Cureus
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Open Access Review Article

Magnesium Status and Its Association With Glycemic Control and Diabetes-Related Complications in Type 2 Diabetes Mellitus: A Systematic Review

Review began 09/29/2026
Review ended 10/12/2026
Published 10/26/2026

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DOI: 10.7759/cureus.118610

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Abstract

Type 2 diabetes mellitus (T2DM) is frequently accompanied by disturbances in magnesium homeostasis, which may influence insulin action, glycemic regulation, and the development of vascular and neurological complications. Despite increasing interest in magnesium deficiency, evidence remains inconsistent because of variation in magnesium assessment, study design, clinical populations, and evaluated outcomes. This systematic review examined the relationship between magnesium status, glycemic control, diabetes-related complications, and the potential effects of magnesium supplementation primarily in adults with T2DM. PubMed/MEDLINE, Scopus, Google Scholar, and Web of Science were searched for original studies published between January 2020 and September 5, 2026. Of 252 identified records, 211 were screened after duplicate removal, 47 full-text articles were assessed, and 10 studies were included in the qualitative synthesis. Most included studies were cross-sectional or retrospective, with one randomized crossover trial. Lower magnesium status was commonly associated with poorer glycemic control, including elevated HbA1c and glucose concentrations, greater insulin resistance, and diabetes-related complications, such as retinopathy, neuropathy, nephropathy, and vascular disease. Magnesium exposure was assessed using serum magnesium, ionized and total magnesium, magnesium depletion scores, dietary magnesium intake, or supplementation. The randomized trial demonstrated an increase in serum magnesium concentrations without significant improvements in insulin sensitivity or glycemic outcomes. Current evidence suggests that magnesium status may be a relevant metabolic marker in T2DM; however, predominantly observational findings, methodological heterogeneity, and limited interventional evidence prevent causal conclusions or recommendations for routine magnesium supplementation.

Categories: Nutrition, Internal Medicine, Endocrinology/Diabetes/Metabolism
Keywords: diabetic complications, glycemic control, hypomagnesemia, magnesium, type 2 diabetes mellitus

Introduction And Background

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease characterised by insulin resistance, progressive pancreatic β-cell dysfunction, and persistent hyperglycemia. Its increasing prevalence contributes to a substantial clinical burden, particularly through the development of microvascular and macrovascular complications. Altered magnesium status has been investigated in relation to cardiovascular and microvascular complications, including heart failure, atrial fibrillation, and diabetic microvascular disease [1]. Magnesium deficiency has also been documented among individuals with T2DM, suggesting that disturbances in magnesium homeostasis may be relevant to the broader metabolic abnormalities associated with the disease [2]. A systematic review and meta-analysis examining the global prevalence of hypomagnesemia in T2DM reported considerable variation across observational studies, highlighting the influence of population characteristics and diagnostic criteria [3].

Magnesium is an essential predominantly intracellular cation involved in numerous physiological processes, including carbohydrate metabolism, energy production, membrane function, and insulin signalling. Its potential clinical relevance extends to diabetes-related complications, with observational research investigating associations between hypomagnesemia and adverse diabetic outcomes [4]. Studies examining serum magnesium and glycemic status have reported associations between reduced magnesium concentrations and poorer glycemic control in patients with T2DM [5]. A review examining magnesium and vitamin D described their potential involvement in insulin signalling, insulin sensitivity, and glycemic regulation [6]. These findings support further investigation of magnesium homeostasis in T2DM, although observational associations cannot establish a direct causal relationship.

Hypomagnesemia is frequently reported among individuals with T2DM, although its prevalence varies according to the study population, diagnostic thresholds, and magnesium assessment methods. A primary-care cohort study identified associations between serum magnesium concentrations and metabolic characteristics, including glycated hemoglobin (HbA1c), body mass index, and the use of certain glucose-lowering medications [7]. The clinical significance of reduced magnesium levels may extend beyond

glycemic regulation, as retrospective evidence has associated lower serum magnesium concentrations with diabetic retinopathy [8]. Additional observational investigations have examined fasting serum magnesium in relation to T2DM and its chronic complications, supporting the need to evaluate magnesium status alongside established clinical and metabolic indicators [9].

The relationship between magnesium status and glycemic control also requires consideration of other biochemical abnormalities. Hospital-based research has examined associations between HbA1c and serum electrolyte imbalance in patients with T2DM, highlighting the broader relevance of electrolyte disturbances in diabetic populations [10]. A systematic review and meta-analysis involving patients with type 1 diabetes reported an association between reduced serum magnesium concentrations and poorer glycemic control, while evidence regarding individual diabetic complications remained inconclusive. These findings provide context regarding magnesium-related metabolic disturbances but should not be directly extrapolated to T2DM [11]. Differences in the underlying pathophysiology and clinical characteristics of type 1 and type 2 diabetes emphasise the importance of evaluating magnesium-related outcomes within the specific population under investigation.

Assessment of magnesium status presents additional challenges because circulating magnesium represents only a small proportion of total body magnesium. Total serum magnesium includes protein-bound and unbound fractions, whereas ionised magnesium represents the physiologically active fraction. Intracellular magnesium constitutes a substantial proportion of magnesium stores and is not directly reflected by routine serum measurements. Consequently, serum magnesium concentrations may not fully characterise intracellular magnesium availability. The distinction between circulating and intracellular magnesium is relevant when interpreting biochemical measurements and comparing findings across studies. Differences in magnesium assessment methods may contribute to variation in reported associations with glycemic control and diabetes-related complications.

