



Review Article

Hypomagnesemia and Type-2 Diabetes Mellitus

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Abstract

Diabetes mellitus (DM) has been suggested to be the most common metabolic disorder associated with several macrovascular and microvascular complications. Hypomagnesemia has been reported to occur at an increased frequency among patients with type-2 DM. Those who have poor glycemic control and longtime DM are more likely to decrease the blood magnesium (Mg) level. Mg deficit may also coexist with deficiencies of other dietary elements, such as vitamins, calcium (Ca⁺⁺) and potassium (K⁺). Despite numerous reports linking hypomagnesemia to chronic diabetic complications, attention to this issue is poor among clinicians. This article reviews the literature on physiology & biochemistry of Mg⁺⁺ diagnosis and incidence, features, causes, complications and management of hypomagnesemia in patients with type-2 DM.

Keywords: Serum Mg⁺⁺, Hypomagnesemia, Type-2 DM

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Introduction

Type-2 DM is a non-autoimmune, complex, heterogeneous and polygenic metabolic disease in which body fails to produce enough insulin characterized by abnormal glucose homeostasis¹. It is the predominant form of diabetes, accounts for approximately 90-95% of all diagnosed cases of diabetes². Macrovascular and microvascular complications of diabetes increase as a function of the duration of hyperglycemia. DM is associated with alteration of the metabolism of many micronutrients. Over the last decades, evidence is accumulating that hypomagnesemia is frequently present in patients with type-2 diabetes³.

Mg⁺⁺ is the fourth most abundant extracellular and the second most prevalent intracellular cation in the human body⁴. Mg⁺⁺ is involved in more than 300 essential and fundamental metabolic reactions, including hormone receptor binding, gating of calcium channels, second messenger system, transmembrane ion flux, regulation of muscle contraction and vascular tone, cardiac excitability and neurotransmitter release⁵⁻⁷.

The concentrations of Mg⁺⁺ in serum of healthy people are remarkably constant whereas 25-39% of diabetics have low concentrations of serum Mg⁺⁺ and many of these cases are clinically undetected in the asymptomatic stage⁸. Several evidences suggest that Mg⁺⁺ depletion may play a key role in the pathophysiology of insulin-resistance in Diabetes Mellitus, hypertension and dyslipidemia⁹⁻¹¹. Hypomagnesemia in diabetics can be due to: osmotic renal losses from glycosuria, decreased

intestinal Mg⁺⁺ absorption and redistribution of Mg⁺⁺ from plasma to red blood cells caused by insulin effect¹².

Biochemistry and Distribution of Magnesium

Mg⁺⁺ apparently derives its name from Magnesia, a district in the Volos area of Thessaly in northeastern Greece. Mg⁺⁺ metal was first prepared by Sir Humphrey Davy around 1810 by making the amalgam of Mg⁺⁺ with mercury and then distilling off the mercury electrolytically¹³. Mg⁺⁺ is a Group 2 (alkaline earth) element within the periodic table and has a relative atomic mass of 24.305 Da a specific gravity at 20°C of 1.738 a melting point of 648.8°C and a boiling point of 1090°C^{14,15}.

Mg⁺⁺ exist as a protein-bound, complexed or free cation. Approximately 50% of total body Mg⁺⁺ is present in bones. Other 50% is found predominantly inside the cells of tissues and organs. Only 1% of Mg⁺⁺ is found in blood¹⁶. The Mg⁺⁺ content of bone decreases with age and Mg stored in this way is not completely available during Mg⁺⁺ deprivation¹⁷. Nonetheless, bone provides a large exchangeable pool to buffer acute changes in serum Mg⁺⁺ concentration¹⁸. Overall one third of skeletal Mg⁺⁺ is exchangeable, serving as a reservoir for maintaining physiological extracellular Mg⁺⁺ levels¹⁸.

Physiological Role of Magnesium

It has long been known that Mg⁺⁺ is important for normal neurological and muscular function¹⁹. Mg⁺⁺ is primarily found within the cell, where it is a

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metallic cofactor for over 300 enzymatic reactions involved in protein and nucleic acid synthesis and in energy metabolism²⁰. Mg^{++} frequently modulates ion transport by pumps, carriers and channels and thereby may modulate signal transduction and the cytosolic concentrations of Ca^{++} and K^{+} ^{21,22}. It is also important to note that Mg^{++} contributes to the regulation of vascular tone, heart rhythm, platelet-activated thrombosis and bone formation²³.

There is also evidence that Mg^{++} and Ca^{++} compete with one another for the same binding sites on plasma protein molecules²⁴. It was shown that Mg^{++} antagonizes Ca^{++} -dependent release of acetylcholine at motor endplates²⁵. Thus, Mg^{++} may be considered a natural 'Ca⁺⁺ antagonist'. While Ca^{++} is a powerful 'death trigger', Mg^{++} is not²⁴; Mg^{++} inhibits Ca^{++} -induced cell death^{24,26,27}.

