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Magnesium and Type 2 Diabetes: An Update

Mario Barbagallo* and Ligia J. Dominguez

Geriatric Unit, Department of Internal Medicine and Medical Specialties (DIMIS), University of Palermo, Italy

***Corresponding author:** *Mario Barbagallo, MD, PhD, Geriatric Unit, Department of Internal Medicine and Medical Specialties (DIMIS), University of Palermo, Via del Vespro 129, 90127 Palermo, Italy, Tel: 0039-091-6552885, Fax: 0039-091-6552952, E-mail: mario.barbagallo@unipa.it*

Abstract

The link between magnesium (Mg) deficiency and type 2 diabetes mellitus is well known. Type 2 diabetes is frequently associated with both extracellular and intracellular Mg deficits. A chronic latent Mg deficit or an overt clinical hypomagnesaemia is common in subjects 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 profile in diabetic subjects 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 objective of this review is to revise current evidences on the mechanisms of Mg deficiency in diabetes mellitus type 2 and on the possible role of Mg supplementation in the prevention and management of the disease.

Keywords

Magnesium, Diabetes, Metabolic syndrome, Hypertension, Insulin resistance, Inflammation, Aging, Endothelium, Hypomagnesaemia, Metabolism

Introduction

Magnesium (Mg) is the fourth most abundant mineral present in the human body and the second intracellular cation in living cells after potassium. Most Mg located in the human adult's body is distributed in the intracellular compartment (99%), and only 1% in the extracellular fluid [1]. The link between Mg deficiency and type 2 diabetes mellitus is well known. Type 2 diabetes is frequently associated with both extracellular and intracellular Mg depletion. Several epidemiologic studies have recognized a high prevalence of hypomagnesaemia in subjects with type 2 diabetes, especially in those with poorly controlled glycemic profiles, with longer duration of the disease and with the presence of micro-macrovascular chronic complications [2-6].

The definition of Mg deficiency seems simpler than it is, primarily because accurate clinical tests for the assessment of Mg status are lacking. Patients are considered frank hypomagnesaemic with serum Mg concentrations ≤0.61mmol/L or 1.5mg/dL [7-9]. Mg concentrations ≤0.75mmol/L or 1.8mg/dL may be considered a preclinical hypomagnesaemia [10,11].

Because of the lack of sensitivity of total serum Mg, a Mg deficiency can be present without hypomagnesaemia. However, hypomagnesaemia is usually indicative of a systemic Mg deficit. Depletion in intracellular and serum ionized Mg can be found in many subjects with total serum Mg still in the normal range [12]. We have recently confirmed that diabetic older patients are more prone to hypomagnesaemia; this condition being closely related with metabolic control as measured by glycated hemoglobin even after adjustment for relevant confounders. Ionized Mg may help to identify older diabetic adults with low concentrations of blood Mg that are not evident with the only measurement of total Mg [12].

At the cellular level, cytosolic free Mg levels are consistently reduced in subjects with type 2 diabetes mellitus, when compared with nondiabetic subjects [1,13,14]. An impairment of cellular Mg uptake mechanism, and a the decrease in the cellular ATP level, may contribute, at least in part, to explain the decrease in cellular Mg content observed under diabetic conditions [15]. The relationship between intra-cellular 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 objective of this review is to revise current evidences on the mechanisms of Mg deficiency in diabetes mellitus type 2 and on the possible role of Mg supplementation in the prevention and management of the disease.

Mechanisms of Mg Deficiency in Diabetes

A low Mg intake and an increased Mg urinary loss appears the most important mechanisms that may favor Mg depletion in patients

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with type 2 diabetes, while Mg absorption and retention of dietary Mg seems not to be impaired in patients with type 2 diabetes [1,16,17]. With regard to low Mg intake, changes in dietary habits in the western world have resulted in daily Mg intake close to, or even below, the recommended daily allowances. The ARIC study demonstrated a relationship between serum Mg and the development of diabetes in the general population [18]. Diabetes is associated with renal calcium and Mg wasting [19-21], but the molecular mechanism(s) of these defects are not completely elucidated [22]. Recent findings in obese diabetic rats found that TRPM6 was down regulated explaining renal Mg wasting [23]. The findings from Mandon, showing a insulin-induced Mg uptake in the thick ascending loop of Henle may also have a role [24], since hyperinsulinemia and insulin resistance may lead to a decreased Mg uptake, and an increase Mg excretion. Hyperglycemia also contributes to an increased urinary Mg wasting contributing to Mg depletion. Plasma Mg levels were found inversely correlated with the urinary Mg excretion rate and with fasting blood glucose values, suggesting that the tubular reabsorption of Mg is decreased in presence of severe hyperglycemia [19].