The therapeutic value of magnesium supplementation in T2DM remains uncertain. A prospective, open-label, single-arm study investigated a combined intervention involving *Gymnema sylvestre*, magnesium, and vitamin D3 in relation to glycemic control in patients with T2DM [12]. The absence of a magnesium-only intervention group prevents the independent effects of magnesium from being determined. Evidence concerning magnesium supplementation alone remains insufficient to determine whether correcting magnesium deficiency consistently improves insulin sensitivity, glycemic regulation, or long-term diabetic outcomes. Differences in baseline magnesium status, intervention duration, supplementation dose, and study design further complicate the interpretation of available findings.

Important knowledge gaps remain regarding the consistency, clinical significance, and direction of associations between magnesium status and T2DM outcomes. Existing studies differ in participant characteristics, magnesium assessment methods, definitions of glycemic control, and evaluation of diabetes-related complications. The predominantly observational evidence limits causal interpretation, while the therapeutic implications of magnesium supplementation remain uncertain. These methodological differences make it difficult to establish whether altered magnesium status contributes independently to metabolic dysfunction or primarily reflects underlying disease severity. A systematic synthesis of recent evidence is needed to evaluate these associations, identify methodological limitations, and establish priorities for future research.

Objective of the Review

The purpose of this systematic review is to evaluate the association between magnesium status and glycemic control in adults with T2DM, including its relationship with major diabetes-related microvascular and macrovascular complications. The review also examines evidence regarding magnesium supplementation, considers differences in magnesium assessment and study methodology, and identifies knowledge gaps that warrant further investigation through prospective studies and adequately powered randomised controlled trials.

Review

Methodology

Study Design and Reporting

This systematic review examined original observational and interventional studies investigating the associations between magnesium status, glycemic control, and diabetes-related complications among adults with T2DM. The review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [13]. Eligible studies were published between 2020 and 2026 and evaluated circulating magnesium concentrations, magnesium depletion measures, dietary magnesium intake, or magnesium supplementation in relation to metabolic or clinical outcomes. The systematic review protocol was not prospectively registered. Differences in study design, magnesium assessment methods, participant characteristics, and outcome definitions precluded a meaningful quantitative synthesis; therefore, findings were synthesized qualitatively.

Search Strategy

A systematic literature search was conducted in PubMed/MEDLINE, Scopus, Google Scholar, and Web of Science. The final literature search was conducted on September 5, 2026. Search concepts encompassed T2DM, magnesium status, glycemic regulation, diabetes-related complications, and magnesium supplementation. The search terminology included "type 2 diabetes mellitus", "magnesium", "hypomagnesemia", "glycemic control", "HbA1c", "fasting glucose", "insulin resistance", "diabetic retinopathy", "neuropathy", "nephropathy", "cardiovascular complications", and "magnesium supplementation". Search terms were combined using Boolean operators (AND and OR), with syntax adapted to the indexing and search functionality of each database. Studies published between January 1, 2020, and September 5, 2026, were considered. The database-specific search strategies are presented in Table *1*.

Database	Search strategy
PubMed/MEDLINE	("type 2 diabetes mellitus" OR "T2DM") AND ("magnesium" OR "hypomagnesemia") AND ("glycemic control" OR "HbA1c" OR "insulin resistance" OR "diabetic complications")
Scopus	("type 2 diabetes mellitus" OR "T2DM") AND ("magnesium" OR "hypomagnesemia") AND ("glycemic control" OR "retinopathy" OR "neuropathy" OR "nephropathy" OR "supplementation")
Google Scholar	"type 2 diabetes mellitus" AND "magnesium" AND ("glycemic control" OR "diabetic complications" OR "supplementation")
Web of Science	("type 2 diabetes mellitus" OR "T2DM") AND ("magnesium" OR "hypomagnesemia") AND ("glycemic control" OR "diabetic complications" OR "cardiovascular complications")

TABLE 1: Database-Specific Literature Search Strategies

Two independent reviewers screened the titles and abstracts of identified records and subsequently assessed potentially eligible full-text articles against the predefined inclusion and exclusion criteria. The reviewers conducted their initial assessments independently, without access to each other's screening decisions, ensuring blinding of initial eligibility decisions. Blinding to study authorship and journal information was not implemented. Any disagreements regarding study eligibility were resolved through discussion and consensus between the two reviewers. Studies selected for final analysis were those with accessible full texts and adequate outcome information for qualitative synthesis.

Eligibility Criteria

The eligibility criteria were structured using the population, exposure, comparator, and outcomes (PECO) framework, with adaptations for interventional studies. The eligibility framework is summarized in Table *2*.

PECO component	Eligibility criteria
Population (P)	Adults aged 18 years or older with T2DM, including studies involving broader diabetes mellitus populations where findings on magnesium status and diabetes-related complications were relevant to T2DM but not separately stratified by diabetes type.
Exposure (E)	Serum magnesium, ionized magnesium, total magnesium, magnesium depletion scores, dietary magnesium intake, or magnesium supplementation
Comparator (C)	Different magnesium concentrations or exposure categories, participants with and without hypomagnesemia, or placebo/control conditions in interventional studies, where applicable
Outcomes (O)	HbA1c, fasting or postprandial glucose, insulin resistance/sensitivity, retinopathy, neuropathy, nephropathy, cardiovascular disease, peripheral vascular disease, hypertension, and renal outcomes

TABLE 2: PECO Framework for the Study Eligibility Criteria

PECO, population, exposure, comparator, and outcomes; T2DM, type 2 diabetes mellitus

Eligible designs included cross-sectional, retrospective, other observational studies, and randomized clinical

trials published between 2020 and 2026. Studies were required to report original findings concerning magnesium status or supplementation in relation to glycemic control or diabetes-related complications. Studies involving broader diabetes mellitus populations were considered where the findings were relevant to the review objectives, with limitations regarding diabetes-type specificity acknowledged during interpretation. Reviews, meta-analyses, editorials, conference abstracts, non-English publications, non-original studies, and studies with insufficient outcome data or those not meeting the predefined population or exposure criteria were excluded. A qualitative synthesis was performed using the eligible original studies.