Diagnosis and Features of Hypomagnesemia

In plasma Mg^{++} , like Ca^{++} , can be found in three fractions; in an ultrafiltrable fraction consisting of ionized Mg^{++} (70–80%), complex-bound Mg^{++} (1–2%) and in a protein-bound non-ultrafiltrable fraction (20–30%)²⁸. Determination of total Mg^{++} in a variety of human samples is available by a variety of techniques. Photometry using a number of chromogenic reagents such as xylidyl blue, calmagite, methyltymol, magon and titan yellow are most frequently used²⁹. Another frequently used technique is atomic spectroscopy in two modes: flame emission (FEAS) or absorption after electro-thermal atomization (AAS). The latter is especially useful in the analysis of hair. In all of these techniques, it is possible to obtain data with a relative standard deviation of 1–3%³⁰.

Evaluation of serum Mg^{++} concentration and collection of a 24-h urine specimen for Mg^{++} excretion are at present the most important laboratory tests for the diagnosis of hypomagnesemia²⁰. Hypomagnesemia may be defined as a serum Mg^{++} concentration less than 1.6 mg/dl or 2 SD (standard deviation) below the mean of the general population¹². If the serum Mg^{++} level is normal in the patient having sign symptoms, then other more sensitive tests should be performed^{31–32}.

Clinical signs of hypomagnesemia and hypermagnesemia overlap often and are rather non-specific. Anorexia, nausea, vomiting, lethargy and weakness are typical early symptoms of Mg^{++} deficiency. If severe Mg^{++} deficiency develops, paresthesia, muscular cramps, irritability, decreased attention span and mental confusion often occur³³. Severe hypomagnesemia is usually accompanied by other imbalances of electrolytes such as low levels of Ca^{++} and K^{+} in the blood³⁴. However even in patients with severe hypomagnesemia, clinical signs associated with Mg^{++} deficiency may be absent²⁰.

Therefore physicians should not wait for clinical signs to occur before checking serum Mg^{++} levels²⁰.

Causes of Hypomagnesemia

The causes of hypomagnesemia in humans are listed below³²:

A. GIT losses	Chronic diarrhea, Malabsorption syndromes, Laxative abuse, Pancreatitis, Specific magnesium malabsorption, Prolonged nasogastric suctioning.
B. Renal excretion	Acute renal failure, Renal tubular acidosis, Post-obstructive diuresis, Primary renal tubular magnesium wasting.
C. Drug induced	Acetazolamide, Alcohol, Aminoglycosides, Amphotericin B, Capreomycin, Carbenicillin, Chlorthalidone, Cisplatin, Digoxin, Ethacrynic acid, Furosemide, Mannitol, Methotrexate, Pentamidine, Theophylline, Thiazides, Viomycin.
D. Nutritional deficiencies	Malnutrition, Magnesium-free parenteral feedings, Long-term alcohol abuse.
E. Endocrine disorders	Hyperaldosteronism, Hyperparathyroidism, Hyperthyroidism, Diabetes mellitus, Ketoacidosis, Hypoparathyroidism, SIADH, Bartter syndrome.
F. Redistribution	Insulin treatment for diabetic ketoacidosis, High-catecholamine states, Major trauma or stress, Hungry-bone syndrome.
G. Multiple mechanisms	Chronic alcoholism, Alcohol withdrawal, Major burns, Liquid-protein diet.

Magnesium and Insulin Activity

The relationship between insulin and Mg^{++} is a complex one. Insulin regulates Mg^{++} homeostasis but in turn, Mg^{++} itself is a major determinant of insulin and glucose metabolism³⁵. Mg^{++} is an essential cofactor for multiple enzymes involved in glucose metabolism and is hypothesized to play a role in glucose homeostasis and may precedes and contributes to the development of insulin resistance and altered glucose tolerance and even type-2 diabetes³⁶. Mg^{++} also plays a role in the release of insulin and the maintenance of the pancreatic β cell cycle³⁷. Low levels of Mg^{++} reduce secretion of insulin by the pancreas³⁸. A large body of evidence shows that a link between hypomagnesemia and reduction of tyrosine-kinase activity at the insulin receptor level, which may result in the impairment of insulin action and development of insulin resistance³⁹. Dietary magnesium intake was inverse related to the plasma insulin concentration in the

study by Jing et al⁴⁰. Therefore Mg^{++} supplementation seems to be able to favourably alter insulin sensitivity and prevent or retard the development of type-2 diabetes.

Hypomagnesemia in Type-2 DM

Hypomagnesemia in DM is usually observed in patients with poor metabolic control or associated to the diabetic chronic complications, according to clinical and epidemiological studies^{32,41}. DM has been suggested to be the most common metabolic disorder associated with Mg^{++} deficiency, having 25-39% prevalence⁸. On the other hand hypomagnesemia has been reported to occur in 13.5-47.7% of non-hospitalized patients with type-2 diabetes compared with 2.5-15% among their counterparts without diabetes^{12,41-44}. Hypomagnesemia was observed in 23.2% and intracellular Mg^{++} depletion in 36.1% of patients with metabolic syndrome⁴⁵. The wide range in the reported incidence of hypomagnesemia most likely reflects the difference in the definition of hypomagnesemia, techniques in Mg^{++} measurements and the heterogeneity of the selected patient cohort³⁶. In terms of gender difference, it is interesting to note that independent studies have reported a higher incidence of hypomagnesemia in women compared with men, at 2:1 ratio^{42,46}.

