

Review Article

Hypomagnesemia and Type2 Diabetes Mellitus: A Review of the Literature

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Abstract

Globally, diabetes Mellitus is the most prevalent disease among all race and ethnicities, and hence attaches extraordinary medical importance. The body of medical literature studying both macro and micro nutrients in regard to their association with diabetes has been growing continuously making it one of the most widely studied medical complication. The study of trace elements is a branch of diabetes literature that is considered vital due to their links to the aetiology and consequences of the disease. Mg is one of the trace elements that has enjoyed numerous experiments owing to its involvement with insulin sensitivity and carbohydrate metabolism and other vital physiological functions. As more and more researches are being carried out, its important to stay updated with the most recent research outcomes. The volume of studies on diabetes is overwhelmingly large and continues to grow. But the result remain mixed to some extent. This review aims to provide 1) a most recent epidemiologic evidence on the correlation between Mg and diabetes mellitus based on the researches that have been carried out on this topic so far. 2) and the potential benefits of Mg repletion in hypomagnesemic patients with DM.

Method: The Medline and Embase database were searched for publications between January 1989 and December 2013, using the following search terms: diabetes, trace elements, Mg, insulin sensitivity, causes of Mg deficiency, dietary supplement, oral solution. No language restriction was applied. The original articles were selected manually and only human clinical studies were selected for this review.

Conclusions: Hypomagnesemia occur at an increased frequency among patients with type 2 diabetes. There exists a positive link between hypomagnesemia and hyperglycemia. The cause of diabetic hypomagnesemia is multifactorial and diabetic patients have significantly lower mean serum Mg levels compared with healthy counterparts.

Keywords: Magnesium; Insulin resistance; Type 2 diabetes; Hypomagnesemia; Dietary management.

Abbreviations

NIDDM: Non-insulin Dependent Diabetes Mellitus; RDI: Recommended Dietary Allowance; TNF: Tumor Necrosis Factor.

Introduction

Mg is the second most abundant intracellular cation and is involved in numerous enzymatic pathways including those of glucose metabolism. Less than 1% of the total body Mg is present in blood, one-third as protein bound, and two-third in ionized form; thus serum Mg does not provide reliable information about total or intracellular magnesium concentration [1]. Intracellular Mg plays a key role in regulating insulin action, insulin-mediated-glucose uptake and vascular tone. Small intestine is the main site for Mg absorption, whereas Mg excretion is mainly performed through renal pathways. It is a vital cofactor for many enzymatic reactions and a key player in glucose metabolism and insulin homeostasis. Diabetes mellitus is a serious chronic metabolic disorder that has a significant impact on the health, quality of life, and life expectancy of patients, as well as on the health care system. There is accumulating evidence that the

changes which occur in the metabolism of some micronutrients in diabetes mellitus might have a specific role in the pathogenesis and complications of this disease [2]. Several minerals have been found to benefit people with diabetes, either because they help to cope up with the risk factors, or because of the beneficial effect on glucose metabolism. Amongst the most important minerals for supplementation are chromium, magnesium, and vanadium [3]. There exists a complex interplay between Mg and carbohydrate metabolism. Mg deficiency is the most evident disturbance of metal metabolism in insulin-dependent diabetes mellitus. Hypomagnesemia has been linked both to the acute metabolic and late chronic complication of diabetes. Mg levels can become low due to low dietary intake, poor ingestion, increased urinary loss. Studies have shown that Mg levels are lower in patients with diabetes compared with nondiabetic controls [4,7,8,14].

Diabetes is a also key factor accounting for the low serum Mg levels. Diabetes once diagnosed is for life and exercise, diet, and weight control continue to be essential and effective means of improving glucose homeostasis. As hypomagnesemia is frequently present in

diabetic patients, increasing dietary intake and supplement is also prescribed routinely. Diet is widely believed to play an important role in the development of type 2 diabetes [12]. Mg is involved with carbohydrate metabolism and has beneficial effects in the action of insulin [1]. A number of prospective cohort studies of Mg intake and diabetes incidence have been conducted, but the results remain mixed.