Study Selection and Data Extraction

A step-wise approach was used to screen all identified records. Before title and abstract screening, duplicate records were removed. Two reviewers independently screened the titles and abstracts of retrieved records and subsequently assessed potentially eligible full-text articles against the predefined eligibility criteria. Disagreements concerning study inclusion were resolved through discussion and consensus.

Two reviewers independently extracted data from the included studies using a standardized data-extraction framework. The extracted information was cross-checked for accuracy and completeness, and any discrepancies were resolved through discussion and consensus. The extracted variables included author, publication year, country, study design, sample size, participant characteristics, magnesium assessment method or intervention, glycemic outcomes, diabetes-related complications, and principal findings. Where reported, quantitative results, including correlation coefficients, odds ratios, means, measures of variability, p-values, and confidence intervals, were recorded to support comparison across studies.

Ten studies fulfilled the eligibility criteria and were included in the final qualitative synthesis. The overall study selection process is presented in the PRISMA 2020 flow diagram (Figure *1*).

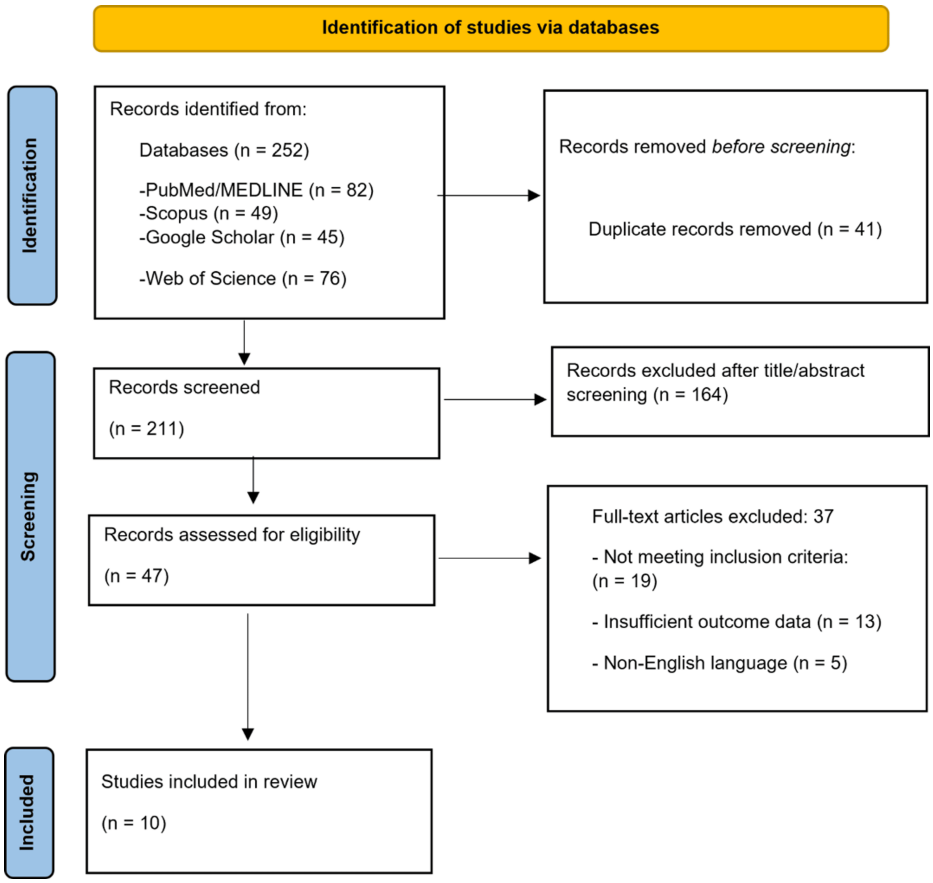


FIGURE 1: Flow Diagram of the Study Selection Following PRISMA Guidelines 2020

Risk of Bias Assessment

Two reviewers independently assessed the risk of bias of the included studies using study-design-appropriate assessment tools. The nine observational studies were evaluated using the Joanna Briggs

Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies [14]. The assessment covered participant inclusion criteria, descriptions of study participants and settings, exposure measurement, diagnostic criteria, identification and management of confounding factors, outcome measurement, and statistical analysis. Checklist responses were recorded according to the available evidence and the applicable JBI response categories (Yes, No, Unclear, or Not Applicable). Disagreements between reviewers were resolved through discussion and consensus.

The randomized, double-blind, placebo-controlled crossover trial was evaluated separately using the Cochrane Risk of Bias 2 (RoB 2) framework, with consideration of the additional methodological issues relevant to crossover trials [15]. The assessment addressed randomization, deviations from intended interventions, missing outcome data, outcome measurement, selection of reported results, and potential period or carryover effects. Risk-of-bias judgments were interpreted at the domain level and overall, where sufficient information was available. The appraisal findings were considered during qualitative synthesis, and no numerical quality scores were calculated.