Causes of Hypomagnesemia in Type-2 Diabetes

Hypomagnesemia in the patient with diabetes may result from poor oral intake, poor gastrointestinal absorption and enhanced renal Mg^{++} excretion. Possible causes of hypomagnesemia in patients with type-2 DM are³⁶:

A. Decreased intake	Poor oral intake, esophageal dysfunction, diabetic gastroparesis
B. Enhanced GIT loss	Diarrhea as a result of autonomic dysfunction.
C. Enhanced renal Mg^{++} loss	Enhanced filtered load, glomerular hyperfiltration, osmotic diuresis (glucosuria), volume expansion as a result of excessive volume replacement, metabolic acidosis (diabetic ketoacidosis), overt proteinuria, microalbuminuria, hypoalbuminemia
D. Reduced renal reabsorption	Endocrinological dysfunction (insulin deficiency or resistance), metabolic acidosis (diabetic ketoacidosis), electrolyte abnormalities (phosphate and potassium depletion), diuretics.
E. Others	Use of antibiotics and antifungals such as aminoglycosides and amphotericin in diabetic patients may also contribute to renal Mg^{++} wasting.

Complications of Hypomagnesemia

Mg^{++} deficiency in DM has been found to be associated with various complications. Abou-Seif and Youssef 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 the chronic complications⁴⁷. The complications mostly associated to the deficiency of Mg^{++} are:

A. Hypokalemia: It is a common event in hypomagnesaemia patients, occurring in 40-60% of cases. This relationship is in part due to underlying disorders that cause both Mg^{++} and K^+ loss, such as diuretic therapy and diarrhea⁴⁸.

B. Hypocalcemia: The most classical sign of severe hypomagnesaemia is hypocalcemia. Suppressive effect of hypomagnesaemia on parathormone (PTH) secretion, bone resistance to PTH and low plasma levels of calcitriol are the important causes of hypocalcemia associated with hypomagnesaemia in type-2 DM⁴⁹.

C. Hypophosphatemia: Both micropuncture studies in phosphate-depleted dogs and in vitro studies involving phosphate depleted mouse distal convoluted tubular cells have demonstrated reduced Mg^{++} uptake^{50,51}.

D. Retinopathy: Hypomagnesemia has been demonstrated in patients with diabetic retinopathy with lower Mg^{++} levels predicting a greater risk of severe diabetic retinopathy⁵².

E. Neuromuscular hyper-excitability: Although hypocalcemia may contribute to the neurological signs, Mg^{++} deficiency without hypocalcemia has been reported to result in neuromuscular hyper excitability⁵³.

F. Cardiovascular complications: There is a substantial body of epidemiological and experimental evidence linking Mg^{++} deficiency and atherosclerotic cardiovascular diseases⁵⁴. Experimental studies suggest that Mg^{++} deficiency may play a role in the pathogenesis of atherosclerosis⁵⁵. Mg^{++} deficiency may contribute to the progression of atherosclerosis by its effect on lipid metabolism, platelet aggregation and blood pressure⁵⁶.

G. Foot Disease: It has also been suggested that hypomagnesemia is associated with foot ulcers in patients with type-2 DM⁵⁷.

H. Pregnancy: Gestational magnesium deficiency is associated with pre-term birth, increased incidence of leg cramps and constipation during pregnancy,

development of pre-eclampsia and fetal growth restriction⁵⁸.

Management of Hypomagnesemia in Type-2 DM

Poor dietary intake as a result of gastrointestinal autonomic dysfunction must be controlled. Tight glycemic control is recommended to minimize recurring renal Mg⁺⁺ wasting. Control of glomerular hyperfiltration with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers or both may offer additional benefits in reducing renal Mg⁺⁺ wasting. When hypomagnesemia persists despite all measures, oral or intravenous Mg⁺⁺ supplementation is indicated³⁵. In cases of mild hypomagnesaemia in otherwise healthy individuals, oral Mg⁺⁺ administration is used successfully⁵⁹. Intravenous administration of magnesium mostly as magnesium sulphate, should be used when an immediate correction is mandatory as in patients with ventricular arrhythmia and severe hypomagnesemia⁶⁰.

Conclusion

Hypomagnesemia in patients with DM is well established and have an inverse correlation between Mg⁺⁺ level and glycemic control. Hypomagnesemia is now considered as a cardiovascular risk factor and favors diabetic complications. So, early measurement of Mg⁺⁺ level in blood and appropriate Mg⁺⁺ replacement may help to decrease the hypomagnesemia related complication in type-2 diabetic patients.

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