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Magnesium Intake and Its Relationship With Type 2 Diabetes

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MAGNESIUM INTAKE AND ITS RELATIONSHIP WITH TYPE 2 DIABETES

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Abstract:

Magnesium is an alkaline earth metal and is the second most abundant cation in the human body. Magnesium plays important roles in the structure and the function of the human body; it is involved in more than 300 essential metabolic reactions in the body. Magnesium has been implicated in the prevention and treatment of many diseases including diabetes. Magnesium depletion is commonly associated with both insulin dependent and non-insulin dependent diabetes. A significant number, (between 25% and 39%) of diabetics have been shown to have decreased serum levels of magnesium. There are many possible reasons and mechanisms for this. Diabetics experience increased losses of urinary magnesium due to glucosuria and osmotic diuresis. Magnesium depletion has also been shown to increase insulin resistance in diabetic individuals. More research is needed to determine what type, how much, and which at-risk groups would benefit from magnesium supplementation.

Magnesium intake and its relationship with Type 2 Diabetes

Magnesium is the second most abundant intracellular cation in the human body. 60% of intracellular magnesium is found in the bone, and 34% in the soft tissues. Less than 1% of the total magnesium circulates in the extracellular fluid (1). Magnesium is involved in more than 300 enzymatic systems, such as adenosine tri-phosphate (ATP) metabolism, activation of creatine kinase, adenylate cyclase, and sodium-potassium-ATPase (1, 2).

Magnesium plays a structural role in bone integrity, cell membranes, and chromosomes. Magnesium is also required for the active transport of ions like potassium and calcium across cell membranes. Because of this function, patients with refractory hypokalemia will often not respond to potassium supplementation until magnesium deficiency is corrected. As a result, magnesium deficiency should be considered whenever severe potassium deficiency is found (2). Through the interaction of magnesium with the maintenance of transmembrane gradients, magnesium affects the conduction of nerve impulses, muscle contraction, and the normal rhythm of the heart.

Magnesium is involved with cell signaling and cell migration. Cell signaling requires MgATP for the phosphorylation of proteins and the formation of the cell molecule, cyclic adenosine monophosphate (cAMP). cAMP is involved in many processes, including the secretion of parathyroid hormone (PTH) from the parathyroid glands. Cell migration deals with the calcium and magnesium levels in the fluid surrounding the cells. This affects the migration of a number of different cell types. These effects on cell migration may be important in wound healing (3).

Enzymes in the body depend on magnesium to activate carbohydrate and protein metabolism, as well as any reaction that involves ATP. Magnesium also acts as a cofactor in

many enzymatic reactions that affect the transfer, storage, and energy used for the phosphate bonds of ATP (1). Magnesium is also required at a number of steps during the synthesis of nucleic acids (DNA and RNA) and proteins. Many enzymes participating in the synthesis of carbohydrates and lipids require magnesium for their activity. The antioxidant, glutathione, also requires magnesium for its synthesis (3).

The Recommended Daily Allowance for magnesium is 400 mg for adult males and 310 mg for adult females (3). A large national survey indicated that the average magnesium intake for adult men is about 320 mg/day and 230 mg/day for adult women (3). These levels are significantly below the current Recommended Daily Allowances. In men and women over 70 years of age, magnesium intakes were even lower (3). Green, leafy vegetables are an excellent food source of magnesium because magnesium is a part of chlorophyll, the green pigment in plants (3). Whole-grains, nuts, milk, and meats are also good dietary sources of magnesium (1, 2, 3, 4). Water can also be a variable source of magnesium; harder water usually contains a higher concentration of magnesium salts than softer water (3).

Magnesium deficiency is rare because magnesium is abundant in both plant and animal foods and because the kidneys in healthy individuals are able to limit urinary excretion of magnesium when dietary intake is low (3). Magnesium deficiency can stem from many conditions including increased renal and gastrointestinal excretion, decreased dietary intake, chronic alcoholism, and alterations in absorption (1). Magnesium deficiency is almost always asymptomatic. There are no pathognomonic signs and symptoms of the magnesium deficient state. Clinical manifestations of a magnesium deficiency only occur when the situation is severe (2). When symptoms do occur, they generally fall into three categories: cardiac effects,

metabolic effects, and neurological effects. Some signs and symptoms that are associated with magnesium deficiency are summarized in Table 1. (See appendix A.)

