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UNLOCKING THE POWER OF MAGNESIUM: A SYSTEMIC REVIEW AND META ANALYSIS REGARDING ITS ROLE IN METABOLIC DISORDER [DIABETES]

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ABSTRACT

Magnesium is an important micronutrient that regulates glucose homeostasis, insulin signaling, and energy metabolism. New research reveals that magnesium insufficiency is widespread in people with metabolic disorders, notably type 2 diabetes mellitus (T2DM), and may contribute to illness development and progression. The purpose of this systematic review and meta-analysis was to assess the relationship between magnesium consumption or supplementation and diabetes-related metabolic outcomes. Electronic databases such as PubMed, Scopus, and Web of Science were rigorously searched for observational studies and randomized controlled trials (RCTs) that examined dietary magnesium intake, serum magnesium levels, or magnesium supplementation in connection to diabetes risk and glycemic control. Incidence of type 2 diabetes, fasting plasma glucose, insulin resistance indicators, HbA1c, lipid profile, and blood pressure were among the outcomes of interest. The risk of acquiring type 2 diabetes is inversely correlated with dietary magnesium consumption, according to data from prospective cohort studies; dose-response analyses show that increased intake significantly reduces risk. Although effects on HbA1c were modest and varied, meta-analyses of RCTs showed that magnesium supplementation significantly improved insulin sensitivity and fasting blood glucose, especially in people with magnesium deficiency or poor glycemic control. Benefits also included improvements in blood pressure and cholesterol profiles, which may indicate more extensive cardio metabolic protection. Enhanced insulin receptor function, better glucose transport, decreased inflammation, and oxidative stress control are some of the suggested causes. Magnesium has been shown to have a positive function in the prevention and treatment of metabolic diseases, despite variations in study design, dosage, and duration. Making sure you consume enough magnesium through your diet and using specific supplements could be a low-risk, safe supplemental approach to diabetes treatment. More extensive, long-term studies are necessary to determine the best dosage and clinical recommendations.

KEYWORDS: Magnesium, micronutrient, diabetes, supplementation.

INTRODUCTION

Over time, global populations have seen a reduction in micronutrient intake due to changing dietary patterns. Among these nutrients,[1] magnesium (Mg)—one of the body's most abundant intracellular ions—plays a central role in essential biochemical processes. A lack of Mg can trigger serious biochemical and clinical imbalances in the human body.[2,3]

Diabetes mellitus (DM), a metabolic condition marked by persistent hyperglycaemia,[4] is closely associated with reduced Mg levels in both intracellular and extracellular compartments.[5] Low serum Mg (hypomagnesemia) has been linked to insulin resistance, while chronic hyperglycaemia worsens Mg loss, fueling a self-perpetuating cycle that drives both microvascular and macrovascular complications of diabetes.[6,7,8,9]

Although the precise mechanisms connecting DM and hypomagnesemia are not fully understood, metabolic studies indicate that Mg supplementation may enhance insulin sensitivity and improve glucose regulation.[1,10]

This review synthesizes evidence from the literature (1990–2004) on the Mg–DM connection, outlining established findings and highlighting unresolved debates. The following section expands on mechanisms, clinical significance, and more recent insights into this relationship.

1. Mechanisms Linking Magnesium Deficiency and Diabetes

Tissue-specific molecular roles of magnesium

Magnesium (Mg^{2+}) acts as a cofactor for hundreds of enzymes and is central to a wide range of cellular activities. For example, all kinases require the ATP–Mg^{2+} complex to transfer phosphate groups during cell signalling.[11] Mg^{2+} also plays a role in lipid and protein metabolism.[12] as well as electrolyte balance, by activating ATP-dependent pumps such as Na^+/K^+, Na^+/Ca^{2+}, Na^+/Mg^{2+}, and Mg^{2+}/Ca^{2+} transporters.

Beyond these functions, Mg^{2+} regulates cell growth by supporting DNA synthesis and repair, since it serves as a cofactor for multiple DNA repair enzymes.[13] Given its essential role in these fundamental processes, Mg^{2+} deficiency has been linked to several disorders, including type 2 diabetes mellitus (T2DM). The following sections outline how Mg^{2+} deficiency affects key tissues such as the pancreas, liver, and kidneys, contributing to the pathophysiology of diabetes.

