commonly observed<sup>[12]</sup>. These often undetected Mg insufficiencies have clinical importance, since Mg is a main co-factor in numerous enzymatic reactions (> 300 enzymatic reactions including all the enzymes of glycolysis). Mg also is deeply involved in the regulation of insulin signaling, in the phosphorylation of insulin receptor kinase, in the post-receptorial action of insulin, and in insulin-mediated cellular glucose uptake<sup>[17,23]</sup>.

The clinical consequence of a chronic Mg deficit is post-receptorial insulin resistance and consequent reduced glucose utilization in the cells, worsening the reduced insulin sensitivity present in DM2<sup>[18]</sup>.

Another possible link between Mg deficiency and reduced insulin sensitivity is the presence of oxidative stress and/or inflammation. Thus, free radicals are often increased in DM2, hypertension, metabolic syndrome and aging, conditions also associated with Mg deficits<sup>[24,25]</sup>. In particular, we demonstrated an age-dependent deficit of cellular Mg in persons aged 65 years and over, as well as in patients with essential hypertension or DM2, independently of age<sup>[14,25]</sup>.

Nevertheless, independently of the mechanisms of Mg deficits in DM2, metabolic syndrome, essential

hypertension and aging, it is apparent that this Mg deficiency may contribute to enhance the insulin resistance status of these conditions<sup>[17,18]</sup>. Mg deficit could precede and cause post-receptorial resistance of insulin and alter glucose tolerance.

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## MG DEFICIENCY AND CARDIO-METABOLIC DISEASES

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Mg deficiency may be also a factor implicated in DM2 complications. We found a relation between ionic changes and echocardiographic indices alterations<sup>[26]</sup>. We observed an significant association of reduced cellular Mg with cardiac hypertrophy in DM2 patients<sup>[26]</sup>.

Cellular Mg measured *in vivo* in skeletal muscle and in the brain with <sup>31</sup>P-NMR, was directly related to aortic distensibility<sup>[27]</sup>.

Reduced Mg levels were also associated with an increased prevalence of arrhythmias in DM2 obese subjects<sup>[6]</sup>, and with a more rapid decline of renal function. Thus, hypomagnesemia is currently considered an accurate predictor of progression of diabetic nephropathy<sup>[28-30]</sup>. Mg deficits have also been associated with cognitive decline<sup>[31]</sup>, multimorbidity<sup>[32]</sup> and aging<sup>[25,33]</sup>.

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## DIETARY MG DEFICIENCY MAY PREDISPOSE TO DM2

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Dietary Mg deficiency may cause insulin resistance as shown by several studies both in humans and in experimental animals<sup>[34-40]</sup>. In sheep, Mg-deficient diet caused a significant impairment of insulin-mediated glucose uptake<sup>[35]</sup>. In rats, Mg supplements were able to postpone the onset of diabetes<sup>[36]</sup>. In healthy women (without DM2), the higher was the intake of Mg, the lower were fasting levels of insulin<sup>[37]</sup>. In young, nondiabetic African Americans, low dietary Mg was associated with insulin resistance and insulin responses to an oral glucose tolerance test<sup>[38]</sup>. A low Mg diet in rats produced an increase in triglyceride and plasma glucose levels<sup>[39]</sup>. In rats, a maternal restriction of dietary Mg was able to cause insulin resistance in pups<sup>[40]</sup>. Suárez *et al.*<sup>[41]</sup> suggested that the worsening of glucose metabolism induced by Mg dietary restriction in experimental rats is due to an impairment of both, insulin secretion and insulin action.

Deficiencies of Mg status including both hypomagnesemia and/or reduced dietary Mg intake have been linked to an enhanced risk to develop DM2 or glucose intolerance<sup>[19,42-44]</sup>. Higher Mg intakes were conversely associated with a reduced incidence of DM2<sup>[45]</sup>.