Recently, magnesium deficiency and its relationship to clinical diseases has become increasingly more recognized due to increased research in the area. Magnesium deficiency has been implicated in such diseases as cardiac arrhythmias, acute myocardial infarction, atherosclerosis, eclampsia and preeclampsia, osteoporosis, hyperlipidemia, hypertension, and diabetes mellitus (1, 2, 5).

Diabetes mellitus is a group of diseases characterized by high blood glucose levels resulting from either defects in insulin secretion, insulin action, or both. People with diabetes have bodies that do not produce or respond to insulin, which is a hormone that is produced by the beta cells of the pancreas. Insulin is necessary for the use and storage of body fuels. Diabetes mellitus affects about 5.9% of the total American population (6). There are two types of diabetes. Type 1 usually occurs in people younger than 30. It is known as insulin-dependent diabetes mellitus or IDDM. Type 1 diabetes can either be immune-mediated or idiopathic. Type 2 diabetes accounts for 90-95% of all diagnosed diabetes cases. It usually occurs in people who are older than 30. Risk factors for Type 2 diabetes include older age, obesity, a family history of diabetes, a prior history of gestational diabetes, impaired glucose homeostasis, physical inactivity, and race or ethnicity (6). Type 2 diabetes is characterized by insulin resistance and relative insulin deficiency. Endogenous insulin levels may be normal, decreased, or elevated in type 2 diabetes, but they are inadequate to overcome associated insulin resistance (6).

Few studies have addressed the association between specific micronutrient components of the diet and diabetes risk. However, many studies have shown that magnesium intake and diabetes mellitus are inversely related (2, 4, 5, 7, 8). Both insulin dependent diabetes and non-

insulin dependent diabetes have been associated with magnesium depletion. In the USA, 25-39% of outpatient diabetics have low levels of serum magnesium (5, 7).

The clinical correlation between decreased plasma magnesium and the diabetic condition was first proposed in 1971. This was shown in diabetic children after a glucogon injection induced a significant decline in plasma magnesium levels (2). Another study was done where plasma magnesium concentrations were determined in 109 type 2 diabetics and 156 age- and sex-matched healthy controls. Plasma magnesium concentrations were below the reference range in 37.6% of the diabetic patients and 10.9% of the control subjects. This study concluded that lower plasma magnesium concentrations and poor magnesium status are common in type 2 diabetics (8).

Magnesium depletion does have a negative impact on glucose homeostasis and insulin resistance in people with type 2 diabetes as well as on the evolution of complications such as retinopathy, thrombosis, and hypertension. One study indicated that there are three biologic mechanisms that could explain the physiologic effects of magnesium on specific complications of diabetes (2). First, magnesium deficiency causes a dysregulation of the sodium-magnesium (Na-Mg) exchanger, resulting in higher intra-cellular sodium and therefore, higher blood pressure. Second, a relatively low magnesium level creates an intracellular imbalance between calcium and magnesium, which results in increased vascular tone in the smooth muscle of the artery and therefore, increased blood pressure. Third, magnesium deficiency causes insulin resistance by negatively affecting the post-receptor signaling of insulin, which in turn causes hyperinsulinemia, resulting in hypertension, diabetes, and hyperlipidemia (2).

In another study, two main mechanisms were shown to play a role in the pathophysiologic consequences of diabetes mellitus (1). One is that magnesium deficiency

negatively affects inositol transport, which might lead to some of the complications of diabetes. Inositol is necessary for Na-K-ATPase activity, and its depletion is proposed as a mechanism for the diseased peripheral system, particularly in patients with type 2 diabetes. Another interest is the role of magnesium in micro- and macroangiopathy because magnesium deficiency has been implicated in playing a role in the development of atherosclerosis in patients without diabetes (1). This role of magnesium has been the subject of several investigations. Two particular studies suggested that atherosclerotic disease may be prevented by normal magnesium homeostasis by counteracting the adverse affects of excessive intra-cellular calcium. Normal magnesium homeostasis lead to the retention of intracellular potassium and contributed both to the stabilization of plasma membranes and subcellular structures (9, 10).