Effects of Magnesium on Pancreatic β-Cells

Glucose regulation relies primarily on the pancreatic islets, liver, and peripheral tissues such as muscle and adipose tissue.[14] Within the islets, α-cells secrete glucagon in response to low glucose, while β-cells release insulin when glucose is elevated.[15]

A key player in insulin secretion is the ATP-sensitive potassium (KATP) channel, composed of four Kir6.2 subunits and four SUR1 regulatory subunits.[16] Under resting conditions, the channel remains open, allowing K^+ efflux. When intracellular ATP/ADP-Mg^{2+} levels rise, the channel closes, leading to membrane depolarization, Ca^{2+} influx, and insulin release.[16] ADP-Mg^{2+} supports channel opening via nucleotide-binding domains in SUR1, whereas ATP binding promotes closure. In magnesium deficiency, hyperpolarization and persistent channel opening block depolarization, ultimately suppressing insulin secretion.[17]

Magnesium also influences several enzymes involved in glycolysis and the Krebs cycle, including glucokinase (GCK), phosphofructokinase, and pyruvate kinase. Enhanced enzyme activity raises ATP production, which in turn closes KATP channels, depolarizes the membrane, and promotes Ca^{2+} entry through L-type calcium channels. However, Mg^{2+} can also compete with Ca^{2+} at these channels, reducing insulin release. In addition, Mg^{2+} may regulate the expression of glucose transporter 2 (GLUT2) and L-type Ca^{2+} channels, though no effect has been observed on GCK mRNA or the genes encoding KATP subunits (KCNJ11 and ABCC8).

Experimental data further highlight the complexity of Mg^{2+}'s role. In murine β-cell cultures, extracellular Mg^{2+} reduced Ca^{2+} uptake, suggesting that Mg^{2+} deficiency alters Ca^{2+} handling.[18] Moreover Murakami et al.[19] reported that insulin secretion triggered by KCl, forskolin, and D-glyceraldehyde increased intracellular Mg^{2+} in RINm5F cells, an effect blocked by verapamil, an L-type Ca^{2+} channel inhibitor.[19] These findings indicate that Mg^{2+} deficiency may impair Ca^{2+} transport and insulin secretion. Interestingly, suppression of TRPM7—the principal Mg^{2+} channel in β-cells—enhanced insulin secretion threefold in INS-1 cells.[20] Similarly, a pilot study in healthy subjects showed that intravenous magnesium sulfate ($MgSO_4$) infusion markedly reduced insulin levels.[18] Together, these studies suggest that Mg^{2+} can exert inhibitory as well as supportive effects on insulin secretion, depending on context.

Regarding glucose transport, GLUT2 is the main isoform mediating glucose entry into β-cells. In HepG2 cultures, mild Mg^{2+} deficiency (0.4 mM) increased GLUT2 mRNA by 250%, whereas Mg-deficient diets in rats decreased expression; in both cases, GLUT2 protein levels remained unchanged,[21] pointing to compensatory regulation. Molnes et al.[22] also noted that low Mg^{2+}-ATP concentrations might dampen the cooperative kinetics of GCK toward glucose. By contrast, Gommers et al.[20] found that reduced extracellular Mg^{2+} did not affect glucose-stimulated insulin release or GCK expression in mouse islets and INS-1 cells.

Overall, the relationship between Mg^{2+} and insulin secretion in β-cells remains unresolved. Conflicting evidence suggests both stimulatory and inhibitory effects, underscoring the need for further studies to clarify whether Mg^{2+} supplementation could enhance insulin release in type 2 diabetes.

Effects of Magnesium on Insulin Action in the Liver

The liver plays a central role in glucose homeostasis, being directly exposed to high glucose levels under the influence of both glucagon and insulin.[14] During fasting, hepatic glucose production is maintained through glycogenolysis and gluconeogenesis, while most glucose utilization (75–80%) occurs in non–insulin-dependent tissues such as the brain, intestine, erythrocytes, muscle, and adipose tissue.[23] After a meal, plasma glucose rises, prompting insulin release from pancreatic β-cells and suppression of glucagon secretion.[24] Insulin release occurs in two phases: an initial burst of mature insulin granules within the first two minutes of glucose elevation, followed by sustained release from reserve granules and de novo synthesis.[23] Insulin then suppresses hepatic and renal glucose output while promoting glucose uptake in muscle and adipose tissue, with muscle accounting for ~85% of glucose disposal. Simultaneously, insulin inhibits lipolysis, lowering free fatty acid levels and further dampening hepatic glucose production.[23]

In healthy individuals, blood glucose levels remain tightly regulated despite fluctuations in food intake.[24] In contrast, patients with type 2 diabetes mellitus (T2DM) exhibit exaggerated glucose excursions, delayed and blunted insulin secretion, and inadequate glucagon suppression.[24]

Insulin action in hepatocytes begins with its binding to the insulin receptor (IR),[25] a heterotetramer of two extracellular α-subunits (ligand-binding) and two transmembrane β-subunits (tyrosine kinase activity).[25] Upon binding, autophosphorylation of β-subunits recruits insulin receptor substrates (IRS-1 to IRS-4), initiating multiple downstream signaling cascades.