Hypomagnesemia in Type 2 diabetes mellitus: Symptomatic Mg depletion is often associated with multiple biochemical abnormalities such as hypokalemia, hypocalcemia, and metabolic alkalosis [39]. Hypomagnesemia is defined as a plasma total Mg concentration lower than 0.7 mmol/L. Mg (Mg) is primarily found within the cell, where it is a metallic cofactor for over 300 enzymatic reactions involved in protein and nucleic acid synthesis and in energy metabolism [12]. Body Mg homeostasis is very strictly regulated and balanced by intestinal absorption and renal excretion. The levels of Mg in the plasma of healthy people are extremely constant, with a reference interval for total serum levels of 0.75–0.96 mmol/L, and a mean of 0.85 mmol/L [37]. The association of hypomagnesemia and insulin resistance in diabetes patients has been documented previously. Hypomagnesemia occurs at an incidence of 13.5 to 47.7% among patients with type 2 diabetes [38].

According to popular hypothesis, low serum Mg affects diabetes through modulating insulin activity. Figure 1 illustrates a conceptual framework of the link between Mg and NIDDM (Non-insulin dependent diabetes mellitus). Diabetes is frequently associated with both extracellular and intracellular Mg depletion. Epidemiologic studies have found a high prevalence of hypomagnesemia in subjects with type 2 diabetes, especially in those with poorly controlled glycemic control. Cross sectional studies on diabetic patients showed lower serum Mg concentrations in comparison with non-diabetic patients [22]. Hyperinsulinemia per se may also contribute to the urinary Mg depletion [36]. Since serum Mg levels have been related to high blood pressure and oxidative stress which are risk factors of diabetes, hypomagnesemia can induce development of type 2 diabetes by affecting those risk factors. Hypomagnesemia was also associated with poorer glycemic control and nephropathy [25]. According to a case-control study on 200 obese subjects, type 2 diabetes was found to be the main factor accounting for the low serum Mg levels in morbidly obese subjects [22]. Hypomagnesemia is therefore both, a contributing factor for development of type 2 diabetes and also involved in low Mg levels in the diabetic patients.

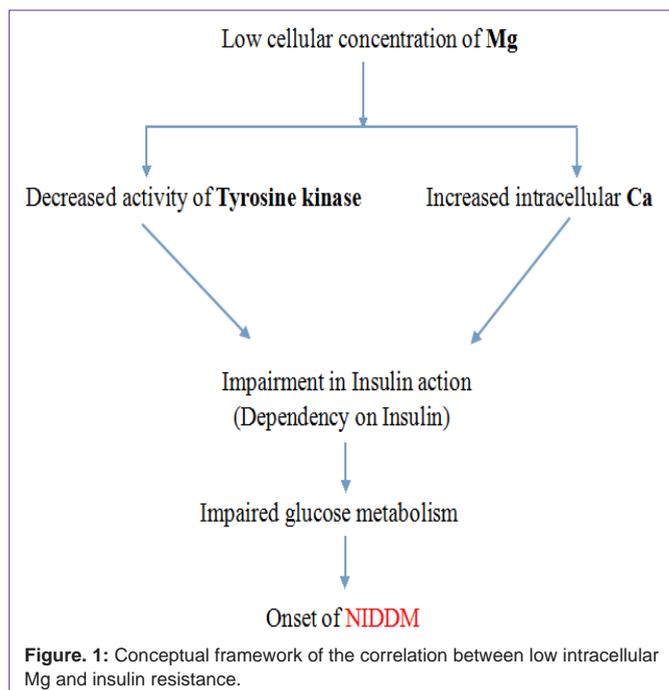
Mg and insulin activity: Diabetes mellitus, one of the chronic diseases, is most frequently associated with Mg deficiency [6]. The relationship between insulin and Mg is a complex one. Insulin regulates Mg homeostasis but, in turn, Mg itself is a major determinant of insulin and glucose metabolism. Insulin resistance is a major risk factor for type 2 diabetes and various other metabolic disorders. Diabetes mellitus is a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of macronutrients metabolism resulting from defects in insulin secretion, insulin action, or both. Mg is an essential cofactor for multiple enzymes involved in glucose metabolism and is hypothesized to play a role in glucose homeostasis, insulin action and in the development of type 2 diabetes [4–6]. Mg plays an important role in glucose homeostasis and is involved in glucose homeostasis at multiple levels.