Data Synthesis

Due to differences in methodology, sample size, magnesium assessment methods, study populations, and outcome definitions, a qualitative synthesis was performed. The feasibility of conducting a meta-analysis was considered; however, substantial clinical and methodological heterogeneity, including differences in exposure measurements, study designs, outcome definitions, and reported statistical measures, precluded meaningful quantitative pooling. Findings were organized into two principal categories encompassing magnesium status in relation to glycemic control and diabetes-related complications.

Glycemic outcomes included HbA1c, fasting glucose, postprandial glucose, insulin resistance, and insulin sensitivity. Clinical complications included diabetic retinopathy, neuropathy, nephropathy, cardiovascular disease, peripheral vascular disease, and hypertension.

Observational associations were summarized according to their direction, magnitude, and statistical significance when these data were available. Reported correlation coefficients, odds ratios, group means, p-values, and confidence intervals, where available, were examined descriptively without combining estimates across studies. Positive, inverse, and statistically nonsignificant associations were distinguished, while the magnitude of individual findings was interpreted in relation to the reported measurement scales and clinical outcomes. Statistical significance was considered alongside effect magnitude and study limitations rather than as the sole indicator of clinical relevance. Differences in exposure definitions, study designs, and reported outcomes were considered during interpretation. No pooled effect estimates were calculated because the included studies were not considered sufficiently comparable for quantitative synthesis. Consequently, pooled heterogeneity statistics, meta-regression, and formal assessments of publication bias based on pooled estimates were not performed.

The randomized magnesium supplementation trial was evaluated separately from the observational studies to distinguish associations between magnesium status and clinical outcomes from evidence concerning the therapeutic effects of supplementation. Its findings were summarized according to the reported intervention effects, statistical significance, and clinical relevance without combining them with observational association estimates. This distinction was maintained when interpreting the overall findings and their clinical implications.

Results

Study Selection

A total of 252 records were retrieved from the database search, of which 82 were from PubMed/MEDLINE, 49 from Scopus, 45 from Google Scholar, and 76 from Web of Science. Following the removal of 41 duplicate records, 211 titles and abstracts were screened. Of these, 164 records were excluded during title and abstract screening, leaving 47 full-text articles for eligibility assessment. Following full-text assessment, 37 articles were excluded: 19 did not meet the predefined eligibility criteria, 13 provided insufficient outcome data, and five were non-English publications. Ten original studies fulfilled the eligibility criteria and were included in the final qualitative synthesis. The process of selection of the studies following PRISMA 2020 is presented in Figure *1*.

Study Characteristics

The 10 included studies were conducted in India, Türkiye, Oman, China, the United States, Saudi Arabia, and the Netherlands, and were published between 2021 and 2026. The majority of studies employed cross-sectional or retrospective observational designs, while one was a randomized, double-blind, placebo-controlled crossover trial. Sample sizes ranged from 14 to 4,487 participants. Magnesium status or exposure was assessed using serum magnesium concentrations, ionized and total magnesium measurements, magnesium depletion scores, dietary magnesium intake, and oral magnesium supplementation. The

reported outcomes included HbA1c, fasting and postprandial glucose, insulin resistance, diabetic retinopathy, neuropathy, nephropathy, cardiovascular conditions, and peripheral vascular complications. A summary of the characteristics and key findings of the included studies is presented in Table 3.