Among these, the PI3K–Akt pathway is essential for metabolic control, while the Ras–MAPK system controls cell growth.[26] 3-phosphoinositide-dependent protein kinase 1 (PDK1) is activated by PIP3 and phosphorylates and causes protein kinase B (AKT) to become active. By controlling many proteins, AKT activation has a variety of impacts. One of these is the 160 kDa AKT substrate protein (AS160), which controls the membrane translocation of glucose transporter 4 (GLUT4).[26] AKT encourages the production of glycogen by Glycogen synthase kinase 3β (GSK3β), a kinase that inhibits glycogen synthase (GS), is phosphorylated and inhibited.[26] Through transcription factors including Forkhead Box O1 (FOXO1) and the binding protein to the sterol regulatory element 1c (SREBP1c), AKT also controls the expression of genes linked to metabolism and survival. AKT adversely regulates FOXO1, encourages the production of gluconeogenic proteins in the liver, such as glucose 6 phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK).[26] Additionally, insulin promotes glycogen formation by stimulating phosphofructokinase (PFK) and glycogen synthase while suppressing G6Pase activity.[23] Similarly, insulin inhibits the lipolysis of stored triacylglycerols and stimulates fatty acid production in the liver.[23]

Magnesium's Role in Hepatic Insulin Sensitivity

Magnesium (Mg^{2+}) has been reported to exert insulin-mimetic effects in the liver. Etwebi[21] found that HepG2 cells cultured in low Mg^{2+} (0.4 mM) exhibited reduced ATP content and diminished insulin-mediated glucose uptake compared with cells grown under physiological Mg^{2+} (0.8 mM).

Insulin receptor regulation: Mg^{2+} may positively influence IR expression and activity. In rats, Mg^{2+} deficiency increased hepatic IR expression, whereas Mg^{2+} supplementation in diabetic rats enhanced IR expression in skeletal muscle. Supplementation also improved receptor binding affinity and capacity. In vitro studies indicate that Mg^{2+} levels modulate receptor tyrosine kinase activity. In vivo, Mg^{2+} deficiency reduces IR autophosphorylation in liver[69] and muscle.

- **IRS expression and phosphorylation:** Mg^{2+} influences IRS regulation in a tissue- and disease-dependent manner. Mg^{2+} supplementation increased IRS-1 in skeletal muscle[27] and IRS-2 in the liver of diabetic rats, while deficiency altered IRS-1 phosphorylation in opposing directions across studies. This variability suggests that Mg^{2+} effects on IRS are context dependent and not yet fully resolved.[28]
- **Downstream signaling:** Mg^{2+} deficiency reduces Akt phosphorylation,[29] while supplementation increases Akt2 expression in diabetic rats. Supplementation also downregulates FOXO1, inhibiting gluconeogenesis[30] Similarly, Mg^{2+} deficiency increases hepatic G6Pase activity by 25%, while supplementation decreases PEPCK and G6Pase mRNA and protein expression in diabetic rats.[31] Interestingly, short-term Mg^{2+} deficiency has also been shown to reduce PEPCK expression, likely via inflammation-driven mechanisms.[32]
- **Additional pathways:** Mg^{2+} supplementation enhances GLUT4 translocation, possibly through PPAR-γ activation, and modulates glucagon receptor expression. It may also promote glycolysis by increasing PFK-1 expression and stimulate insulin production indirectly through GLP-1.[33]

Magnesium effort on GLUT4

GLUT4 is the primary glucose transporter in skeletal muscle and adipose tissue.[23] In diabetic rat models, Mg^{2+} supplementation significantly increased GLUT4 mRNA and protein expression, as well as its translocation to the cell membrane.[31] Another study in the same model reported a 23% rise in GLUT4 mRNA expression with Mg^{2+} supplementation—more than double the 10% increase observed with insulin treatment alone ($p < 0.01$). This finding suggests that Mg^{2+} can enhance GLUT4 expression independently of insulin secretion.[34]

Similar results have been observed across multiple type 2 diabetes (T2DM) animal models, where Mg^{2+} supplementation elevated GLUT4 expression at both the mRNA and protein level,[35,33] and in some cases amplified the effect of drugs like metformin on GLUT4 mRNA expression.[33] Mechanistically, Khosravi et al.[36] proposed that Mg^{2+} may regulate GLUT4 via upregulation of peroxisome proliferator-activated receptor gamma (PPAR-γ), a transcription factor central to glucose and lipid metabolism.