Major causes of hypomagnesemia in diabetic patients

- **Diet tend to be low in Mg content**
- **Renal excretion of Mg is high**
- **Insulin deficiency and/or resistance**
- **Reduced renal adsorption**
- **Insensitivity to insulin affects Mg transport as well as glucose metabolism**
- **Use of loop and thiazide diuretics promotes Mg wasting**
- **Metabolic acidosis (diabetic ketoacidosis)**

Mg also plays a role in the release of insulin and the maintenance of the pancreatic beta cell cycle [10]. Several studies suggested that hypomagnesemia leads to a reduction of inositol transport and subsequent inositol depletion that might increase the development of diabetic complications [15,19]. It plays an important role in the activities of various enzymes which are involved in glucose oxidation, and it may play a role in the release of insulin [17–19]. It is mainly intracellular and its uptake is stimulated by insulin [19,20]. A cellular Mg deficiency causes reduction of inositol transport and depletion. This can alter the activity of membrane bound sodium, potassium ATPase [15,21], which is involved in the maintenance of gradients of sodium and potassium and in glucose transport. Low levels of Mg reduces secretion of insulin by the pancreas [23]. A large body of evidence that shows 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 resistance [30]. Evidence says that low intracellular Mg substantially reduces the proper functioning of tyrosine kinase which hinders the muscular relaxation which in turn interferes in the usage of cellular glucose [3]. Decreased cellular Mg rendered normal individuals resistant to the ionic effects of insulin. Glucose appears to contribute to cellular ion homeostasis independently of insulin [8]. Insulin has specific ionic effects to stimulate the transport of Mg from the extracellular to the intracellular compartment, thus increasing cellular Mg content.

The relevance of altered cellular Mg metabolism to tissue insulin sensitivity suggest a critical role of Mg in contributing to the clinical coincidence of Mg depletion to states of insulin resistance such as hypertension, metabolic syndrome, type 2 diabetes [8]. Apart from diabetic complications and the mortality rate, hypomagnesemia could influence both insulin secretion and insulin action. In this regard it has been suggested that reduced intracellular Mg concentrations result in an altered cellular glucose transport, a defective tyrosine-kinase activity, post-receptor impairment in insulin action by influencing intracellular signaling and processing, and reduced pancreatic insulin secretion [23]. In addition, chronic Mg deficiency has also been associated with elevated concentrations



of TNF-alpha, and this fact may also contribute to post-receptor insulin resistance [24]. Therefore, T2DM could facilitate low serum Mg levels and this could in turn worsen glycemic control of diabetes, thus establishing a vicious circle that could lead to a progressive impairment in metabolic control and more risk of diabetic complications. Mg-supplemented subjects showed a significant reduction in HOMA-IR index values. Low Mg concentration results in defective tyrosine-kinase activity with negative effects on glucose metabolism due to insulin sensitivity reduction which leads to poor metabolic control in diabetic patients.

