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A Review of Recent Meta-Analyses and Systematic Reviews of Vitamin and Mineral Supplements for Improved Glycemic Control in Adults with Type II Diabetes Mellitus

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Abstract

Mechanistic and observational studies suggest that various vitamins and minerals are efficacious for managing glycemic control parameters in patients with diabetes. The results of randomized controlled trials, however, are inconsistent. Here, recent (2023-2025) systematic reviews and meta-analyses are reviewed that considered primary RCTs or earlier meta-analyses that evaluated vitamins and minerals for their usefulness at lowering glycemic control parameters (fasting blood/plasma sugar (FBS/FPG), glycated hemoglobin (HbA1c), homeostatic model assessment for insulin resistance (HOMA-IR) and fasting insulin (FIN)). By drawing on study results and study author's conclusions, chromium, vitamin E, vitamin C, and vitamin D are proposed to be efficacious for modulating various glycemic control parameters. Additional high-quality research is needed to confirm our findings, clarify mechanisms of action, and identify and properly dose patients who are likely to benefit from personalized vitamin and/or mineral interventions.

Keywords: Diabetes Mellitus; Vitamins; Minerals; Systematic Reviews; Glycated Hemoglobin; Meta Analysis

Abbreviations: RCTs: Randomized Controlled Trials; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; FIN: Fasting Insulin; T1DM: Type I Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus; MA: Meta-Analyses; SR: Systematic Reviews; PPG: Post Prandial Glucose; HOMA-B: Homeostatic Model Assessment of Beta Cell Function; SRMA: Systematic Reviews and Meta-Analyses; UBMA: Umbrella Meta-Analysis; MD: Mean Differences; SMD: Standard Mean Differences; WMD: Weighted Mean Differences; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; CrPic: Chromium Picolinate; CY: Chromium Yeast; FPG: Fasting Plasma Glucose; NMA: Network Meta-Analysis; CINeMA: Confidence in Network Meta-Analysis; RoB: Risk of Bias; GRADE: Grading of Recommendations Assessment, Development, and Evaluation

Introduction

Diabetes is a chronic disease of disordered glucose metabolism that is characterized by hyperglycemia, which can be caused by dysregulated insulin production by beta cells or insensitivity to the physiological effects of insulin in target tissues. The global prevalence of diabetes in 2021 was estimated to be 529 million among adults (20-79 years) and is projected to reach 1.31 billion in 2050 [1].

Type I diabetes mellitus (T1DM), which accounts for roughly 10% of cases, is caused by the autoimmune destruction of beta-cells. Type 2 diabetes mellitus (T2DM) accounts for 90% of the case burden; and while its etiology remains obscure, several risk factors (age, family history, dietary factors, physical activity, obesity, socioeconomic status, etc.) have been identified [1,2].

Biochemical risk factors for T2DM have also been identified. Observational studies suggest, for example, that blood vitamin D levels, serum magnesium levels, and plasma chromium levels are negatively correlated with T2DM risk [1-3]. However, the results from randomized controlled trials that have investigated the effects of supplementation with vitamins and minerals on glycemic parameters in T2DM populations are inconsistent

[4-6]. On the other hand, in vitro and in vivo studies point to mechanisms by which vitamins and minerals (Cr, Mg, Mn, Zn, Mo, V) can promote insulin secretion, sensitize tissue to the effects of insulin, and influence glucose metabolism [6-9].

Given the preceding information, there is a need for a review of recent RCTs on the use of vitamins and minerals as potential complementary treatments to help T2DM patients better control their glycemic parameters. Hence, this review aims to present and synthesize findings from recent (2023-2025) meta-analyses (MA) and systematic reviews (SR) of primary RCTs and earlier meta-analyses published between 2023 and 2025, with a focus on evaluating the efficacy of various vitamin and mineral supplements for improving established markers of glycemic control among adults with T2DM.

