The Review of DIABETIC STUDIES

RESEARCH

Magnesium Supplements and Type 2 Diabetes Mellitus Control: A Narrative Review

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■ Abstract

Background: Long-term hypomagnesemia is associated with an increased risk of hyperinsulinemia and insulin resistance, and thus the incidence of type 2 diabetes mellitus (T2DM). This study reviewed the available studies on magnesium (Mg) supplementation in patients with T2DM. **Methods:** Using databases (PubMed, Scopus, Medline via the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov), a literature was conducted for hypomagnesemia and its impact on T2DM and the effect of Mg supplements on blood Mg concentrations and long-term associations with T2DM control or prognosis. **Results:** Observational studies and evidence from randomized clinical trials have demonstrated that low serum Mg concentrations in T2DM patients are associated with higher fasting blood glucose and glycated hemoglobin A1c, along with a higher incidence of diabetic retinopathy, nephropathy, neuropathy, and cardiovascular disease. In T2DM, evidence for the routine use of Mg supplements to improve disease control and prognosis is inconsistent and inconclusive. This is due to heterogeneity in Mg supplementation duration (4-16 weeks), variety in dosage (36.49-500 mg per day), and differences in the salt component of the tablets used in these studies. **Conclusion:** Mg supplementation is a simple and inexpensive modality for improving T2DM control. Therefore, the appropriate dose and duration of Mg supplementation should be determined.

Keywords: T2DM, Magnesium, Glucose Tolerance, Insulin Resistance.

1. Introduction

Magnesium (Mg) is an alkaline earth metal and the fourth most abundant divalent cation in the body [1,2]. The majority of Mg (60%) in the body is found in the bones, with only 1% in the blood [2]. Mg is absorbed by the small intestine and excreted by the kidney, maintaining an apparent serum concentration of 0.7–1.0 mmol/L [3]. Mg is a cofactor for over 300 enzymes and is involved in various essential metabolic functions such as neuromuscular conduction, glycolysis, glycemic control, and blood pressure regulation [1-5]. Therefore, changes in Mg homeostasis can cause serious abnormalities such as impaired lipid metabolism, impaired glucose tolerance, and insulin resistance. This narrative review aims to provide a comprehensive understanding of the existing literature on the use of Mg supplements to guide the control of diabetes mellitus (DM) and minimize the macrovascular and microvascular complications associated with a poor prognosis.

1.1. Diabetes Mellitus

DM is a chronic metabolic disorder characterized by hyperglycemia, and increased blood glucose levels above the normal range, caused by insufficient insulin secretion, insulin sensitivity, or both [6, 7]. It is mainly classified into two sub-types: type 1 DM (T1DM) and type 2 DM (T2DM). Polyuria, polydipsia, polyphagia, blurred vision, and weight loss are the recognized symptoms of hyperglycemia, and they also result in potentially life-threatening conditions such as ketoacidosis or non-ketotic hyperosmolar syndrome [6]. The long-term consequences of hyperglycemia can be observed at either the microvascular or macrovascular levels. These include nephropathy leading to renal failure, retinopathy causing vision loss, peripheral neuropathy causing ulcers and amputations, and autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular disease (CVD) and sexual dysfunction [6].

Diabetes is a major public health concern that affects over 400 million people worldwide [8]. According to the International Diabetes Federation, 642 million patients will be diagnosed with diabetes by 2040 [9]. Additionally, DM was responsible for the deaths of 33.2 million people worldwide, and the associated morbidity and mortality

from DM complications account for most of the global health burden [9].

1.2. Glycemic Control

The International Expert Committee, organized by the American Diabetes Association in 2009 and the World Health Organization in 2011, recommended a fasting plasma glucose of >7.0 mmol/L along with a glycated hemoglobin A1c (HbA1c) level of >6.5% as a threshold for the diagnosis of DM.