Mg supplementation and dietary management: Opinion on chronic administration patients with metabolic syndrome had lower serum and intramononuclear Mg concentrations as compared with subjects without the condition of Mg supplement for type 2 diabetes is mixed [32]. Oral supplementation with MgCl₂ solution restores serum Mg levels, improving insulin sensitivity and metabolic control in type 2 diabetic patients with decreased serum Mg levels [29]. Mg-supplemented subjects, serum Mg concentration showed a significant decrease by the first month, followed by a gradual and sustained increase in the following months [30]. Mg supplementation improves insulin sensitivity as well as insulin secretion in patients with type 2 diabetes. Diabetic subjects who received Mg oxide (41.4 mmol/l) for 1 month achieved serum Mg levels similar to those of healthy control subjects [31]. A study concludes that oral Mg replacement therapy helps to recover hypomagnesemia after a minimum treatment period of 3 months [22]. A month long study by Paolisso et al. [18] described in type 2 diabetic patients an improved insulin response and a fall of fasting blood glucose level after Mg administration. Another 12 weeks long study concluded that Mg therapy does not further improve the metabolic state in type 2 diabetic patients treated with oral hypoglycemic agents, whereas a beneficial effect of Mg therapy in dietary-treated obese type II diabetics was found [22]. Some researchers maintain that its not about the benefits of Mg supplementation in the treatment of diabetic patients,

List of drugs that affect Mg level in Human body	List of drugs whose effectiveness is reduced by Mg supplementation
Aminoglycosides	Diclofenac
Amphotericin	Quinidin
Cetuximab	Indomethacin
Cyclosporin	Naproxen
Digoxin	Quinolone Antibiotics
Diuretics	Tetracyclin
Cisplatin	
Gentamicin	

but rather to the type, dose, and time of administration of Mg salts [30]. Its also suggested by some that clinical care should therefore focus on increasing dietary Mg intake or Mg supplementation to improve metabolic control in diabetic patients. Mg deficiency is present in 10% of patients admitted to general hospitals, and as many as 65% of patients in intensive care units [34]. The wrong nutritional habits of obese people, with low ingestion of whole grains, green leafy vegetables and other foods rich in Mg may contribute to Mg depletion. Diabetes is frequently associated with both extracellular and intracellular Mg depletion. Among the mechanisms that may favor Mg depletion in diabetes the most important are a low Mg intake and an increased Mg urinary loss, while dietary Mg absorption and retention are not impaired in patients with type 2 diabetes [35]. Some drugs are also associated with a lowering of body Mg (Table 1). Inadequate dietary intake of Mg is independent risk factor for the development of T2DM [25] and studies showed that subjects in the highest quintile of Mg intake had a 33 percent less risk of developing T2DM than those in the lowest quintile of Mg intake [26].

Finally, Mg supplementation in subjects with T2DM resulted in an improvement of insulin sensitivity and metabolic control. Poor dietary intake, increased consumption of fast food, changes in dietary habits in the western world have resulted in daily Mg intake fall below RDI. Decreased levels of trace elements cause disturbances in glucose

Management of hypomagnesemia in diabetic patients

- **Increase intake of Mg rich food**
- **Control of diabetic gastroparesis**
- **Oral supplementation**
- **Control gastrointestinal loss**
- **Reducing renal Mg loss**

Table 2: Major studies demonstrating the link between hypomagnesemia, low dietary intake of Mg and risk of type-2 diabetes