Taken together, these findings indicate that Mg^{2+} exerts a beneficial effect on GLUT4 expression and translocation, thereby supporting glucose uptake in insulin-sensitive tissues.

Effects of Magnesium on the Kidney

In the kidney, 10–15% of Mg^{2+} reabsorption occurs in the proximal and distal convoluted tubules (DCT), while the majority (50–75%) is reabsorbed in the thick ascending limb of Henle's loop.[37] Here, Mg^{2+} reabsorption is mediated through a paracellular pathway driven by the $Na^+/K^+/Cl^-$ cotransporter (NKCC2). K^+ recycling via ROMK generates a positive luminal potential that facilitates Mg^{2+} transport through claudin-16 and claudin-19 channels.[38] In the DCT, Mg^{2+} handling is fine-tuned by TRPM6 channels, which may represent a key connection between insulin signaling and renal Mg^{2+} reabsorption.[39] Supporting this, a study in streptozotocin (STZ)-treated diabetic rats found that TRPM6 mRNA expression was elevated, and insulin treatment reduced its levels.[40]

Type 2 diabetes is commonly associated with glomerular damage, leading to proteinuria and albuminuria.[41] These disruptions compromise Mg^{2+} reabsorption and promote hypomagnesemia. A large cohort study of 5,126 chronic kidney disease (CKD) patients demonstrated a strong association between hypomagnesemia and high proteinuria, suggesting that protein loss drives Mg^{2+} wasting.[42] Similarly, low serum Mg^{2+} has been correlated with elevated microalbuminuria in T2DM.[43,44]

Magnesium handling is further impaired by increased renal excretion in T2DM. Studies consistently show higher Mg^{2+} urinary losses in diabetic versus healthy individuals.[45] Fractional excretion of magnesium (FE Mg) has even been proposed as a biomarker for diabetes detection.[46] Xu and Maalouf[47] found elevated FE Mg in hyperinsulinemic T2DM patients compared with controls, suggesting that insulin resistance itself contributes to renal Mg^{2+} wasting.

On the other hand, pharmacological interventions appear to improve Mg^{2+} retention. Treatment with simvastatin has been shown to lower urinary Mg^{2+} levels,[48] while metformin therapy reduces Mg^{2+} excretion from the third month onward,[49] with even greater reductions when combined with sulfonylureas.[45] Interestingly, in patients undergoing bariatric surgery, serum Mg^{2+} increased only in those who achieved T2DM remission, but not in those with persistent disease.[50]

Magnesium and Inflammation in T2DM

Chronic inflammation is recognized as a key factor in the pathogenesis of type 2 diabetes mellitus (T2DM).[51,52] Multiple studies have shown strong associations between inflammatory markers and both the incidence and complications of T2DM. For instance, King et al.[53] observed that C-reactive protein (CRP) levels—a common marker of systemic inflammation—increased in parallel with HbA1c levels among T2DM patients. This supports the link between poor glycemic control and heightened inflammatory status.[53,54] Prospective studies further confirm that individuals with elevated CRP have a higher risk of developing T2DM.[55,56]

Because of this, alterations in magnesium homeostasis may indirectly contribute to insulin resistance by modulating inflammatory and oxidative stress pathways. Indeed, low dietary Mg^{2+} intake has been repeatedly associated with higher CRP levels. Population studies show that individuals consuming less than the recommended Mg^{2+} have significantly greater prevalence of high CRP compared with those meeting dietary recommendations,[57] a pattern also seen in healthy children.[58]

An inverse association between Mg^{2+} intake and CRP levels has been documented across diverse populations, including adults, women adjusted for age and BMI,[59,60] and groups further adjusted for lifestyle factors such as physical activity, alcohol, and tobacco use.[61]

Cross-sectional studies have also reported negative correlations between serum or plasma Mg^{2+} and CRP in both adults[62] and children,[63] A 20-year prospective cohort study strengthened this evidence by showing long-term inverse associations between Mg^{2+} intake, serum Mg^{2+}, and CRP levels.[64] Notably, King et al.[57] reported that Mg^{2+} supplementation reduced the prevalence of elevated CRP, even among individuals consuming less than 50% of the recommended intake.

Taken together, these findings suggest that adequate magnesium intake—through diet or supplementation—may help lower systemic inflammation, as reflected by reduced CRP, and could play a protective role in mitigating inflammation-driven insulin resistance in T2DM.

