RELATION BETWEEN DIABETES MELLITUS AND MAGNESIUM: REVIEW ARTICLE

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Abstract:

The magnesium deficiency has been associated with chronic diseases, amongst them, diabetes mellitus. Epidemiological studies had shown low levels of magnesium ingestion in the general population, as well as a relation between the ingestion of food rich in magnesium and the reduction of diabetes installation and its complications. Hypomagnesemia is frequently present in diabetic patients, however there is not an exact elucidation of the mechanism of magnesium deficiency in diabetes mellitus. On the other hand, in the presence of this illness, it is observed that inadequate metabolic control can affect the corporal concentrations of magnesium, developing hypomagnesemia, which may be still directly related with some micro and macrovascular complications observed in diabetes, as cardiovascular disease, retinopathy and neuropathy. This way, the chronic complications of diabetes can appear precociously. Based on this, the supplementation with magnesium has been suggested in patients with diabetes mellitus who have proven hypomagnesemia and the presence of its complications.

Keywords: DM, MG, Complications.

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Introduction:

As a result of alterations in dietary practices, it has been noted over time that populations globally are consuming less micronutrients. Magnesium (Mg) is one of the most abundant intracellular ions with an essential role in fundamental biological reactions, whose deficiency provokes biochemical and symptomatic alterations in the human organism ***(1)***.

Diabetes mellitus (DM), characterized by metabolic disorders related to high levels of serum glucose, is probably the most associated disease to Mg depletion in intra and extra cellular compartments. Hypomagnesemia has been related as a cause of insulin resistance, also being a consequence of hyperglycemia, and when it is chronic leads to the installation of macro and microvascular complications of diabetes, worsening the deficiency of Mg ***(2)***.

Although certain metabolic investigations show that Mg supplementation has a positive impact on the action of insulin and in the glucose metabolism, the mechanism involving the DM and hypomagnesemia is still unknown ***(3)***.

Mg is the second predominant component in the intracellular compartment, an important regulator of the cellular processes, co-factor of more than 300 essential metabolic reactions, including the ones that produce or use the MgATP complex. However, its functionality is related to the synthesis of tissue constituents, growth, and thermogenesis, and with the activity of tyrosine kinase, in the metabolism of glucose ***(4)***.

The homeostasis of Mg depends on the amount of ingestion, the efficiency of absorption and of the intestinal and renal excretion. The absorption of this mineral occurs along the whole intestinal tract, especially in the ileum and colon, and its regulation is made mainly by the kidney. The homeostatic regulation of Mg is increased by the action of parathormone (PTH), calcitonin, vitamin D, glucagon, antidiuretic hormone, aldosterone, and sexual steroids. Beyond these, insulin is involved in the transport of Mg through the cellular membrane and in the intracellular supply ***(5)***.

The average ingestion of Mg, at a world-wide level, has diminished over the years, being frequently below the Recommended Dietary Allowances—RDA, this induces the development of Mg deficiency. However, the specific clinical manifestations of hypomagnesemia are difficult to be diagnosed, due to the frequent associations of this deficiency with biochemical abnormalities as hypokalemia, hypocalcemia, and metabolic alkalosis ***(6)***.