Glycemic control is defined as an HbA1c value of <7% for patients aged <65 years and other age categories if it can be achieved safely without significant hypoglycemia or other adverse effects of treatment. The glycemic target for patients aged 65 to 75 years is <7.5%, whereas for patients aged >75 years or patients with a history of severe hypoglycemia, limited life expectancy, and advanced microvascular or macrovascular diseases, a value of <8% is acceptable as a glycemic target [10, 11]. T2DM treatment modalities, whether monotherapy or combination therapy, are based on the goal of HbA1c and fasting blood glucose (FBG) levels to optimize glucose levels, reduce chronic diabetic complications, and improve quality of life [8, 11].

2. Search Methodology

We have conducted a literature search for relevant articles in English only, focusing on hypomagnesemia and its impact on T2DM, in addition to articles that reported the effect of Mg supplements on blood Mg concentrations and long-term associations with T2DM control or prognoses. The search was conducted using several databases, including PubMed, Scopus, and Medline via the Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov. The search was performed using the following keywords and quotations: magnesium, magnesium supplementation, magnesium supplements, ionized magnesium, total magnesium, dietary magnesium, hypomagnesemia, dysmagnesemia, Type 2 diabetes, T2DM, diabetes, and diabetes mellitus.

3. Results

3.1. Magnesium Deficiency in T2DM

Long-term Mg deficiency or hypomagnesemia affects the tricarboxylic acid cycle and increases the risk of hyperinsulinemia and insulin resistance, which might increase the incidence of T2DM [2-4, 12-14]. A meta-analysis of 286,668 patients revealed that maintaining a dietary Mg intake of 100 mg/day reduced the risk of T2DM by 15% [15].

The incidence of hypomagnesemia requiring treatment is uncommon in T2DM patients, which is why the use of Mg replacement to care for patients with T2DM is not a routine clinical practice. However, latent long-term Mg deficiency is more common [13, 16]. In one study, the incidence was reported to be 44.8% using a threshold of 0.47 mmol/L of ionized Mg (iMg) concentrations [16]. Additionally, the total Mg (tMg) concentrations were also found to fall below 0.66 mmol/L (estimated mean reference range 0.67 ±0.13 mmol/L) in 52% of patients with T2DM and nephropathy [17].

The relationship between insulin and Mg is complex and has not yet been fully elucidated [18]. The ability of insulin to stimulate intracellular iMg concentrations is impaired in the presence of tMg deficiency [13]. The lower the serum iMg concentration, the lower the cellular insulin stimulation. In contrast, hyperglycemia induced by oral glucose ingestion, independent of insulin, caused *in-vivo* and *in-vitro* iMg depletion [13].

3.2. Effect of Hypomagnesemia on T2DM Control

The relationship between hypomagnesemia and T2DM control was reported in some studies but still requires further research. In one study, patients with T2DM (with or without diabetic complications) had significantly higher FBG and HbA1c levels but significantly lower serum Mg concentrations than healthy subjects ($P < 0.05$) [19]. Similarly, Wang and colleagues studied 1170 subjects with normal glucose regulation, 389 subjects with impaired glucose regulation, and 343 subjects with T2DM and noted that Mg concentrations in the T2DM group were significantly lower than those with the normal glucose regulation group (0.88 *vs.* 0.91 mmol/L; $P < 0.01$). Mg concentrations in the T2DM group were also found to be negatively correlated with FBG, 2-hour prandial glucose (2hPG), and HbA1c ($\beta = -0.29$, -0.17, and -0.34, respectively; all $P < 0.01$) [20]. However, further investigations are required to confirm its clinical relevance. Agrawal and colleagues found that serum tMg concentrations were significantly lower ($P < 0.05$) in the DM group with significantly higher FBG and HbA1c compared to the control group in a case-control study of 150 subjects (60 healthy controls and 90 DM patients) [19]. Another study involving 978 patients with T2DM observed that HbA1c was significantly higher in patients with hypomagnesemia, as measured by tMg than in those with normal tMg concentrations (8.6% *vs.* 7.40%; $P < 0.001$) [21].

3.3. Effect of Hypomagnesemia on T2DM Complications

Long-term hypomagnesemia has been linked to the diagnosis of DM, worsening T2DM control, and increased microvascular and macrovascular complications [22-24].