To facilitate analysis, a PICO framework was adopted fir the present study, with the primary population (P) of interest being adults with T2DM, the interventions (I) under consideration being mineral and vitamin supplements, the primary comparators (C) being placebo or no treatment, and the main outcomes (O) being accepted and quantifiable glycemic control (GC) biomarkers such as fasting blood or plasma glucose (FBG/FPG), fasting insulin (FIN), percentage of glycated hemoglobin (HbA1c), post prandial glucose response (PPG), and homeostatic model assessment of insulin resistance (HOMA-IR) and homeostatic model assessment of beta cell function (HOMA-B).

Overview of Recently Published Meta-Analyses and Systematic Reviews

A comprehensive search of the PubMed database guided by the aforementioned PICO framework with additional restrictions as to years (2023-2025), publication type (meta-analysis or systematic review), language (English), and organism (human) resulted in the identification of 11 articles that were included in the present review. PICO and other relevant characteristics of the 11 articles are summarized in (Table 1). Also listed in the final column of Table 1 is a qualitative indication of the vitamins and/or minerals that were identified as having statistically significant effects on a glycemic control outcome marker.

As can be seen from Table 1, all 11 studies were published during the 2023-2025 period and included systematic reviews (SR), systematic reviews and meta-analyses (SRMA), a network meta-analysis (NMA), and a single umbrella meta-analysis (UBMA). The number of underlying primary RCTs ranged from 9-170 and the number of reported adult diabetes patients ranged from 913-14,223. Some studies included not only T2DM patients but also T1DM patients and other patients with related conditions. In such cases, the focus of the present review is on presenting and analyzing data specific to T2DM patients. The tested interventions included various forms of chromium, selenium, vanadium, zinc, and various forms of vitamins B, D, E and K. All studies included a placebo or other (no treatment, comparator compound, etc.) control group. As mentioned above, the main outcomes of interest are quantifiable measures of glycemic control, with the main ones being FBG/FPG, FIN, HbA1c, and HOMA-IR. As recorded in the column headers in Tables 2-7, some study authors used slightly different nomenclature for glycemic control outcomes.

The sections that follow are divided according to intervention, with relevant studies being reviewed and referenced in narrative format as required. Instead of attempting to combine all key information and results from all 11 studies into a single table, the relevant information and results from each study are presented in separate tables (Tables 2-7). While Table 1 presents qualitative efficacy results, Tables 2-7 provide quantitative insight into the effects of the various interventions relative to controls in terms of mean differences (MD), standard mean differences (SMD), and weighted mean differences (WMD) obtained from pooled analyses; associated confidence 95% intervals are provided in the main text. Importantly, only statistically significant effects calculated for adults with T2DM are presented, and conventions employed by the original authors are typically used.

Building on the information and results presented in Tables 2-7, the main conclusions of each study's authors are provided in Table 8. Finally, Table 9 synthesizes and summarizes the findings of the present review and offers tentative recommendations based on the results and conclusions of the 11 studies reviewed.

Table 1: PICO-based summary of meta-analyses and systematic reviews that explore the impacts of vitamins and minerals on glycemic outcome parameters in adult T2DM patients included in the present review article

Study	Year	Type	RCT	Population	Intervention1	Control	Outcomes2	Significant effect
Georgaki et al.	2024	SR	15	1,223 (T2DM)	Chromium / Chromium + Other	Placebo / Other	GC, ISF, HOMA-IR, HbA1c, FPG, PPG	Chromium