An increased renal Mg transporter abundance was found in diabetic rats and may represent a compensatory adaptation for the increased load of Mg to the distal tubule. Insulin administration completely corrected the hyperglycemia-associated hypercalciuria and hypermagnesiuria, and reversed the increase of Mg transporter abundance [22]. An improved metabolic control was associated with reduced urinary Mg losses [3]. Hyperinsulinemia, which is present in insulin resistant states, may contribute *per se* to the urinary Mg depletion, to the reduced sensitivity to insulin, and may itself affect Mg transport [20]. Djurhuus in healthy volunteers with hyperinsulinemia suggested that in these people is different from hyperinsulinemia in people with prediabetes, metabolic syndrome [20,25].

In addition other factors like metabolic acidosis or hypoalbuminemia also seem to affect renal Mg wasting in diabetes [21]. The use of loop and thiazide diuretics, often prescribed in diabetic patients with hypertension and/or cardiovascular diseases, also promote Mg wasting.

Mg Deficiency and Insulin Resistance

Mg deficiency in type 2 diabetes may take the form of a chronic latent Mg deficit rather than an overt clinical hypomagnesaemia [12], and may have clinical importance because the Mg ion is a crucial cofactor for many enzymatic reactions involved in a myriad of metabolic processes. The Mg ion plays a key role in the regulation of the effects of insulin and insulin-mediated cellular glucose intake. Mg is a necessary co-factor in >300 enzymatic reactions that include all the enzymes determinant of glycolysis. Intracellular Mg is a critical cofactor for enzymes involved in carbohydrate metabolism, and specifically in the process of phosphorylation of the tyrosine-kinase of the insulin receptor as well as all other protein kinases in the insulin signaling, and all ATP and phosphate transfer-associated enzymes, such as the CaATPases in the plasma membrane and the endoplasmic reticulum [1,26].

Mg deficiency may result in disorders of tyrosine kinase activity of the insulin receptor, event related to the development of post-receptorial insulin resistance and decreased cellular glucose utilization, that is, the lower the basal Mg, the greater the amount of insulin required to metabolize the same glucose load, indicating a decreased insulin sensitivity [17]. Cellular concentrations of Mg are in the 100-300nmol/L range, which is close to the dissociation constant of many enzymes systems using ATP or phosphate transference, confirming the clinical importance of Mg deficiency. A deficient Mg status may be a secondary consequence or may precede and cause insulin resistance and altered glucose tolerance, and even diabetes. Inflammation and oxidative stress have been proposed to be a possible link between Mg deficit and insulin resistance/metabolic syndrome. Chronic hypomagnesaemia and conditions commonly associated with Mg deficiency, such as type 2 diabetes mellitus, metabolic syndrome and aging, are associated with increased free radical formation and subsequent damage to cellular processes [27,28]. Aging is frequently associated with insulin resistance and glucose intolerance. A continuous age-dependent fall of intracellular Mg levels in peripheral blood cells of healthy elderly subjects is present, these alterations being indistinguishable from those occurring, independently of age, in essential hypertension or type 2 diabetes [14,28].

The relevance of altered cellular Mg metabolism to tissutal insulin sensitivity suggest a possible role of Mg in contributing to the clinical coincidence of Mg depletion to clinical conditions of insulin resistance such as hypertension, metabolic syndrome, type 2 diabetes as well with the increased incidence of each of these conditions with age, a condition itself characterized by a tendency to Mg depletion [17].

Altogether, independent to the cause of poor plasma and intracellular Mg content, a depletion of Mg seems to contribute to an impairment of insulin sensitivity. A deficient Mg status may not just be a secondary consequence of type 2 diabetes but may precedes and contributes itself to the development of insulin resistance and altered glucose tolerance, and even type 2 diabetes. We have suggested a role for Mg deficit as a possible unifying mechanism of conditions associated to "insulin resistance, including type 2 diabetes mellitus, metabolic syndrome, and essential hypertension [1,17]. The Mg deficit could precede and cause post-receptorial resistance of insulin and alter the glucose tolerance.