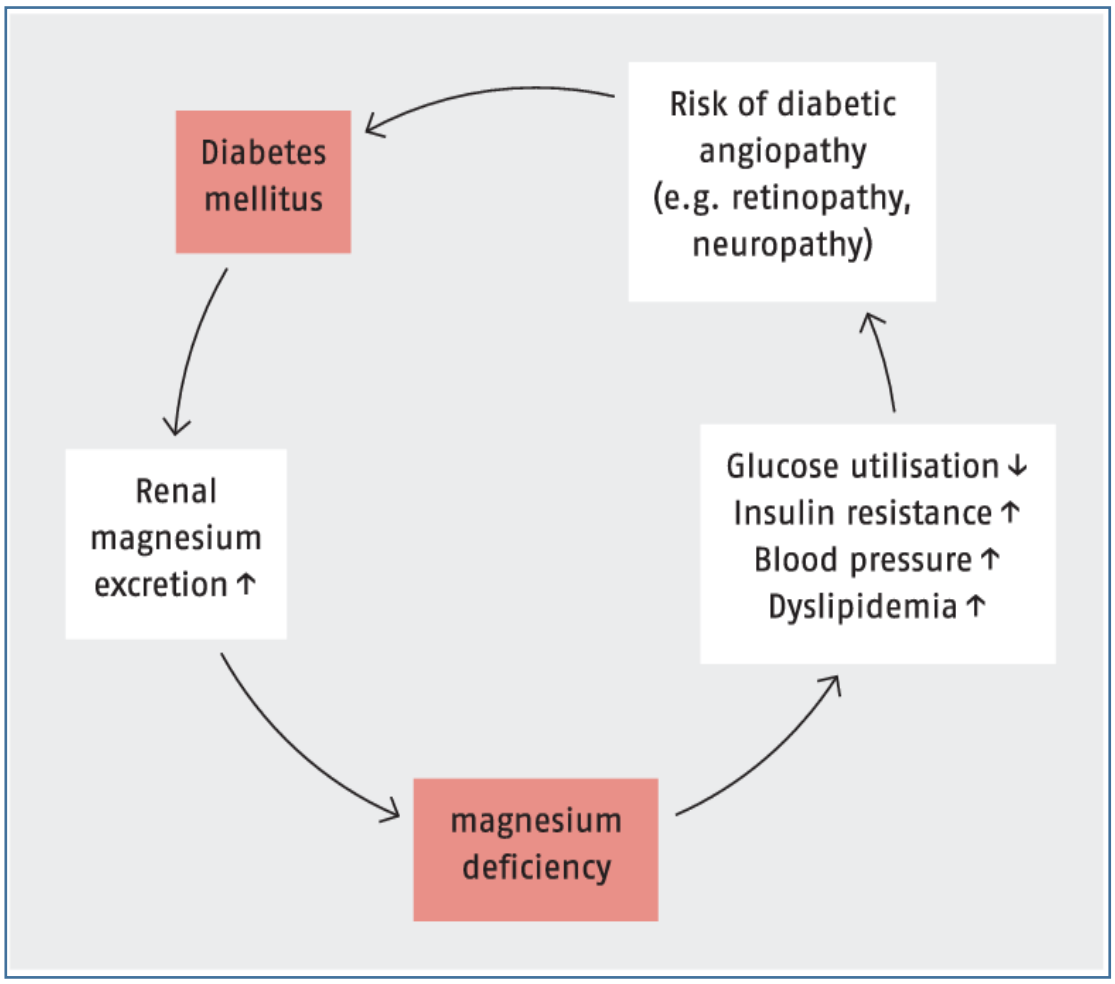

Figure (1): Magnesium deficiency and diabetes ***(7).***

Patients with hypomagnesemia can present cardiovascular alterations, such as ischemic cardiac insufficiency, vascular complications of DM and hypertension. Neurological, hormonal, renal, gastrointestinal, and muscular dysfunction also have been associated to hypomagnesemia ***(3).***

There were speculations about a possible relation between Mg deficiency and climatic variations, contributing to the increase of heart deaths and diabetes. High temperatures would increase sweat losses and, consequently, among the minerals, Mg would be the most affected, because the losses would not be compensated by the diet and water intake, increasing the risk for these diseases ***(2).***

Diabetes and dietary ingestion of magnesium:

The alimentary source of Mg includes the milky products, whole grains, most of the green leafy vegetables, nuts, seeds, meats, poultries, fishes, dry beans, peas, lentils, and products derived from soy. The Dietary Reference Intakes (DRIs) for Mg varies according to the gender, physiological state, and life stage. However, it is important to stand out that these recommendations are for healthy individuals ***(4).***

Several studies showed a significant reduction in the relative risk of diabetes, in women with increased intake of whole grains and other food sources of Mg. Other studies notified a reduction of the metabolic risk factors for the development of diabetes, associated to the whole grain's intake, still demonstrating an inverse association in these grains' consumption and fasting insulin ***(8).***