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Xia et al.	2023	NMA	170	14,223 (T2DM)	Selenium, Vanadium, Thiamine (Vitamin B1), Niacin (Vitamin B3), Biotin (Vitamin B7), Folic acid (Vitamin B9), Cobalamin (Vitamin B12), Ascorbic acid (Vitamin C), Vitamin D, Vitamin E, Vitamin K, Zinc, Chromium, Magnesium, Calcium	Placebo / Other	HbA1c, FBG, FIN, HOMA-IR	Chromium, Zinc, Vitamin D, Vitamin K, Vitamin E, Cobalamin (Vitamin B12), Vitamin C
Asbaghi et al.	2023	SRMA	38	2171 (T2DM, T1DM)	Vitamin E / Other	Placebo / Other	FBG, HbA1c, FIN, HOMA-IR	Vitamin E
Chai et al.	2024	UBMA	883	N.R.4 (T2DM, T2DM, other)	Vitamin B-1, Vitamin B-3, Biotin (Vitamin B7), Folic acid (Vitamin B-9), and Vitamin C	Placebo / Other	FBG, HbAc1 HOMA-IR, FIN	Folic acid (Vitamin B9), Vitamin C
Nosratabadi et al.	2023	SRMA	22	1447 (T2DM)	Vitamin C / Vitamin C + Other	Placebo / Other	HbA1c, FIN, FBG, HOMA-IR	Vitamin C
Lei et al.	2023	SRMA	18	N.R.	Vitamin D	Standard	HOMA-IR, FIN, FBG	Vitamin D
Farahmand et al.	2023	SRMA	46	4313 (T2DM)	Vitamin D	Placebo	HbA1c, FPG, HOMA-IR	Vitamin D
Afraie et al.	2024	SRMA	61	N.R. (T2DM, T2DM, other)	Vitamin D	Placebo / Other	HbA1c, FBS	Vitamin D
Chen et al.	2024	SRMA	39	2982 (T2DM)	Vitamin D	Placebo	HbA1c, FBG, HOMA-IR, FIN	Vitamin D
Zhang et al.	2025	SRNMA	40	4181 (T2DM)	Vitamin D	Placebo / Other	HbA1c, FBG, FIN	Vitamin D
Probosari et al.	2025	SRMA	9	913 (T2DM)	Vitamin D / Vitamin D + other	Placebo	FBG, FIN, HOMA-IR, HOMA-B, HbA1c	Vitamin D

[1]Primary intervention (other interventions are sometimes noted); [2]GC - glycemic control, ISF – insulin sensitivity, HOMA-IR – Homeostatic Model Assessment of Insulin Resistance, HbA1c – glycated hemoglobin, FPG -fasting plasma glucose, PPG – post prandial glucose, FBG – fasting blood glucose, FIN / FINS – fasting insulin, T2DM – type 2 diabetes mellitus, HOMA-B – Homeostatic Model of Beta Cell Function; [3]Conclusion mentions 92 RCTs; [4]None reported

Table 2: Summary of significant results for adults with T2DM reported by Georgaki et al.

Study	Intervention	Dose (μg/day)	FPG1	Insulin1	HbA1c1	HOMA-IR1
Georgaki et al.	Chromium	50 to 1000	Down	Down	Down	Down

[1]No units reported (N.R.).

Table 3: Summary of significant results for adults with T2DM reported by Xia et al.

Study	Intervention	Dose1	FBG (MD, mmol/liter)	FIN (MD, μIU/mL)	HbA1c (MD, %)	HOMA-IR (MD)
Xia et al.	Chromium		-1.32	-1.87	-0.58	-1.25
Xia et al.	Zinc		-1.28		-0.41	
Xia et al.	Vitamin D		-0.51	-2.14		
Xia et al.	Vitamin K				-1.63	
Xia et al.	Vitamin E				-0.44	
Xia et al.	Cobalamin				-1.08	
Xia et al.	Vitamin C			-2.26		

[1]Not reported (N.R.).

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Table 4: Summary of significant results for adults with T2DM reported by Asbaghi et al.

Study	Intervention	Dose (mg/day)	FPG (WMD, mg/dl)	FIN1 (WMD, μIU/mL)	HbA1c (WMD, %)	HOMA-IR (WMD)
Asbaghi et al.	Vitamin E	90 -1620		-1.03	-0.16	-0.47

Table 5: Summary of significant results for adults with T2DM reported by Chai et al.