The reasons why magnesium deficiency is commonly found in diabetic individuals are not clear, but there are many theories that offer possible explanations. One theory is that diabetics experience increased losses of urinary magnesium due to glucosuria and osmotic diuresis. Another study observed that in the presence of hypomagnesemia, magnesium plasma levels were inversely correlated with fasting blood glucose values and urinary magnesium. The conclusion was that net tubular reabsorption of magnesium was decreased in severe hypoglycemia (11). Another reason is simply a lower dietary intake of magnesium among diabetics. Type 2 diabetics are often overweight, and may consume diets that are higher in fat and energy and lower in magnesium than non-diabetic individuals. Also, low dietary intake of magnesium may play a role in the development of diabetes and in the development of insulin resistance in non-diabetic adults (7).

In one study, the relationship of magnesium deficiency to glycosolated hemoglobin was researched. Glycosylated hemoglobin or HbA1c is an excellent measure of diabetic control. It is

expressed as a percentage of total hemoglobin with glucose attached over the preceding two to three months. The patients with diabetes in this study had significantly lower muscle and plasma magnesium levels as compared with control patients. There were strong negative correlations between glycosylated hemoglobin as well as muscle and cell magnesium levels (12).

There have been several studies that have suggested a protective role of magnesium intake against diabetes, and many experimental studies have shown the benefits of magnesium supplementation on glucose metabolism and insulin secretion. In a rat model for type 2 diabetes, magnesium supplementation of 1% of the diet markedly lowered glucose disposal above the levels seen in rats fed a magnesium adequacy of 0.2% of the diet. Magnesium supplementation in the rats also appeared to delay the onset of diabetes in this model (13). Another randomized study concluded that high-dose dietary supplements with magnesium improved magnesium status and significantly reduced fructosamine levels, which is an indicator of metabolic control (14).

One study concluded that magnesium supplementation of 400 mg/day improved glucose tolerance in the elderly (3). The type of magnesium supplement that would be of the most benefit is unknown. Magnesium supplements are available as magnesium oxide, magnesium gluconate, magnesium chloride, and magnesium citrate salts. A number of amino acid chelates are also available, such as magnesium aspartate. Magnesium hydroxide is also used as an ingredient in many types of antacids (3). Collectively, these data suggest that magnesium supplementation may aid in the prevention and treatment of type 2 diabetes; more research would need to be conducted to determine exactly what at-risk groups would benefit from supplementation, which form of supplement to use, and whether it would alter the natural history of the diabetes disease (5).

Caution must be used however with magnesium supplementation; adverse affects from excess magnesium have been observed with intakes of various magnesium salts. The initial symptom of magnesium toxicity is diarrhea, a well-known side effect of magnesium that is used therapeutically as a laxative. People with impaired kidney function are at a higher risk for adverse effects from magnesium supplementation; symptoms of magnesium toxicity have occurred in people with impaired kidney function taking moderate doses of magnesium-containing laxatives or antacids (3). Some of the later effects of magnesium toxicity include lethargy, confusion, disturbances in normal cardiac rhythm, and the deterioration of kidney function. These symptoms are related to severe hypotension that results from elevated levels of serum magnesium. As hypermagnesemia progresses even more, muscle weakness, difficulty breathing, and even cardiac arrest may occur (3). The tolerable upper level (UL) for supplemental magnesium intake in healthy adolescents and adults is 350 mg/day (3). People with renal impairment should be cautioned about the use of supplements, since they are at a higher risk of adverse effects from excess supplemental magnesium intake (3).

Magnesium is responsible for a very large number of physiologic events in the human body, and is critical to normal homeostasis. Magnesium deficiency states have been proven to correlate with many chronic diseases and especially diabetes. The research that has been done has only begun to give us a glimpse of the impact that magnesium may have on the diagnosis and development of type 2 diabetes. Hopefully, continued research will be done to see whether magnesium supplementation truly could alleviate the debilitating affects of diabetes mellitus.

Appendix A

Table 1. Signs and Symptoms of magnesium deficiency (1)

- Confusion, dizziness and impaired memory
- Moodiness and hallucinations
- Seizures progressing to coma
- Tremors, tetany, and increased deep tendon reflexes
- Cardiac rhythm disturbances-premature ventricular contractions
- Ventricular tachycardia and fibrillation
- Multiple arterial premature beats and mutifactorial atrial tachycardia

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