Other cohort studies carried out with men and women, had also verified an inverse association involving the Mg intake and the risk of type 2 DM; however, in the Women's Health Study, only the women with Body Mass Index (BMI) over 25 kg/m2 had demonstrated this association. A positive correlation between insulin sensitivity and the Mg intake has been detected, suggesting that the Mg can delay the development of type 2 DM ***(3).***

Magnesium and diabetes mellitus:

DM is a metabolic disease of multiple etiology, characterized by hyperglycemia resulting from defects in the insulin secretion and/or the insulin action. According to the American Diabetes Association—ADA, this syndrome is classified as:

- Type 1 DM—characterized by the b-cells destruction, usually leading to absolute insulin deficiency, can be of auto-immune or idiopathic nature.
- Type 2 DM—ranging from predominantly of insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance.
- Gestational DM—the most common clinical disturbance that affects pregnancy, characterized by glucose intolerance, which onset or first recognition during pregnancy.
- Other specific types of diabetes as: iatrogenic, specific genetic defects of pancreatic b-cells or insulin action, exocrine diseases of the pancreas, endocrinopathies, induction by drugs or chemical reagents, infectious, uncommon forms of auto-immune diabetes, and other genetic syndromes associated as, for example, Down syndrome ***(9)***

Hypomagnesemia in diabetics is usually observed in patients with deficient metabolic control, or associated with the DM chronic complications, according to clinical and epidemiological studies. The responsible mechanisms for Mg deficiency in patients with diabetes have still not been clarified, mainly about the impact in the insulin resistance, in the development of diabetes and its chronic complications. It is speculated as triggering factors the increase urinary excretion of Mg, especially in patients with unsatisfactory metabolic control, dietary deficiency, or absorption reduction ***(6).***

The scientific evidence indicates the role of calcium and Mg as mediators of the insulin action. In the DM occur chronic alterations of homeostasis of Mg intracellular, unchained by the unbalance between calcium and Mg. The effects result in damage to the tyrosine kinase activity, in level of receptors unchaining the outlying insulin resistance ***(5).***

Other studies had demonstrated positive effect in the administration of insulin over intracellular Mg concentrations. One of them demonstrated an improvement of the intracellular Mg concentration in obese children and patients with type 1 and 2 DM, after the stimulation with 100 mU/mL of insulin ***(2).***

Hyperglycemia, independent of insulin, or other responses due to oral glucose ingestion has potential role in cellular ionic changes of free Ca and Mg. In experimental DM has been related alterations in the tissue redistribution of Mg. Spontaneous diabetic rats showed increased urinary excretion of Mg, correspondent to 1,5 times, compared with controls. It was also evidenced that an increasing of Mg in the pancreas and reduction in the lungs, kidneys, testicles, and adipocytes, in the early stages of diabetes ***(4).***

Despite the deduction that hypomagnesemia is caused by diabetes and not the opposite, the Mg deficiency also can influence the onset of this disease. This was demonstrated in many prospective studies (ARIC), predominantly in the white participants. The Mg deficit interferes with enzymatic reactions that use or produce adenosine triphosphate (ATP), in consequence modifies the enzymatic cascade that involves the carbohydrates metabolism, triggering DM ***(3).***