Study	Country	Study design	Sample size	Magnesium assessment/exposure	Main outcomes assessed	Key findings
Sri et al. [16]	India	Cross-sectional analytical study	55 T2DM patients	Serum magnesium; hypomagnesemia defined as <1.70 mg/dL	HbA1c, fasting blood sugar (FBS), postprandial blood sugar (PPBS)	Hypomagnesemia was present in 21.8% of participants. Serum magnesium correlated inversely with HbA1c (r = −0.41), FBS (r = −0.28), and PPBS (r = −0.34). Patients with hypomagnesemia had significantly higher HbA1c (9.72 ± 2.85% vs 7.65 ± 1.94%; p = 0.011).
Konur et al. [17]	Türkiye	Retrospective cross-sectional study	502 T2DM patients	Serum magnesium concentration	HbA1c-defined glycemic control, hypertension, cardiovascular comorbidities, medication use	Patients with poor glycemic control had significantly lower magnesium levels. Magnesium was associated with hypertension, sex, metformin and indapamide use, and showed an inverse association with congestive heart failure. Its discriminatory ability for glycemic control was limited (AUC = 0.41).
Al-Maqbali et al. [18]	Oman	Cross-sectional study	329 T2DM patients	Ionized Mg (iMg), total Mg (tMg), and iMg/tMg ratio	HbA1c, retinopathy, hypertension, renal function, and other diabetic complications	Hypomagnesemia occurred in 10.0% using iMg and 56.2% using tMg. An iMg/tMg ratio >80% was associated with elevated HbA1c, whereas a ratio <60% was associated with diabetic retinopathy and hypertension. The Mg ratio showed potential as a marker of glycemic status and complications.
Liu and Hu [19]	China	Retrospective cross-sectional study	136 T2DM patients	Serum Mg divided into quartiles	Corneal nerve fiber length (CNFL), density (CNFD), branch density (CNBD), FBG, HbA1c	Higher serum Mg was independently associated with better corneal nerve morphology. Mg correlated positively with CNFL (r = 0.550), CNFD (r = 0.432), and CNBD (r = 0.425), all p < 0.001, supporting a potential relationship between low magnesium and diabetic small-fiber neuropathy.
Gu et al. [20]	United States	Cross-sectional analysis of NHANES 2005–2018	4,487 T2DM patients; 942 with DR	Magnesium depletion score (MDS)	HbA1c, glycemic control, diabetic retinopathy (DR), interaction between MDS and HbA1c	Both high MDS (≥2) and poor glycemic control (HbA1c ≥7%) were independently associated with greater DR risk. MDS and HbA1c showed significant interaction, particularly among women, patients ≥60 years, and those with cardiovascular disease.
Luo et al. [21]	China	Retrospective observational cross-sectional study	1,694 T2DM patients	Serum magnesium measured by colorimetric method	HbA1c, FPG, HOMA-IR, lipid parameters and glycemic control	Serum Mg was lower among patients with poor glycemic control and correlated negatively with HbA1c (r = −0.29), FPG (r = −0.20), and HOMA-IR (r = −0.05), all statistically significant.
Chen et al. [22]	United States	Cross-sectional analysis of NHANES 2005–2018	4,308 participants with diabetes mellitus (diabetes type not explicitly restricted)	Magnesium depletion score and dietary magnesium intake	Diabetic retinopathy, glycemic control and magnesium intake	Participants with DR had lower dietary magnesium intake (259.1 ± 113.6 vs 269.8 ± 113.2 mg; p < 0.001). Higher MDS was associated with increased DR risk, whereas greater dietary magnesium intake was associated with lower DR risk.
Alswat [23]	Saudi Arabia	Cross-sectional study	285 T2DM patients	Serum Mg; hypomagnesemia defined as <0.7 mmol/L	HbA1c, neuropathy, nephropathy, retinopathy, diabetic foot, cardiovascular parameters	28.4% of participants had hypomagnesemia. Low magnesium was associated with significantly poorer glycemic control and a greater prevalence of diabetic foot/peripheral artery disease; most other complications were also more frequent in the hypomagnesemic group.
Feng et al. [24]	China	Observational comparative study	103 participants: 20 healthy controls, 24 T2DM, 59 T2DM with diabetic	Serum and urinary magnesium, together with zinc	Diabetic nephropathy, renal functional impairment, inflammatory cytokines	Serum Mg was significantly lower in patients with T2DM and diabetic nephropathy than in healthy controls. Urinary Mg concentrations decreased with worsening nephropathy-associated renal dysfunction, supporting an association between disturbed Mg status and renal complications.

			nephropathy			
Drenthen et al. [25]	Netherlands	Randomized, double-blind, placebo-controlled crossover trial	14 insulin-treated T2DM patients with low serum Mg	Oral magnesium 15 mmol/day for 6 weeks vs placebo	Insulin sensitivity by hyperinsulinemic-euglycemic clamp, HbA1c, CGM parameters, insulin requirement, BP and lipids	Supplementation significantly increased serum Mg (0.75 vs 0.70 mmol/L; p = 0.016) but did not significantly improve insulin sensitivity, HbA1c, CGM outcomes, insulin dose, or BP compared with placebo.

TABLE 3: Characteristics and Key Findings of the Studies Included in the Systematic Review

BP, blood pressure; CGM, continuous glucose monitoring; CNBD, corneal nerve branch density; CNFD, corneal nerve fiber density; CNFL, corneal nerve fiber length; DR, diabetic retinopathy; FBG/FBS, fasting blood glucose/fasting blood sugar; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; iMg, ionized magnesium; MDS, magnesium depletion score; Mg, magnesium; PPBS, postprandial blood sugar; tMg, total magnesium; T2DM, type 2 diabetes mellitus

Risk of Bias Assessment

The methodological quality of the included studies varied across study designs. Most observational studies reported objective magnesium measurements and used statistical methods appropriate to their study designs. The principal methodological concerns involved potential residual confounding, differences in participant selection, and limitations in outcome assessment. The cross-sectional and retrospective designs also restricted the ability to establish temporal relationships or draw causal conclusions. The JBI critical appraisal findings for the nine observational studies are presented in Table *4*.

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Sri et al. 2026 [16]	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Konur et al. 2026 [17]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Al-Maqbali et al. 2025 [18]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Liu and Hu 2025 [19]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gu et al. 2025 [20]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Luo et al. 2024 [21]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chen et al. 2023 [22]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Alswat 2021 [23]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Feng et al. 2021 [24]	Yes	Yes	Yes	Yes	No	No	Yes	Yes

TABLE 4: JBI Critical Appraisal of Observational Studies

JBI, Joanna Briggs Institute; Q1, Clearly defined inclusion criteria; Q2, Detailed description of participants and settings; Q3, Valid and reliable exposure measurement; Q4, Objective and standard criteria for measuring the condition; Q5, Identification of confounding factors; Q6, Strategies to address confounding factors; Q7, Valid and reliable outcome measurement; Q8, Appropriate statistical analysis

The randomized crossover trial incorporated randomization, blinding, placebo control, and objective insulin-sensitivity measurement. Its small sample size restricted the precision and generalizability of the findings. However, these design features alone do not establish a low risk of bias, and the assessment must also consider missing outcome data, selective reporting, and potential period or carryover effects. The risk-of-bias assessment of the randomized crossover trial is presented separately in Table *5*.