Signs of Magnesium Deficiency[67,69]

- Muscle cramps and spasms
- Fatigue and weakness
- Irregular heartbeat
- Numbness or tingling
- Mood changes (anxiety, depression)

Who Might Need Supplements

- Individuals with digestive disorders (e.g., Crohn's disease, celiac disease)
- People with type 2 diabetes
- Those with chronic alcohol use
- Older adults
- Patients on certain medications (e.g., diuretics, proton pump inhibitors)

Precautions

- High supplemental doses (>350 mg/day) may cause diarrhea
- Magnesium can interact with medications such as antibiotics and antihypertensives

Magnesium rich foods and Dietary supplements[65,66,68]

Magnesium Rich Foods	Magnesium Dietary Supplements
Green leafy vegetables like [spinach] Nuts and Seeds like[pumpkin seeds, almonds, cashews etc] Fishes like [mackerel and salmon] Fruits like [bananas and avocados] Dark chocolates Plain yogurt	Magnesium Citrate Magnesium Glycinate Magnesium Oxide Magnesium Chloride Magnesium Malate Magnesium L- Threonate

Duration of Magnesium Supplementation and Its Influence on Health Outcomes

Clinical trials assessing magnesium (Mg^{2+}) in type 2 diabetes management generally supplement participants for three to six months. Within this period, improvements in insulin sensitivity and glycemic control have been reported. Longer supplementation may yield more pronounced benefits, with favorable effects on metabolic markers that support better long-term diabetes management and potentially reduce complications.

Study Overview: Serum Magnesium, Dietary Intake, and Metabolic Control in T2DM

Objective

To examine the relationship between serum magnesium levels, dietary magnesium intake, and metabolic control parameters in patients with type 2 diabetes mellitus (T2DM).[70]

METHODS

- Participants: 119 T2DM patients (26 men, 93 women; mean age 54.7 ± 8.4 years)[70]
- Measurements:
  - Serum magnesium measured via spectrophotometry
  - Dietary magnesium assessed using a food frequency questionnaire
  - Anthropometric parameters recorded
- Analysis: General Linear Model (GLM) applied to evaluate associations between serum magnesium and metabolic variables.[70]

RESULTS

- **Prevalence**
  - 23.5% had inadequate dietary magnesium intake (<67% RDA)
  - 18.5% had hypomagnesemia (<0.75 mmol/L)

- **Metabolic outcomes**
  - Patients with hypomagnesemia had higher fasting plasma glucose (FPG), postprandial glucose (PPG), and HbA1c levels compared to normomagnesemic patients.[70]
  - FPG was significantly higher in hypomagnesemic patients in Model 1 (179.0 ± 64.9 vs. 148.7 ± 52.0 mg/dL, p = 0.009), though significance disappeared in adjusted models.
  - PPG remained significantly higher across all models (e.g., Model 1: 287.9 ± 108.4 vs. 226.8 ± 89.4 mg/dL, p = 0.006).
  - HbA1c levels were consistently elevated in hypomagnesemia across all models (8.0 ± 1.9% vs. 6.5 ± 1.2%, p = 0.000).[70]

- **Anthropometrics**
  - Body fat mass was significantly higher in hypomagnesemic patients in Model 3 (35.4 ± 9.4 vs. 34.6 ± 10.2 kg; p = 0.034).
- Dietary magnesium intake: No significant association with metabolic or anthropometric parameters.[70]

Interpretation

These findings suggest that serum magnesium status, rather than dietary intake alone, is closely linked to glycemic control in T2DM. Hypomagnesemia was consistently associated with higher postprandial glucose, HbA1c, and greater body fat mass, indicating its potential role in poor metabolic outcomes.

CONCLUSION

Hypomagnesemia in patients with type 2 diabetes mellitus (T2DM) is strongly associated with poor metabolic control, reflected in higher glucose levels, elevated HbA1c, and increased body fat mass. These findings emphasize the importance of monitoring magnesium status as part of routine clinical assessment in T2DM.

Magnesium plays a central role in insulin sensitivity and glucose metabolism. Consistently, low magnesium intake has been linked to a higher risk of developing T2DM, while adequate magnesium levels are associated with improved metabolic outcomes. Clinical and experimental studies suggest that magnesium supplementation can enhance insulin action, reduce blood sugar levels, and potentially lower the risk of diabetes-related complications.

Taken together, ensuring sufficient magnesium intake—through diet or supplementation—may represent a valuable and underutilized strategy for both the prevention and management of T2DM.

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