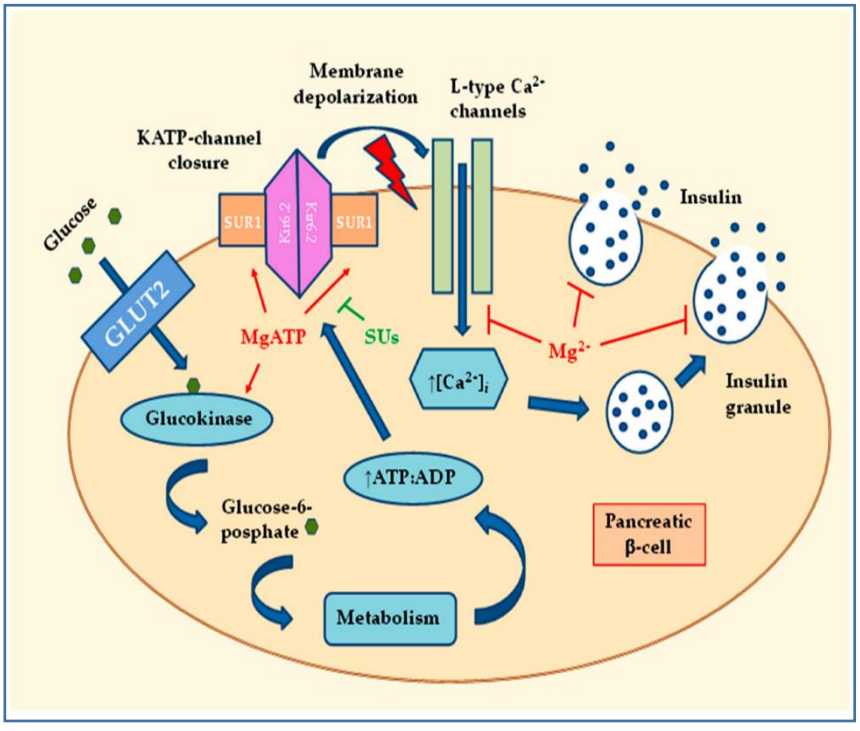

Figure (2): Regulatory role of Mg2+ in the insulin secretion from pancreatic beta cells. Normal intracellular Mg2+ concentrations are of utmost importance for optimal insulin secretion. The first step of beta-cell glucose metabolism is the conversion of glucose to glucose-6-phosphate by glucokinase, which subsequently results in a rise in intracellular ATP. MgD can directly influence the rate of GK activity because the enzyme's action depends on MgATP. Closure of the KATP channel depends on the binding of ATP to the Kir6.2 subunits. Opening of the KATP channel depends on the binding of MgATP to the SUR1 subunits. An important consequence of the closure of KATP channels is the depolarization of the beta-cell membrane, which stimulates Ca2+ influx through L-type Ca2+ channels and insulin release. In MgD, intracellular levels of ATP and MgATP decrease. This disturbs the coupling between the chemical signal (blood glucose) and the electrical stimulation of the beta cells, resulting in a disturbance of the normal phases of insulin release. SUs antagonizes the binding of MgATP to the SUR1, which induces channel closure and potentiates insulin secretion. Legend: GLUT2, glucose transporter type 2; KATP, ATP-sensitive K+ channel; SUR1, sulfonylurea receptor 1 subunit of KATP; Kir6.2, inwardly rectifying K+ channel subunit of KATP; SUs, sulfonylurea drugs; Mg2+, magnesium; MgATP, Mg2+-ATP complex; ↑[Ca2+]i, increased intracellular Ca2+ concentrations; ↑ATP:ADP, increased ATP/ADP ratio ***(10).***

In the same way as observed by many authors, in hyperglycemia, existing ionic alterations in the cells, there is an increase of the intracellular ATP concentration, that induces a reduction of the intracellular ionized Mg levels ***(4).***

Magnesium and macrovascular chronic complications of diabetes:

The chronic complications of diabetes are developed when cells or cellular components are chronically exposed to high concentrations of glucose. The non-enzymatic glycosylation of proteins and the accumulation of polyol as sorbitol, result in the formation of end products of the advanced glycosylation in the tissues, causing irreversible changes. This process culminates in cellular damage, being able to trigger macrovascular complications as dyslipidemia and hypertension, associated to the DM; and microvascular as neuropathy, retinopathy, and nephropathy ***(8).***

Many authors observed lower Mg concentrations in the plasma of patients with type 2 DM and reduction of antioxidative protection in the two types of diabetes, which can be an increasing factor of chronic complications. The vascular complications mostly associated to the deficiency of Mg are heart ischemic disease, atherosclerosis, hypercholesterolemia, hyper-triglyceridemia and hypertension, and probably the mechanisms of metabolic syndrome ***(2).***