Study	Intervention	Dose (mg/day)	FBG[1]	FIN[1]	HbA1c[1]	HOMA-IR[1]
Chai et al.	B9	0.15-10	WMD=-2.17	WMD=−1.63		WMD=−0.40
Chai et al.	C	22-6,000	WMD=-0.44 MD=-0.74 MD=-20.59 MD=−11.96		MD=-0.54 MD=−0.37	

[1]no units reported (N.R.).

Table 6: Summary of significant results for adults with T2DM reported by Nosratabadi et al.

Study	Intervention	Dose (mg/day)	FBG (WMD, mg/dL)	Insulin (WMD, uU/mL)	HbA1c (WMD, %)	HOMA-IR
Nosratabadi et al.	C	250-2000	-10.67	-1.74	-0.51	

Table 7: Summary of significant results for adults with T2DM reported by Zhang et al.

Study	Intervention1	Dose (IU/day)[2]	FBG (MD, mmol/liter)[3]	FIN (MD, mU/L)	HbA1c (MD, %)	HOMA-IR (MD)
Zhang et al.	D	D2	−0.81(placebo)			
		D2	−1.13 (no treatment)			
		D3, EHDS	−0.56 (no-treatment)			
		D3, MDS		-4.76 (no treatment)		
		D3, MDS		-7.3 (placebo)		
		D3, LDS			-0.41 (placebo)	

[1]Both vitamin D2 and D3 were evaluated

[2]Vitamin D2 or D3; LDS- low dose, MDS- medium dose, HDS - high dose, EHDS - extremely high dose

[3]Compared to control group (placebo or no treatment)

Table 8: Author's conclusions based on systematic reviews and meta-analyses of RCTs that studied the effects of vitamins and minerals on glycemic control parameters in adults with T2DM

Study	Author conclusion
Georgaki et al.	Dietary supplements containing chromium may lead to potential benefits in the management of type 2 diabetes mellitus. Glycemic control markers, including FPG, insulin, HbA1C, and HOMA-IR levels, significantly decrease following chromium supplementation, mainly in studies with a longer intervention period.
Xia et al.1	Our findings, which are based largely on studies with very low certainty of evidence, suggest that micronutrient supplements, especially chromium, vitamin E, vitamin K, vanadium, and niacin supplements, may be more effective in the management of T2DM compared with other micro-nutrients.
Asbhagi et al.	We found that vitamin E intake significantly reduces levels of HbA1c, fasting insulin, and HOMA-IR in diabetic patients, particularly patients with T2DM. Also, a significant reducing effect of vitamin E intake on fasting blood glucose was found in studies with an intervention duration of < 10 weeks.
Chai et al.	Vitamin C supplementation can improve glycemic control in type 2 diabetes mellitus by reducing FBG and HbA1c, while folic acid supplementation can improve insulin resistance.

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Nosratabadi et al.	In summary, this meta-analysis explored a substantial decrease in serum HbA1c, fasting insulin, and FBG levels in vitamin C-treated T2DM patients compared with their untreated counterparts.
Lei et al.	Vitamin D supplementation is expected to be integrated into conventional medical approaches as a promising adjuvant therapy for T2DM patients and to mitigate the burden of diabetes for individuals and society.
Farhamand et al.	The present meta-analysis found that vitamin D supplementation may be beneficial for the reduction of FPG, HbA1c, and HOMA-IR in patients with type 2 diabetes and deficient vitamin D status. This effect was especially prominent when vitamin D was given in large doses and for a short period of time albeit with substantial heterogeneity between studies and a probability of publication bias.
Afraie et al.	The findings of this meta-analysis suggest that vitamin D supplementation can significantly decrease indicators related to T2DM and, subsequently, reduce the risk of complications, particularly CVDs.
Chen et al.	In conclusion, the current study found that vitamin D supplements have beneficial effects on serum FBG, HbA1c, HOMA-IR and fasting insulin levels in T2D patients. The improvement in glycaemic control is particularly remarkable when vitamin D is given at a short-term, high dosage, and to those T2D patients with a vitamin D deficiency, who are overweight, or have an HbA1c of 8% or higher at baseline.
Zhang et al.	The findings indicate that vitamin D supplementation significantly affects biomarkers associated with T2DM. Daily supplementation with lower doses may be sufficient to improve glycemic markers in individuals with T2DM.
Probosari et al.	The analysis of various biomarkers and the evidence from multiple studies suggests that while vitamin D supplementation shows potential benefits in managing T2DM, these effects are complex and may require individualized approaches.