3.4. Macrovascular Complications

Mg is mainly excreted through the kidneys, and its homeostasis is affected by intestinal absorption. Thus, kidney disorders can lead to depletion and overload, both of which have been linked to an increased risk of CVD [24]. Wang et al. reported a significantly lower tMg concentration in T2DM patients with CVD (n = 306) than in those without CVD (n = 37) (0.88 *vs.* 0.85; $P = 0.004$) [20, 23]. A recent study reported a significantly higher pulse rate ($P = 0.039$) in patients with T2DM along with hypomagnesemia [23].

Mg effect on lipid profile was also studied. Data from a pooled analysis of multiple systematic reviews of different randomized controlled trials (RCTs) revealed an improvement in high-density lipoprotein (HDL) concentration. However, Mg appears to not affect other types of lipids, and the overall clinical impact of its effect on HDL remains to be confirmed [25-29].

3.5. Microvascular Complications

A case-control study with 100 patients was conducted to compare the presence or absence of diabetic retinopathy (DR) with tMg concentrations. It was found that tMg concentrations in patients with DR were significantly lower than those without DR (1.48 *vs.* 1.92 mg/dL; $P = 0.022$] [30].

The presence or absence of diabetic nephropathy (DN) in comparison with patients' tMg concentrations was also studied, and tMg concentrations in patients with DN were found to be significantly lower than in those without DN (1.62 *vs.* 1.86 mg/dl; $P < 0.001$). Furthermore, tMg concentrations were inversely correlated with serum creatinine ($rho = –0.222$; $P = 0.026$) [17]. A negative correlation between DN measured by an increase in serum creatinine and hypomagnesemia in patients with T2DM with uncontrolled blood sugar levels during medical ward admission was also apparent (*rho* = -0.48; $P = 0.001$) [22]. Moreover, a retrospective study of 978 patients with T2DM found significantly lower serum tMg concentrations in patients with abnormal nerve conduction studies than in those with normal nerve conduction studies (0.87 *vs.* 0.88 mmol/L; $P = 0.048$) [21].

3.6. Magnesium Supplements in T2DM

Several RCTs have shown that Mg supplementation improved disease control in T2DM patients, whereas others did not. The pooled analysis of systematic reviews, on the other hand and, did not yield a conclusive result [24, 26-29, 31-34].

A double-blind RCT from Mexico in 2003 in which 63 patients with T2DM on oral hypoglycemic agents (OHA) with low tMg concentrations (≤0.74 mmol/L) were supplemented with 50 ml $MgCl_2$ solution over 16 weeks demonstrated significant improvements in tMg concentrations (0.74 *vs.* 0.65 mmol/L; $P = 0.02$) and improvement in baseline in FBG (8.0 *vs.* 10.3 mmol/L; $P = 0.01$) and HbA1c (8.0% *vs.* 10.1%; $P = 0.04$) [35]. Using a similar methodology, two more recent RCTs in 2018 by ELDerawi *et al.* [34] and Razzaghi *et al.* [26] found that supplementing patients with T2DM with 250 mg Mg oxide tablets once daily for 12 weeks significantly improved FBG and HbA1c (*P* values ranging from < 0.001 to 0.03). In contrast, Sadeghian et al. conducted a double-blind RCT in Iran in 2009 on patients with T2DM with DN and hypomagnesemia and found no changes in the serum tMg concentrations and no significant difference ($P = 0.36$) in HbA1c levels between the placebo and the group receiving Mg oxide tablets 250 mg over 12 weeks [27].

Several systematic reviews and meta-analyses concerning Mg supplements for T2DM guided by tMg concentrations have been conducted (RCTs covered from 1989 to 2022; N = 1694 subjects from 28 articles) [28, 29, 32, 36]. A pooled analysis of these reviews found no significant improvements in diabetic control as measured by HbA1c among patients with T2DM supplemented with Mg [28, 32, 36], whereas a new study (N = 1325) found significant improvements in HbA1c [29]. Table 1. provides a summary of the effects of Mg supplements in patients with T2DM with or without hypomagnesemia from RCTs and a systematic review and meta-analysis of RCTs.

Table 1: Characteristics of Populations, Interventions, and Outcomes of Included Studies.