In type 2 diabetic patients with essential hypertension, have been detected reduced cytosolic free Mg concentrations, when compared to normotensive or non-diabetic individuals. The inverse relation between intracellular ionic disturbs of Mg and the metabolic compensation has been questioned in relation to the development of rise of arterial pressure and insulin resistance ***(1).***

According to the hypothesis suggested by many authors, the low availability of intracellular Mg diminishes the tyrosine kinase activity and increases the vascular constriction mediated by calcium, hindering the relaxation of cardiac and smooth muscles; and this way, interfering in the usage of the cellular glucose. Such mechanisms contribute to raise the blood pressure and peripheral insulin resistance, suggesting secondary etiological factors of hypertension and type 2 diabetes ***(3).***

Many studies indicated that the serum and dietary Mg may be related to the etiology of cardiovascular diseases, hypertension, and diabetes. Serum Mg was significantly lower in the participants with cardiovascular disease, hypertension and/or diabetes, than in the healthful individuals, registering the lower concentrations in the diabetic patients with hypertension ***(6).***

Moreover, it was observed that patients with cardiovascular disease, the serum Mg was also inversely associated to insulin, fasting serum glucose, systolic arterial pressure, and smoking. The Mg dietary ingestion was positively associated to the high-density lipoprotein cholesterol (HDL-c) and inversely associated to the fasting insulin, systolic and diastolic pressure ***(4).***

Significant difference to the Mg assessed in patients with cardiovascular diseases and in the individuals presenting risk factors for these diseases is not verified. Even so, patients with DM and those with cardiac arrhythmia had lower serum levels of ionized Mg than the healthful controls ***(8).***

On the other hand, many trials showed that the patients with essential hypertension demonstrated higher erythrocyte Mg concentration than control group, which thwarted the hypothesis of the Mg deficiency in these patients. It can be deduced however, that serum Mg concentration as a single parameter of evaluation must be carefully interpreted in this kind of studies ***(5).***

Mg deficiency has also been argued as a probable causal factor of dyslipidemias, what constitutes an alert for the chronic complications of DM, such as atherosclerosis. In patients with type 1 diabetes, was demonstrated that the improvement of the metabolic control seems to reduce the renal excretion of Mg,

increase HDL-c level, and reduce the serum triglycerides ***(3).***

Supplementation with Mg resulted in a negative correlation between serum total Mg and triglycerides concentration, and between the ionized Mg concentration and serum total cholesterol and apolipoprotein A1. These results suggest a probable relation involving the serum Mg concentrations and the lipidic profile ***(6).***

High concentrations of total cholesterol and low-density lipoprotein cholesterol (LDL-c), and low concentrations of HDL-cholesterol had been observed in patients with type 2 diabetes with decompensate fasting glycemia. The HDL-c was positively correlated to serum Mg indicating that hypomagnesemia associates with low levels of HDL-c even in pre-diabetic states ***(2).***

Magnesium and microvascular chronic complications of diabetes:

Experimental researches have shown that patients with diabetic retinopathy present low concentrations of plasma Mg, disposing to a higher risk of advanced retinopathy. Several authors observed a significant negative correlation between plasma Mg concentration and the retinopathy progression, however, there are doubts if the plasma Mg concentration can be considered a causal factor for the retinopathy development ***(1).***

Many studies carried out with type 1 and type 2 diabetic, did not demonstrate a significant correlation between the severity of retinopathy and Mg concentration in the plasma. In type 2 diabetic patients with microalbuminuria or clinical proteinuria showed a significant decrease in serum ionized Mg levels ***(3).***

Moreover, it was also observed a significant negative correlation between serum ionized Mg and HbA1c and triglycerides, in both microalbuminuria and clinical proteinuria groups. According to these results it is possible to associate metabolic control and lipidic profile disturbances with alterations in Mg metabolism in these patients ***(6).***

In numerous focused studies with type 1 diabetic patients, it was evidenced that the erythrocyte Mg was in a lesser concentration in the patients with polyneuropathy than in the diabetics without this complication. After intervention with Mg supplementation, an improvement in the nervous conduction, mainly in the young patients who had initial signals of neurological complications ***(4).***