[1]Vanadium and niacin are mentioned by Xia et al. because of their salutary effects on lipid markers and not glycemic markers.

Table 9: Effective vitamins and minerals for helping to manage glycemic control parameters in adults with T2DM.

Supplement	Dose range	Outcomes	Supporting SRMAs
Chromium	50 to 1,000 μg/day	FBG, FIN, HbA1c, HOMA-IR	Georgaki et al., Xia et al.
Vitamin E	400 to 1,300 g/day	HbA1c	Xia et al., Asbaghi et al
Vitamin C	≥ 1,000 mg/day	FBG, FIN, HbA1c	Xia et al., Chai et al., Nosratabadi et al.
Vitamin D	< 1,000 IU/day to ≥ 4,000 IU/day	FBG, FIN, HbA1c, HOMA-IR	Xia et al., Lei et al., Farhamand et al., Afrie et al., Chen et al., Probosari et al., Zhang et al.

Chromium

Georgaki et al. published a systematic review of 15 RCTs investigating the effects of chromium supplementation in T2DM patients that were published between 2002-2023 [10]. The study was carried out based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). The quality of each study was assessed using the Cochrane Risk of Bias tool for Randomized Controlled Trials. Ultimately, 7, 6, and 2 studies were classified as good-quality, fair-quality and weak-quality, respectively. Georgaki and co-workers did not perform a pooled analysis of RCT data and report quantitative results; instead, they provided their analyses and conclusions in narrative format.

The RCTs included a total of 1223 adult (30–70-year-old) male and female patients drawn from 11 countries with controlled or poorly controlled T2DM. The chromium supplement interventions included different formulations of chromium picolinate (CrPic), chromium yeast (CY), chromium chloride (CrCL3), and chromium nicotinate CrN. Dosages ranged from 50 to 1000 μg/day, and some studies combined chromium with other treatments (niacin, vitamin D, C, and E, polyphenolic extracts, sitagliptin). Of the 15 RCTs, 14 were placebo-controlled. The trials were run for 2-6 months. Several glycemic control outcomes were investigated including insulin, hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), postprandial glucose (PPG), and the homeostatic model assessment for insulin resistance (HOMA-IR). Based on the available primary RCT research, Georgaki et al. concluded that dietary supplements containing chromium may have potential benefits in the management of T2DM and that glycemic control markers, including FPG, insulin, HbA1c, and HOMA-IR levels, can significantly decrease following chromium supplementation (Tables 2,8). The authors cautioned, however, that the studies they reviewed were limited by relatively short durations, relatively small numbers of subjects, and using heterogeneous chromium formulations and dosages. The authors recommended that more robust RCTs with longer durations and increased statistical power be conducted to provide a better understanding of the beneficial contributions and adverse side effects of chromium in patients with T2DM, which may include constipation, skin changes, flatulence, and anorexia.

Xia and co-workers published a systematic review and network meta-analysis (NMA) comparing the effects of vitamin and mineral supplements relative to placebo/no treatment for the management of T2DM in the primary care setting [11]. The study protocol was registered (CRD420223 37810) and adhered to the PRISMA-2020 guidelines and PRISMA extension statement

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for NMA. Several databases were searched from their inceptions to June 1, 2022, and RCTs that satisfied various inclusion and exclusion criteria were retained for analysis. The Cochrane Collaboration's risk-of-bias tool was used, and the confidence in Network Meta-Analysis (CINeMA) tool was applied.