Several studies have shown a clear association of Mg intake with DM2 and with cardio-metabolic syndrome, suggesting that a higher Mg consumption is related to a reduction of the incidence of these conditions. Two meta-analyses of prospective studies concluded that Mg intake is inversely associated with the onset of DM2<sup>[46,47]</sup>. In addition, the development of the cardio-metabolic

syndrome has been linked to dietary Mg content<sup>[34,48]</sup>. Hypomagnesemia itself in a 10-year follow-up study was associated with glucose tolerance impairment<sup>[49]</sup>. Conversely, higher Mg intake was associated with increased insulin sensitivity<sup>[50]</sup> and with decreased risk of incident DM2, with a decreased risk of 0.68 in the higher compared with the lower quintiles<sup>[51,52]</sup>.

Similar findings were obtained in the CARDIA study, during a 20-year follow-up, which also confirmed the reverse relationship of dietary Mg with inflammation markers<sup>[53]</sup>.

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## POSSIBLE USE OF MG SUPPLEMENTS IN THE MANAGEMENT OF DM2

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The detection and correction of altered Mg status in diabetic patients is clinically appropriate, although many physicians tend to ignore Mg status. The increased risk of developing impaired glucose tolerance and/or frank DM2 in persons with dietary or serum Mg deficits have suggested a potential benefit of Mg supplements in patients with DM2 or in the presence of risk factors for DM2. Mg supplements have been proposed as a complementary tool for the prevention of DM2 and its metabolic control<sup>[54,55]</sup>. Some benefits of Mg supplements on glycemic profiles have been found in most but not all studies.

Regrettably, results from clinical trials are still limited<sup>[56]</sup>. Thus, the clinical evidence of a clear effect of Mg supplementation on metabolic indices in persons with DM2 are controversial. Some benefit has been found in several<sup>[8,54,57,58]</sup>, but not in all clinical studies<sup>[59]</sup>. The hypothesis of a role of supplemental Mg in the control of DM2 still needs to be ascertained by large randomized clinical trials<sup>[60,61]</sup>. Mg supplementation may improve glycemic concentrations in fasting and postprandial states, and insulin sensitivity. We found a significant relationship between the increase in serum and cellular Mg and insulin sensitivity<sup>[62]</sup>. We also showed that Mg supplementation is able to improve an altered endothelial function in DM2 older adults<sup>[63]</sup>. Barragán-Rodríguez *et al.*<sup>[64]</sup> suggested a positive effect in the treatment of depression in older persons with DM2 and hypomagnesemia. Presumably, the main problem is that all RCTs were underpowered, partially through overestimation of the treatment effect. Differences may be related to the fact that most of the existing studies have included a small number of subjects, using different Mg doses and different Mg salts.

Several studies have linked high Mg content present in fiber with the positive action of whole grains to improve insulin sensitivity<sup>[65-68]</sup>. Oral Mg supplements have been shown to improve fasting and postprandial glucose levels and insulin sensitivity in hypomagnesemic DM2 patients<sup>[57]</sup>, to improve insulin sensitivity in non-diabetic subjects with insulin resistance<sup>[8]</sup>, and to decrease C-reactive protein levels in hypomagnesemic patients with prediabetes<sup>[69]</sup>.

In summary, oral Mg supplements appear to be useful in persons with DM2 to restore Mg deficiencies, to improve insulin resistance, oxidative stress, and systemic inflammation.

The absence of large trials in DM2 patients specifically focusing on those with Mg deficit may help to explain the inconsistency between epidemiological (mainly positive) and clinical (mostly controversial) studies. Since most, but not all, DM2 patients have Mg deficiency, it would be useful to focus on those with deficit in order to correct it. Differences in Mg balance, glycemic control, and age are other potential factors that may help to explain the differences among the studies. Most studies used total serum Mg concentration instead of the free, ionized (bioactive) Mg concentration, which make it a challenge to correlate Mg deficiency to diseases.

Future prospective large RCTs would be important to support the possible inclusion of Mg supplements in the guidelines for the management of DM2.

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