Many authors observed in type 1 diabetic with chronic Mg depletion (supplemented and not supplemented) that the polyneuropathy was determined by the duration of diabetes and by the low erythrocyte Mg concentration. Supplementation with Mg increased the erythrocyte Mg concentration, as well as reduced the incidence of polyneuropathy. It has also been suggested that hypomagnesemia is associated with feet ulcers in patients with type 2 DM ***(8).***

Diabetes and other complications (pregnancy, aging, bone metabolism, hormones):

Some research involving Mg concentrations have been developed in pregnant women; however, the findings are still not consistent. Many researchers observed lesser ionized and total Mg concentrations in pregnant patients in the third trimester of pregnancy in relation to non-pregnant normal patients, being more accentuated in the gestational diabetes ***(5).***

Beyond this, it was evidenced lower intracellular free Mg levels in pregnancy diabetic women compared with non-pregnant and normal pregnant women. It has been argued that pregnancy itself induces the losses of this mineral, which are increased in the presence of diabetes. On the other hand, no alteration in the ionized Mg concentration was observed in the first trimester of pregnancy of women with and without gestational diabetes ***(6).***

Beyond pregnancy, aging can also be associated with the reduction of blood Mg concentrations. Patients with type 2 DM, over 65 years old, had presented alterations in the metabolism and compartmentation of Mg, especially in platelets, when compared to plasma and erythrocytes of healthful elderly and young with type 2 DM and healthful young ***(1).***

Some studies are being developed in the attempt of demonstrating the relation between Mg and the alterations of bone metabolism, common in diabetes. Many experiments speculated disorders in bone mineral content and in bone bio-mechanism in male rats' type spontaneous hypertensive/NIH corpulent—SHR/N-cp (model of rodent that shows many similar characteristics of type 2 DM) obese and thin, submitted to dietary intervention during a period of 8 months. Urinary excretion of Mg was higher in obese rats with bone growth disorders, and before alterations in the concentration of bone Mg ***(2).***

In humans, the increase of urinary calcium and Mg excretion in relation to the glycemic control of type 1 diabetic patients was verified, mainly in the female gender. This is worrying due to the damage on bone mass, predisposing even more the triggering of diabetic osteopenia ***(4).***

Supplementation with magnesium:

In patients with diabetes, the supplementation with micronutrients must be individualized, based on dietary history, clinical features, and laboratorial evaluation of the nutritional state. Even so the oral supplementation with Mg improves the secretion and sensitivity to insulin in type 1 and 2 diabetic patients, there are still controversies based on human and animal studies accomplished. In elapsing

investigations with humans, the oral supplementation with Mg was related to insulin sensitivity and the metabolic control in patients with type 2 DM ***(3).***

Barbagallo demonstrated that the supplementation with Mg improved the circulating glucose levels and the oxidation of the tissue glucose in patients with type 2 DM, besides favoring in the action of the peripheral insulin. Contrary results were verified in type 2 diabetic patients with hypomagnesemia after supplementation with 600 mg of Mg oxide daily. The only beneficial effect observed in this study was on the lipidic profile ***(6).***

Type 2 diabetics supplemented with nature water with a high Mg content had a significant increase of total serum, urinary and excretion Mg levels. Positive clinical effects were showed by significant decrease of the insulin resistance and fasting immunoreactive insulin ***(5).***

Still in type 2 diabetics, the Mg associated with Zn, vitamin C and E improved the values of HDL-c and apolipoprotein A; fact not observed when Mg was offered only with zinc. Previously this had been evidenced in humans increasing the positive effect in the carbohydrate's metabolism, besides being co-adjuvant in the treatment of hypertension. It is worth to stand out that, in rats, many authors had not verified adding beneficial effects of supplementation with zinc, only with Mg ***(2).***

Although Mg supplementation seems to have beneficial effect in diabetic patients, no rule about dosage and duration of the treatment with this mineral has been established until the moment. Nowadays, ADA recommends the replacement of Mg based on the reduction of serum concentrations of this element ***(1).***

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