A total of 170 RCTs that involved 14,223 male and female adult T2DM patients (mean age of 55.7 years) were included in the NMA, with 50.6% of the trials rated as having a low risk of bias. Assessed interventions included different formulations of selenium, vanadium, thiamine (vitamin B1), niacin (vitamin B3), biotin (vitamin B7), folic acid (vitamin B9), cobalamin (vitamin B12), ascorbic acid (vitamin C), vitamin D, vitamin E, vitamin K, zinc, chromium, magnesium, and calcium. Interventions were compared to placebo or no treatment. The primary glycemic control outcomes of interest were fasting blood glucose (FBG) and glycated hemoglobin A1c (HbA1c); the secondary outcomes were fasting insulin (FIN) and homeostasis model assessment of insulin resistance (HOMA-IR). While beyond the scope of this review, it is noted that effects on selected lipid and cholesterol markers were also evaluated (vanadium and niacin were singles out as being the best options).

Compared to placebo or no treatment, the NMA study confirmed that chromium supplementation had beneficial effects (Table 3) on the glycemic control outcome markers of FBG (MD: -1.32; 95% CI: -1.8 to -0.85), HbA1c (MD: -0.58; 95% CI: -0.9 to -0.26), and HOMA-IR (MD: -1.25; 95% CI: -2.29 to -0.21). While not explicitly mentioned quantitatively in the main body of the text by Xia et al., their reported results (MD: -1.87; 95% CI: - 0.16, -3.58) and qualitative discussion indicate efficacy for chromium in lowering FIN. In their SUCRA analysis, chromium was identified as the single best micronutrient for lowering FBG levels and HOMA-IR. Nevertheless, Xia et al. noted that due to the limitations of current RCT studies, further research with larger sample sizes, improved quality, and extended supplementation periods were necessary to enhance understanding.

Vitamin K

The NMA of Xia et al. described above (Table 3) found that vitamin K supplements were more effective than placebo or no treatment at reducing HbA1c (MD: -1.63; 95% CI: -2.64 to -0.61) and ranked it as the most effective intervention for decreasing HbA1c. Interestingly, in the NMA comparison with placebo or no treatment the efficacy of vitamin K with respect to FIN failed to achieve statistical significance but was nonetheless found to be the single best treatment for reducing fasting insulin levels in the SUCRA analysis. A recent meta-analysis investigating the glycemic control potential of vitamin K by Qu et al. was identified by our search strategy but was not included as it did not allow for the meta-analysis of RCTs of T2DM patients [12]. It is worth noting that the study by Qu et al. showed that vitamin K supplementation was able to significantly reduce glycemic control parameters and according to observational studies was associated with a significantly reduced risk of developing T2DM.

Vitamin E

Based on their network meta-analysis, Xia and co-workers reported no significant effects of vitamin E supplements on FBG, insulin levels, or HOMA-IR. They did, however, find that vitamin E supplements were more efficacious than placebo/no treatment at reducing HbA1c (MD: -0.44; 95% CI: -0.75 to -0.12), with moderate to very low certainty of evidence (Table 3).

Asbaghi et al. performed a meta-analysis on 38 RCTs investigating the effects of vitamin E supplementation on glycemic indices and insulin resistance in patients with either type 1 (T1DM) or type 2 diabetes mellitus (T2DM) (26 RCTs) [13]. These studies were published between 1988 and 2021 and included a total sample size of 2171 patients with diabetes (1110 in the vitamin E group and 1061 in the control group). Most studies recruited male and female patients. Sixteen of the studies were conducted in Western countries and the remainder were conducted in non-Western countries. Regarding the vitamin E types, 19 studies used alpha-tocopherol for the intervention, one study employed mixed alpha- and gamma-tocopherols, and 6 studies prescribed tocotrienols. In the remaining 12 studies, the type of vitamin E administered was unclear. Vitamin E dosages in included studies varied from 90 to 1620 mg/day. All studies were placebo controlled, with 5 RCTs including additional comparator compounds. Glycemic outcomes included fasting blood glucose (FBG), HbA1c, fasting insulin (FIN), and HOMA-IR. The study was registered (CRD42022343118), and the Cochrane Quality Assessment Tool was used to assess the risk of bias for each study.