Assessment component	Risk-of-bias judgment	Explanation
Randomization process	Low risk	Pharmacy-administered block randomization ensured balanced treatment sequences and supported allocation concealment.
Deviations from intended interventions	Low risk	Double-blind, placebo-controlled design with comparable treatment adherence across periods.
Missing outcome data	Low risk	All 14 participants completed the trial, with complete primary outcome data. Some secondary outcomes had smaller denominators.
Outcome measurement	Low risk	Insulin sensitivity was objectively measured using a standardized hyperinsulinemic-euglycemic clamp.
Selection of reported results	Some concerns	The primary outcome was specified, but consistency with the prespecified analysis plan requires verification.
Period and carryover effects	Some concerns	No additional washout period was included, although the statistical analysis accounted for treatment period.
Overall risk-of-bias judgment	Some concerns	Potential selective-reporting and carryover-related bias cannot be fully excluded.

TABLE 5: Risk-of-Bias Assessment of the Randomized Crossover Trial

RoB 2, Risk of Bias 2

Magnesium Status and Glycemic Control

Several included observational studies reported an association between reduced magnesium status and poorer glycemic control in patients with T2DM [16,17,21,23]. Inverse correlations between serum magnesium concentrations and HbA1c, fasting glucose, and postprandial glucose were reported, while an association with insulin resistance, assessed using Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), was also observed [16,21]. Patients with hypomagnesemia generally exhibited higher HbA1c levels than those with normal magnesium concentrations [16,23]. Studies employing ionized magnesium measurements and magnesium depletion scores provided additional evidence of relationships between magnesium status and metabolic outcomes [18,20]. These findings suggest that magnesium status may be associated with glycemic regulation across different populations and assessment methods, although the observational designs limit causal interpretation [16-18,21]. In contrast, the randomized crossover trial demonstrated that short-term oral magnesium supplementation did not significantly improve insulin sensitivity, HbA1c, or continuous glucose-monitoring parameters despite increasing serum magnesium concentrations [25]. The glycemic parameters evaluated in relation to magnesium status are displayed in Figure *2*.

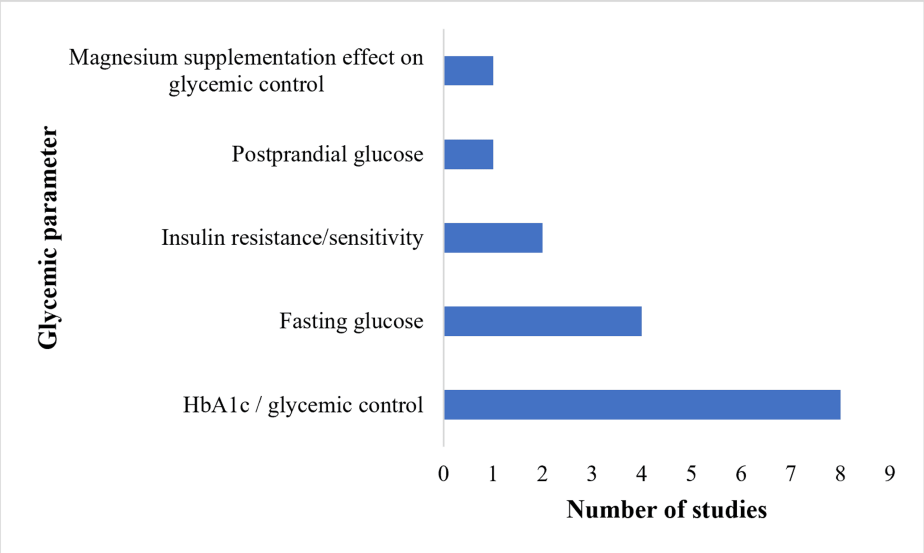


FIGURE 2: Glycemic Parameters by Magnesium Status

Magnesium Status and Diabetes-Related Complications

The included studies also examined the association between magnesium status and diabetes-related complications. Higher magnesium depletion scores were associated with an increased risk of diabetic retinopathy [20,22], whereas greater dietary magnesium intake was associated with a lower risk of diabetic retinopathy [22]. Diabetic foot disease and peripheral artery disease were more frequently reported among patients with hypomagnesemia [23]. Altered magnesium status was also associated with nephropathy-related renal dysfunction and abnormalities in corneal small-fiber nerve morphology [19,24]. In the neuropathy study, higher levels of magnesium were associated with longer, denser, and more branching corneal nerves [19]. The ionized-to-total magnesium ratio was additionally associated with indicators of retinopathy and hypertension [18]. These findings suggest that disturbances in magnesium homeostasis may be associated with both microvascular and macrovascular complications in patients with T2DM [18,19,23,24]. Figure *3* shows the diabetes-related complications associated with magnesium status.