Authors, Year, Study Design (Reference)	Population (Number)	Intervention	Outcomes			
			Serum tMg	FBS	HBA1c (%)	Others
Rodríguez-Morán*et al.* [33] Double-blind RCT, (33)	T2DM with decreased serum Mg concertation (n=63)	50 ml $MgCl_2$ solution for 16 weeks	Increased (0.74 ± 0.10 vs 0.65 ± 0.07 mmol/L, P=0.02)	Reduced (8.0 ± 2.4 vs 10.3 ± 2.1 mmol/L, P=0.01)	Lowered (8.0 ± 2.4 vs 10.1 ± 3.3%, P=0.04)	Lowered HOMA-IR index (3.8 ± 1.1 vs 5.0 ± 1.3, P=0.005)
Chua*et al.* [32] Meta-analysis of 7 RCTs (32)	T2DM with and without hypomagnesemia (n=689)	Various forms and doses of Mg supplements	N/D	NS	NS	
Verma*et al.* [28] Systematic review & meta-analysis of 17 RCTs (28)	T2DM with and without hypomagnesemia (n=1694)	Various forms and doses of Mg supplements	N/D	Reduced (WMD = -4.641 mg/dL, 95% confidence interval (CI) = -7.602, -1.680, P=0.002)	NS	Improved high-density lipoprotein, low-density lipoprotein, and systolic blood pressure. During subgroup analysis, a more beneficial effect of magnesium supplementation was observed in diabetic subjects with hypomagnesemia.
WA*et al.* [34] RCT (34)	T2DM with and without hypomagnesemia (n=40)	250 mg of elemental Mg tablets once daily for 12 weeks	N/D	NS	Lowered (8.32 to 7.96%, P < 0.001)	Lower insulin levels (15.56 to 12.18 µIU/mL, P < 0.001) Lower C-peptide (2.28 to 1.90 ng/mL, P = 0.001), Lower HOMA.IR (6.16 to 4.44, P < 0.001) Lower HOMA.ß% (59.99 to 52.37, P = 0.036)
Razzaghi. et al., 2018 Double-blind RCT (26)	T2DM with and without hypomagnesemia with diabetic foot ulcer (n=70)	250 mg Mg oxide tablets once daily for 12 weeks	Increased (+0.3 ± 0.3 vs. -0.1 ± 0.2 mg/dL, P < 0.001)	Reduced (-45.4 ± 82.6 vs -10.6 ± 53.7 mg/dL, P = 0.04)	Lowered (-0.7 ± 1.5 vs -0.1 ± 0.4%, P = 0.03)	Reductions in ulcer length (-1.8 ± 2.0 vs -0.9 ± 1.1 cm, P = 0.01), width (-1.6 ± 2.0 vs -0.8 ± 0.9 cm, P = 0.02), and depth (-0.8 ± 0.8 vs -0.3 ± 0.5 cm, P = 0.003). Lower serum insulin values (-2.4 ± 5.6 vs +1.5 ± 9.6 µIU/mL, P = 0.04)
Sadeghian et al., 2019 Double-blind RCT (27)	T2DM with hypomagnesemia and early-stage nephropathy (n=80)	Mg oxide tablet 250 mg for 12 weeks	NS	N/D	NS	Greater insulin resistance (0.3 ± 2.3 µIU /mL vs - 0.04 ± 2.05, P = 0.04).
Xu et al., 2022 Pooled analysis of 24 RCT (29)	T2DM with and without hypomagnesemia (n=1325)	Various forms and doses of Mg supplements	N/D	Reduced (WMD = -0.20mM (95% CI:–0.30,–0.09))	Lowered (WMD = 0.22% (95% CI:–0.41,–0.03))	Reduced systolic blood pressure and diastolic blood pressure. Subgroup analyses showed that magnesium treatment in patients with hypomagnesemia or treated for ≥ 90 days exhibited a stronger effect on reducing FPG of T2D cases than respective other subgroups. Analysis of dose and duration effect showed that 279 mg per day- 116 days might be the average optimal for improving glycemic controls.

N/D: not done or documented, NS: not significant, T2DM: type 2 diabetes mellitus, RCT: randomized controlled trial, WMD: weighted mean difference., Mg: magnesium, FBS: fasting blood sugar/glucose, HBA1c: glycated hemoglobin 1c, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, HOMA-β: homeostasis model assessment of β-cell function.