The results of the Asbaghi et al. study are summarized in Table 4. Full and subgroup analysis revealed no overall (T1DM and T2DM) significant effect of vitamin E on fasting blood glucose and no significant effect on FBG in patients with T2DM. Sub-group analysis, however, suggested a significant short-term benefit (< 10 weeks of usage). In terms of HbA1c, vitamin E was found to have a significant overall beneficial effect (WMD = -0.21 (-0.33, -0.09)) and significant beneficial effects in patients with T2DM (WMD = -0.16 (-0.30, -0.02)). Subgroup analysis further revealed significant benefits on HbA1c at dosages ≥ 500 mg/day and in vitamin E formulations that did not use α-tocopherol. A dose response analysis found that the most efficient range for lowering HbA1c was between 400 and 1300 mg/day. A significant lowering effect of vitamin E was seen for fasting insulin (FIN) overall (WMD = -1.05 (-1.53, -0.58)) and for T2DM patients (WMD = -1.03 (-1.55, -0.51)) in a dose range of 400-700 mg/day. Vitamin E was found to significantly lower HOMA-IR in T2DM patients (-0.47 (-0.88, -0.05)) and in the form of alpha-tocopherol at dosages < 500 mg/day no known side effects were reported. In light of their

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meta-analysis, Asbaghi et al. concluded (Table 8) that vitamin E doses in the range of 400-700 mg/day can be recommended as a complementary therapy for controlling HbA1c and insulin levels.

Vitamin B

Based on their network meta-analysis, Xia et al. found that of all the B vitamins evaluated, only vitamin B12 (cobalamin) was shown to have a significant effect on glycemic control (Table 3). In particular, their analysis showed that vitamin B12 was more effective than placebo/no treatment at lowering HbA1c (MD: -1.08; 95% CI: -2.10 to -0.06).

Chai and colleagues published an umbrella review of 14 systematic reviews and meta-analyses (SRMA) of primary RCTs looking at the effects of water-soluble vitamins on glycemic control in T2DM patients and patients with related conditions (metabolic syndrome, etc.) [14]. The quality of the 14 SRMAs was assessed using AMSTAR 2, and the quality of the 88 (92) primary RCT trials was assessed using GRADE. Most SRMAs and RCTs were rated as low/very low quality.

The primary target population under study were adults (≥ 18 years old) with T2DM. Interventions included vitamin C, vitamin B1 (thiamine), vitamin B3 (niacin), vitamin B7 (biotin), and vitamin B9 (folic acid) formulations at various doses (0.15 mg/day vitamin B9 to 1500 mg/day vitamin B3). Most RCTs were placebo controlled. The primary outcome of interest was glycemic control as assessed using FBG, HbA1c, HOMA-IR, and insulin level. Trials were conducted in diverse countries and trial durations ranged from weeks to years.

As presented in Table 5, Chai et al. found significant effects for vitamin B9 in T2DM patients on FBG (WMD=-2.17 (-3.69, -0.65), FIN (WMD=−1.63 (−2.53, −0.73)), and HOMA-IR (WMD=−0.40 (−0.70, −0.09)). While their analysis of the available SRMAs suggested a possible role for folic acid in reducing FBG, Chai et al. ultimately concluded (Table 8) that folic acid (vitamin B-9) significantly improved insulin resistance as indicated by reduced serum/plasma insulin concentrations and HOMA-IR.