Study title	Reference	Method	Result
Effects of oral magnesium supplementation on glycaemic control in Type 2 diabetes: a meta-analysis of randomized double-blind controlled trials.	Song et al. Diabetic Medicine. October 2005.	370, meta-analysis.	Oral magnesium supplementation for 4–16 weeks may be effective in reducing plasma fasting glucose levels in patients with Type 2 diabetes.
Oral magnesium supplementation improves insulin sensitivity and metabolic control in type 2 diabetic subjects: a randomized double-blind controlled trial.	Rodriguez-Moran et al. Diabetes Care. Apr, 2003.	63, double-blind placebo-controlled trial.	Oral supplementation with MgCl(2) solution restores serum magnesium levels, improving insulin sensitivity and metabolic control in type 2 diabetic patients with decreased serum magnesium levels.
Clinical Efficacy of Magnesium Supplementation in Patients with Type 2 Diabetes	Kuninobu et al. Journal of the American College of Nutrition. August. 2004.	6 male, 3 female.	Salt lake water with a high Mg content, MAG21, has shown clinical benefit, as a Mg supplement in patients with mild type 2 diabetes.
Oral magnesium supplementation reduces insulin resistance in non-diabetic subjects - a double-blind, placebo-controlled, randomized trial.	Mooren et al. Diabetes Obes Metab. March. 2011.	27, double-blind placebo-controlled trial.	Oral Mg supplementation improves insulin sensitivity even in normomagnesemic, overweight, non-diabetic subjects
Daily magnesium supplements improve glucose handling in elderly subjects.	Paolisso et al. Am J Clin Nutr. June, 1992.	37, double-blind, crossover study.	Correction of a low erythrocyte magnesium concentration may allow an improvement of glucose handling in aged patients.
Effects of magnesium supplementation on plasma glucose in patients with diabetes mellitus	MELUDU et al. Afr. J. Biomed. Res. 2001.	Twelve apparently healthy (9 males and 3 females) nonobese, and 6 NIDDM (3 males and 3 females)	Plasma glucose concentration in diabetics decreased significantly all through the period of magnesium administration.

transport across cell membrane lead to insufficient formation and secretion of insulin by pancreas which compromise in the antioxidant defense mechanisms. Mg, an important component of many foods, such as whole grains, nuts, and green leafy vegetables, is an essential cofactor for enzymes involved in glucose metabolism. Mg is also important for human growth and body's biological functions acting as cofactors for metabolic reactions and thus support basic cellular reactions required to maintain energy production and life [2]. Some epidemiological studies have described an inverse relationship between a Mg rich food intake and diabetes [33]. Higher dietary intake of Mg was among the factors associated with a reduced risk of stroke in men with hypertension. The Recommended Daily Allowance (RDA) for Mg is 6 mg/kg/d. This means 400 mg/d to 420 mg/d for adult men and 320 mg/d for adult women (and even more for women who are pregnant or lactating). These findings indicate that a diet high in Mg-rich foods, particularly whole grains, is associated with a substantially lower risk of type 2 diabetes in U.S. black women [20]. A similar relationship was reported this year by Meyer and colleagues, who observed that a diet rich in Mg, grains, fruits, and vegetables reduced the likelihood of developing type 2 diabetes. A study by Hruby et al found that a higher Mg intake was associated with lower fasting glucose and insulin [16]. A follow-up study on 176 117 person observed that higher cereal fiber intake was inversely associated with diabetes risk [27]. Prospective studies have observed reduced diabetes risk with high cereal fiber and whole grain consumption [28]. Higher cereal fiber(whole-grain foods) decrease diabetes risk.

Therefore, increased Mg intake may important in diabetes prevention. 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 [37]. More prolonged use of Mg in doses that are higher than usual is needed to establish its routine or selective administration

in patients with type 2 diabetes to improve control or prevent chronic complications.

Conclusion

According to established evidences 1) Mg is crucial for optimum insulin activity and proper functioning of many co-enzymes and tyrosine kinase which is vital for glucose metabolism, 2) Inadequate dietary intake of Mg is associated with increased risk of developing glucose intolerance and Type 2 diabetes, 3) Hypomagnesemia is been linked to poor glycemic control, 4) Mg insufficiency must be supplemented by oral solution or increased dietary intake. There exists an inverse relationship between the incidence of diabetes mellitus and magnesium and dietary fiber intake. Dietary supplementation with Mg besides clinical therapies might be helpful in prevention of diabetic complications. Hypomagnesemia is common among patients with type 2 diabetes which also appears to be cause of low serum Mg level. Hypomagnesemia leads to insulin resistance and reduced functionality of various co-factors which may result in diabetes. A growing body of evidence suggests that Mg plays a pivotal role in the pathogenesis of diabetes itself. Higher cereal fiber and Mg intake may decrease diabetes risk.

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