3.6. Dose and Duration of Magnesium Supplements

Reports have shown no improvement in HbA1c levels in trials involving Mg sulfate or Mg citrate supplements [25, 37]. Interestingly, an RCT from Ivanovic *et al.* [38], explored the short-term effects of three Mg dietary supplements on serum of tMg and iMg concentrations in healthy young female adults. They used a dosage regimen of 375 mg per day for ten days, including Mg oxide, Mg citrate, and Mg carbonate, and found that only Mg oxide increased concentrations of both tMg and iMg compared to the baseline. Meanwhile, Mg citrate increased iMg but decreased tMg. In contrast, Mg carbonate decreased iMg without causing detectable changes in tMg [38]. Xu et al. also studied the dose and duration effects in a meta-analysis. They concluded that 279 mg per day over 116 days, 429 mg per day for 88 days, and 300 mg per day for 120 days might be optimal for improving glycemic, lipid, and blood pressure control, respectively [29].

Mg oxide supplements are inorganic salts of Mg [39]. A systematic review showed that organic formulations are more bioavailable than inorganic formulations. It appears that the solubility of Mg salts is more important than the dose for Mg tissue accumulation [39]. Notably, the solubility of Mg oxide is pH-dependent [40, 41], with 43% solubility under normal acid secretion and only 9% solubility under low acid secretions (achlorhydria conditions) [41]. Despite the low solubility range of Mg oxide, it provides a high loading concentration of iMg, which contrasts with what was observed using other Mg forms [40].

4. Discussion

Mg is an essential mineral involved in several metabolic processes in the body, including the regulation of insulin secretion and glucose metabolism [2, 3]. Some data suggest that magnesium supplementation enhances insulin sensitivity and glucose control in patients with T2DM [2-4, 12, 15].

Several studies have shown a significant inverse relationship between FBG and HbA1c levels and serum Mg concentrations in patients with T2DM [19-21]. In addition, long-term hypomagnesemia has been reported to have deleterious effects on both diabetic macrovascular complications such as CVD, and diabetic microvascular complications such as DN [17, 20, 23]. However, there is no consensus or conclusive evidence that supplements can improve diabetes outcomes or control. A possible explanation for such a discrepancy might be the heterogeneity in Mg supplement duration (4 to 16 weeks), variation in Mg dosage regimen (range from 36.49 mg to 500 mg per day), and the salt component of the tablets (organic Mg, e.g., citrate, lactate carbonate, or inorganic Mg, e.g., oxide, sulfate, chloride). Furthermore, there is no consensus regarding which serum Mg concentration (tMg *vs.* iMg) should be used to guide Mg supplementation or therapy in T2DM.

The strength of this review comes from involving a developed framework and detailed evaluation of the recent evidence with structural and theoretical data analysis. However, the studies reviewed in this article had the following limitations: Due to varying quality of evidence of small sample sizes of different participants' characteristics, varying doses, and different Mg salts, which accounts for high levels of heterogeneity that might affect the interpretation of the conclusions.

In summary, reports on the incidence of hypomagnesemia are increasing, and its association with macrovascular and microvascular complications, especially nephropathy, is unclear. Therefore, in patients with uncontrolled diabetes, routine measurements of serum Mg should be considered, as Mg supplementation appears to be a simple and inexpensive modality for improving T2DM control and reducing complications. However, an acceptable range of Mg concentrations (whether total or ionized) has yet to be established. Moreover, the appropriate dose and duration of Mg supplementation should be determined carefully. Therefore, larger RCTs are required before Mg supplements can be considered for inclusion in clinical practice guidelines for T2DM management.

5. Conclusion

Mg supplementation is a simple and inexpensive modality for improving T2DM control. Therefore, the appropriate dose and duration of Mg supplementation should be determined.

Author Contributions

Conceptualization, J.S.M., A.M.A.; bibliographic research, J.S.M., M.A.; writing—original draft preparation, J.S.M., M.A.; writing—review and editing, I.A., A.M.A.

All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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