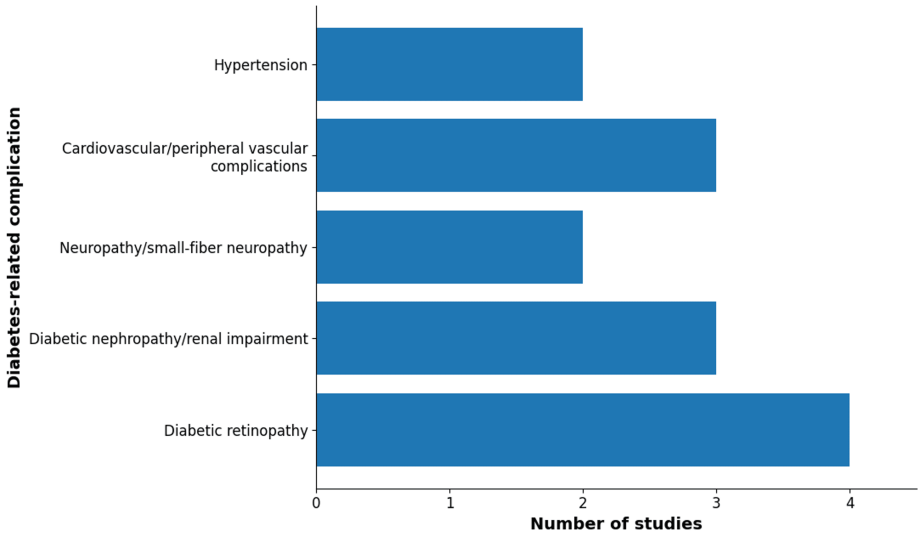


FIGURE 3: Diabetes-Related Complications and Magnesium Status

Discussion

Magnesium Status and Glycemic Control

This systematic review identified a consistent association between reduced magnesium status and poorer

glycemic control among patients with T2DM. Most observational studies reported lower serum magnesium concentrations in patients with elevated HbA1c and fasting glucose levels [16,17,21,23]. The reported prevalence of hypomagnesemia varied across study populations because of differences in diagnostic thresholds, participant characteristics, and magnesium assessment methods [16,18,23]. These findings support an association between altered magnesium homeostasis and metabolic dysregulation in T2DM, although the predominantly observational evidence does not establish causality [21].

Inverse correlations between serum magnesium concentrations and HbA1c, fasting glucose, and postprandial glucose were reported in individual studies [16]. An inverse association between serum magnesium and insulin resistance, assessed using HOMA-IR, was also reported [21]. Magnesium participates in insulin-receptor signaling and glucose metabolism, providing biological plausibility for these associations [6]. Magnesium deficiency may contribute to impaired insulin action, although the direction of this relationship remains uncertain. Hyperglycemia may increase urinary magnesium excretion, suggesting a potentially bidirectional relationship between magnesium depletion and impaired glycemic regulation [7]. These findings emphasize the need to distinguish magnesium deficiency as a possible contributor to metabolic dysfunction from its potential role as a consequence of poor glycemic control.

Magnesium Assessment and Clinical Interpretation

The observed associations were not limited to studies measuring total serum magnesium. Different biochemical measures may reflect different aspects of magnesium homeostasis, including ionized magnesium, total magnesium, and the ratio between these measurements. A higher ionized-to-total magnesium ratio (iMg/tMg) was associated with elevated HbA1c, whereas a lower ratio was associated with diabetic retinopathy and hypertension [18]. These findings highlight the limitations of defining magnesium deficiency using a single laboratory parameter. Differences in measurement methods and diagnostic thresholds may contribute to variability in the reported associations. Standardized magnesium assessment is needed to improve comparability across future investigations.

Magnesium Status and Microvascular Complications

The included studies also identified associations between altered magnesium status and diabetic microvascular complications, particularly retinopathy. Higher magnesium depletion scores were associated with an increased likelihood of diabetic retinopathy [20]. Lower dietary magnesium intake was observed among individuals with diabetic retinopathy, while greater dietary intake was associated with a lower risk [22]. Potential mechanisms linking magnesium status with retinal health include oxidative stress, inflammation, altered vascular regulation, and disturbances in cellular ion homeostasis. These proposed mechanisms remain insufficient to establish a causal relationship between magnesium depletion and diabetic retinopathy. Glycemic control, diabetes duration, hypertension, renal function, and dietary factors may also influence the observed associations.

Magnesium Status and Neurological Complications

Neurological findings suggested a potential relationship between magnesium concentrations and diabetic small-fiber neuropathy. Higher serum magnesium concentrations were significantly associated with greater corneal nerve fiber length, density, and branching after adjustment for several metabolic covariates [19]. These findings indicate that magnesium status may be associated with early structural alterations in peripheral small nerve fibers. Potential biological explanations include oxidative stress, inflammation, and disturbances in neuronal membrane function associated with magnesium deficiency. The observational nature of the evidence prevents determination of whether magnesium depletion contributes to neuropathy progression or reflects underlying metabolic abnormalities. Prospective investigations are required to clarify this relationship independently of glycemic exposure and diabetes duration.

Renal and Vascular Complications

Associations between magnesium status and renal or vascular complications were also reported. Altered serum and urinary magnesium concentrations were observed among patients with diabetic nephropathy and associated renal functional impairment [24]. Hypomagnesemia was associated with a greater prevalence of diabetic foot disease and peripheral artery disease [23]. Additional observational evidence has linked serum magnesium concentrations with cardiovascular and microvascular complications in T2DM [1]. Renal impairment may influence magnesium handling and circulating magnesium concentrations, complicating interpretation of these associations. Reduced magnesium levels may represent a marker of underlying metabolic or renal dysfunction rather than an independent cause of complications. Residual confounding related to medications, renal function, dietary intake, and diabetes severity must also be considered.

Magnesium Supplementation and Therapeutic Implications

The randomized crossover trial provided interventional evidence that differed from the associations observed in the observational studies. Oral magnesium supplementation for six weeks increased serum

magnesium concentrations without significantly improving insulin sensitivity, measured using the hyperinsulinemic-euglycemic clamp, HbA1c, continuous glucose-monitoring parameters, insulin requirements, or blood pressure [25]. The small sample size, short intervention duration, and modest increase in serum magnesium may have limited the ability to detect clinically meaningful treatment effects. These findings indicate that an observational association between reduced magnesium status and poorer glycemic control does not necessarily translate into metabolic improvement following short-term supplementation. Current evidence is insufficient to recommend magnesium supplementation specifically for improving glycemic control or preventing diabetic complications in the absence of other clinical indications.