Mg Deficiency and Cardio-Metabolic Diseases

It has been suggested that Mg deficiency may be a factor implicated in the pathogenesis of diabetes complications. Cellular ionic alterations are related to the cardiovascular structural modifications often present in diabetes. A significant relation was found between fasting levels of intracellular Mg levels and cardiovascular structural indices [29]. In type 2 diabetic subjects, even in the absence of elevated blood pressure, suppressed intracellular Mg levels are associated with cardiac hypertrophy, and specifically with increased echocardiographically measured posterior wall thickness and left ventricular mass index in both diabetic and/or hypertensive subjects [29]. Similarly, aortic distensibility values determined by magnetic resonance imaging in normal and hypertensive humans were closely and positively related to concomitantly measured levels of cellular Mg measured *in situ* in brain and skeletal muscle tissue by ^{31}P-NMR magnetic resonance spectroscopic techniques: the more suppressed the intracellular Mg, the stiffer (less distensible) the aorta [30]. Low serum Mg concentrations are associated with a high prevalence of premature ventricular complexes in obese adults with type 2 diabetes [6]. In patients with type 2 diabetes mellitus, low circulating Mg levels have been associated also with a more rapid decline of renal function. Hypomagnesaemia is currently considered an accurate predictor of progression to end stage renal disease and death and in patients with type 2 diabetic nephropathy [31-33]. A Mg deficit have been associated to cognitive decline [34], multimorbidity [35] and aging [28,36].

Dietary Mg Deficiency May Predispose to Insulin resistance and Type 2 Diabetes Mellitus

The hypothesis that Mg deficit in the diet would induce and/or exacerbate insulin resistance is confirmed by data, both in humans and in experimental animals, which have consistently shown dietary Mg deficiency is associated to insulin resistance [37-43]. Mg-deficient diet in sheep cause a significant impairment of insulin-mediated glucose uptake [38] and Mg supplementation delayed the development of diabetes in a rat model of diabetes [39]. Higher Mg intake is associated with lower fasting insulin concentrations among women without diabetes [40], and a significant negative correlation is present between total dietary Mg intake and the insulin responses to an oral glucose tolerance test [41]. Rats fed a low Mg diet showed a significant increase in blood glucose and triglyceride levels [42]. Suarez et al. investigated the effect of dietary-induced Mg deficiency

on glucose disposal, glucose-stimulated insulin secretion and insulin action on skeletal muscle in rats, which were fed a low Mg-containing diet. Mg depletion provoked a deleterious effect on glucose metabolism due to an impairment of both insulin secretion and action. In rats, maternal Mg restriction induces insulin resistance in pups by 6 months of age, whereas additional perinatal Mg deficiency impairs glucose tolerance [43]. The insulin resistance observed in skeletal muscle of Mg-deficient rats was linked, at least in part, to a defective tyrosine kinase activity of insulin receptors [44].

Dietary Mg deficits have also been associated to the development of diabetes. Deficiencies of Mg status including both hypomagnesaemia and/or reduced dietary Mg intake have been associated with an increased risk to develop glucose intolerance and diabetes [18,45-47] while an increased Mg intake is associated with a significant decline in the incidence of type 2 diabetes [48].

Various epidemiological studies have confirmed a clear and direct relationship between the Mg status in the diet, type 2 diabetes and metabolic syndrome, suggesting that the higher consumption of Mg is related with a reduction of the incidence of these conditions. Two meta-analyses of prospective studies concluded that Mg intake is inversely associated with type 2 diabetes [49,50]. Mg intake has been also strongly and inversely associated with the metabolic syndrome [37,51], while hypomagnesaemia has been independently associated with the development of impaired glucose tolerance [52]. Increased Mg intake is associated with increased insulin sensitivity [53] and a decreased risk of developing type 2 diabetes [54,55]. In a prospective study of more than 85,000 women, followed for 18 months the relative risk of developing type 2 diabetes for women in the highest quintile of Mg consumption was 0.68 compared with women in the lowest quintile after adjustment for a number of potentially confounding variables. A significant inverse association was found between Mg intake and diabetes risk [55]. In the Women's Health Study, a cohort of 39,345 U.S. women aged ≥45 years with no previous history of cardiovascular disease, cancer, or type 2 diabetes was recruited and followed for an average of 6 years. A significant inverse association was found between Mg intake and the risk of developing type 2 diabetes, supporting a protective role of higher intake of Mg in reducing the risk of developing type 2 diabetes [54].