Overall Interpretation and Clinical Implications

Overall, the evidence suggests that magnesium status may serve as a potentially relevant metabolic marker associated with glycemic control and diabetes-related complications in T2DM. Its independent predictive value and therapeutic utility remain uncertain. Dietary intake, nutritional knowledge, and diabetes self-management behaviors have been investigated among individuals with T2DM, highlighting the importance of considering broader nutritional and behavioral factors when interpreting magnesium-related metabolic associations [26].

The potential biological relevance of magnesium extends beyond glucose regulation. Research examining magnesium in diabetes-associated multiorgan damage has discussed its possible involvement in inflammatory responses, oxidative stress, and cellular dysfunction, providing mechanistic context for the observed clinical associations [27]. Additional interventional research has investigated magnesium supplementation and T-cell function in individuals with T2DM and low serum magnesium concentrations, suggesting possible immunomodulatory effects whose clinical significance remains uncertain [28]. Research involving oral magnesium hydroxide administration in patients with insulin-dependent diabetes has also examined magnesium status and insulin requirements, although differences in study populations and methodology limit the applicability of these findings to adults with T2DM [29].

Broader metabolic investigations have examined variations in serum magnesium and lipid parameters among individuals with diabetes, suggesting that magnesium abnormalities may coexist with other biochemical disturbances [30]. Psychological factors may also influence metabolic outcomes, as research involving patients with diabetes has investigated associations between post-traumatic stress disorder and poor glycemic control, highlighting the importance of considering psychosocial factors when interpreting glycemic variability [31]. Research evaluating structured diabetes nutrition education has further demonstrated the relevance of nutritional management to glycemic outcomes, emphasizing that metabolic regulation is influenced by multiple factors beyond magnesium status alone [32].

These additional investigations provide contextual evidence concerning metabolic, nutritional, immunological, and psychosocial influences but were not part of the 10-study qualitative synthesis. The predominance of cross-sectional and retrospective studies within the included evidence introduces concerns regarding residual confounding, temporal ambiguity, and causal interpretation. Variations in magnesium assessment methods, definitions of diabetic complications, participant characteristics, and study sample sizes further limit direct comparisons across investigations. The findings support continued investigation of magnesium homeostasis in T2DM but do not establish that magnesium deficiency independently causes diabetic complications or that supplementation improves long-term clinical outcomes.

Limitations and Future Directions

Several methodological limitations should be considered when interpreting the findings of this systematic review. The majority of included studies were cross-sectional or retrospective, limiting causal inference and increasing susceptibility to selection bias, residual confounding, and uncertainty regarding the temporal relationship between magnesium status and clinical outcomes. Substantial heterogeneity was present in magnesium assessment methods, including serum magnesium, ionized magnesium, total magnesium, magnesium depletion scores, dietary intake, and supplementation. Definitions of glycemic control and diabetes-related complications also varied across studies. One included study examined a broader diabetes mellitus population without explicitly restricting participants to T2DM, limiting the direct applicability of its findings to the target population. Several investigations were conducted in single-center populations with relatively small sample sizes, limiting generalizability. The randomized crossover trial included only 14 participants and evaluated supplementation over a six-week period, restricting the precision and applicability of its findings.

The review was limited to English-language publications with accessible full texts, potentially introducing language and availability bias. Differences in study design, exposure measurements, and reported outcomes prevented quantitative pooling. The absence of prospective protocol registration represents an additional methodological and reporting limitation.

Future research should prioritize large, prospective, multicenter cohorts and adequately powered

randomized controlled trials using standardized magnesium measurements, clearly defined deficiency thresholds, and consistent clinical outcome criteria. Interventional studies should evaluate whether correction of documented magnesium deficiency improves HbA1c, insulin sensitivity, and clinically relevant outcomes, including retinopathy, neuropathy, nephropathy, and cardiovascular complications. Longer follow-up periods and careful adjustment for renal function, diabetes duration, medication use, and dietary factors are needed to clarify the independent contribution of magnesium status to diabetic outcomes.

Conclusions

This systematic review suggests that magnesium status is associated with glycemic control and certain diabetes-related complications among individuals with T2DM. The majority of observational studies reported lower magnesium concentrations among patients with poorer glycemic control, elevated HbA1c, higher fasting glucose, increased insulin resistance, or diabetes-related complications, including retinopathy, neuropathy, nephropathy, and vascular disease. Evidence involving serum magnesium, ionized magnesium, total magnesium, and magnesium depletion scores suggests that altered magnesium homeostasis may reflect broader metabolic and microvascular disturbances in T2DM. In the randomized crossover trial, short-term oral magnesium supplementation increased serum magnesium concentrations without significantly improving insulin sensitivity or glycemic outcomes. These findings suggest that magnesium status may represent a clinically relevant metabolic indicator, although its independent predictive value and therapeutic significance remain uncertain. Assessment of magnesium status may be considered in selected patients with suspected deficiency; however, the available evidence does not establish routine magnesium screening as an effective strategy for predicting diabetes-related complications. Larger prospective studies and adequately powered randomized controlled trials are required to determine whether correction of magnesium deficiency improves long-term glycemic control or reduces diabetes-related complications.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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