In a large cohort of young American adults, participating in the Coronary Artery Risk Development in Young Adults (CARDIA) study, during the 20-year follow-up, Mg intake was inversely longitudinally associated with the incidence of diabetes in this young American population, after adjustment for potential confounders. This inverse association may be explained, at least in part, by the inverse correlations of Mg intake with systemic inflammation and insulin resistance [56].

Hypomagnesemia has been associated with inflammation and increased production of free oxygen radicals [57,58]. Poor Mg status may trigger the development of a proinflammatory state both by causing excessive production and release of interleukins and by elevating circulating concentrations of proinflammatory neuropeptides that trigger activation of low-grade chronic inflammation [28,59]. Thus, dietary-induced Mg deficiency increases thromboxane urinary concentration and enhances angiotensin-induced aldosterone synthesis. These effects are associated with a decrease in insulin action, further confirming that Mg deficiency may be a common factor associated with insulin resistance and vascular disease [60].

Mg Supplementation in the Prevention and Management of Diabetes

The detection and correction of altered Mg status in diabetic patients is clinically appropriate, although many physicians tend to ignore Mg status. The increased risks to develop glucose intolerance and type 2 diabetes mellitus in subjects with dietary and/or serum Mg deficits have suggested potential benefits of Mg supplementation in persons who have type 2 diabetes or risk factors for diabetes. The use of Mg supplements has also been proposed as a potential tool for the prevention and the metabolic control of type 2 diabetes [61,62].

Benefits of Mg supplements on glycemic profile in most but not all studies explain whether according to meta-analysis a net beneficial effect is to be expected. The clinical evidences of a clear effects of Mg supplements on the metabolic profile of diabetic subjects are controversial, benefits having been found in many [8,61,63,64], but not in all clinical studies [65].

While the body of evidence from epidemiological studies consistently shows a strong inverse relationship between dietary Mg intake and the risk of developing type 2 diabetes mellitus, results from clinical trials are scarce and controversial [66]. Still, the risk of residual confounding factors in these kinds of analyses deserves to be taken into consideration. The hypothesis of a role of supplemental Mg in the control of type 2 diabetes still needs to be confirmed by specific and well-designed large randomized clinical trials with Mg [67,68].

Mg supplementation may improve glycemic concentrations in fasting and postprandial states and improves the insulin-mediated glucose uptake measured by euglycemic insulin clamp, with a significant relationship between the parallel increase in plasma and erythrocyte Mg concentration and the progressive increase in insulin sensitivity [69]. Mg supplementation was also able to restore altered endothelial function in elderly diabetic subjects [70], and was suggested to be useful in the treatment of depression in the elderly with type 2 diabetes and hypomagnesaemia [71].

Mooren et al. in normomagnesemic insulin resistant subjects, Mg improved fasting glycemia [72]. Presumably, the main problem is that all RCT 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.

The available studies have shown that Mg may mediate the favorable impact of whole grains on insulin sensitivity cereal on insulin sensitivity [73-76]. A recent clinical randomized double-blind placebo-controlled trial has shown that oral Mg supplementation decreases C-reactive protein levels in subjects with prediabetes and frank hypomagnesaemia [77]. In type 2 diabetic patients with clinical hypomagnesaemia (index of an already advanced Mg deficit) oral Mg supplementation had beneficial effects on fasting and postprandial glucose levels and on insulin sensitivity [63]. A small but significant beneficial effect of Mg supplements on insulin sensitivity among non-diabetic, apparently healthy subjects was suggested [8]. Altogether, Mg supplementation in diabetic patients (with frank Mg deficiency) corrects the deficit in intracellular free Mg levels, improves insulin sensitivity, and may protect against diabetic complications. The positive effects of a high intake of Mg on systemic inflammation and insulin resistance may help to explain at least some of its favorable effects.

We suggest that fact that most but not all diabetic subjects have a Mg deficiency and that no large clinical trial have been specifically focused on subjects with a Mg deficit, diagnosed with an accurate and reliable technique, may help to explain the discrepancy between the unclear role of supplemental Mg on glycemic control in diabetics, and the significant impact on diabetes risk in prospective epidemiologic studies.

Differences in baseline Mg status and metabolic control, and age of the subjects are other potential factors that may help to explain the differences among the studies. Future prospective randomized large clinical studies 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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