Vitamin C

In their systematic review and network meta-analysis (NMA) comparing the effects of vitamin and mineral supplements for the management of T2DM in the primary care setting, Xia et al. reported that vitamin C supplements (MD: -2.26 μ IU/mL; 95% CI: -4.15 to -0.37) were more efficacious than placebo/no treatment in decreasing fasting insulin level (FIN), with very low certainty of evidence (Table 3).

The umbrella review of multiple meta-analyses by Chai et al. (Table 5) found that vitamin C supplementation had a significant beneficial effect on glycemic control in T2DM patients as indicated by reductions in both FBG and HbA1c [14]. In particular, vitamin C supplementation was found to significantly reduce HbA1c in T2DM patients with reported mean difference effects of (MD=-0.54 (-0.9, -0.17) and MD=−0.37 (−0.57, −0.17) and FBG in 4 independent meta-analyses with effect sizes of WMD=-0.44 (-0.81, -0.07)), MD=-0.74 (-1.17, -0.31), MD=-20.59 (-40.77, -0.4), and MD=−11.96 (−19.94, −3.97) (Table 5). In the case of FBG, the effect of vitamin C proved to be consistent across all the primary meta-analyses that were studied. However, discrepancies were noted in the case of vitamin C and its lowering effect on HbA1c.

Nosratabadi et al. conducted a systematic review and meta-analysis on the effects of vitamin C in patients with T2DM [15]. The Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) framework was utilized, and the study protocol as registered in the international prospective register of systematic reviews (PROSPERO: CRD42021289736). Databases were screened for relevant studies until July 2022. Retained studies included RCTs that investigated the impact of vitamin C supplementation on FBG, HbA1c, HOMA-IR, and FIN in T2DM patients who received vitamin C treatment compared to controls. The quality of RCTs were evaluated based on the Cochrane risk of bias (RoB) tool. The quality of evidence was evaluated using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) guideline which classifies evidence as high, moderate, low, or very low.

The SRMA included 22 RCTs that enrolled 1447 male and female adult T2DM patients drawn from numerous countries. The mean age and body mass index (BMI) of the participants ranged from 36 to 72 years and 25.4–34.4 kg/m^2, respectively. The daily dose of the vitamin C intervention was between 250 and 2000 mg. All trials included a control group (placebo, comparator compound, no treatment). Outcomes assessed were FBG, HbA1c, homeostasis model assessment of insulin resistance (HOMA-IR), and fasting insulin (FIN). All RCTs lasted for at least 2 weeks (2-48 weeks).

Of the 22 RCTs, 14 were rated as weak or poor in terms of risk of bias and general quality, with 8 rated as good. There was a low certainty of the evidence for FBG, FIN, and HbA1C outcomes due to the risk of inconsistency; the HOMA-IR outcome was considered to have a very low quality of evidence.

The pooled meta-analysis indicated that supplementation with vitamin C effectively decreased serum levels of FBG in vitamin C-treated T2DM patients compared with controls (WMD: -10.67 mg/dL, 95% CI: -18.46, -2.89; P = 0.007), with significant heterogeneity (Table 6). The pooled analysis revealed a significant reduction in FIN (WMD: -1.74 uU/mL, 95% CI: -3.16, -0.33; P =0.016), with significant heterogeneity between trials. The meta-analysis indicated a significant reduction in serum values of HbA1c in the vitamin C-treated group compared to controls (WMD: -0.51%, 95% CI: -0.81, -0.20; p =0.001), once again with significant between-study heterogeneity. Sub-group analysis pointed to significant effects for FBG, FIN, and HbA1c for trial

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duration ≥ 12 weeks. The sub-group analysis of FBG and FIN also indicated significance for dose ranges ≥ 1,000 mg/day, while for HbA1c both dose ranges (≥ 1,000 mg/day and < 1,000 mg/day) were found to be significant. The meta-analysis did not detect a significant effect on HOMA-IR.

In summary, the meta-analysis of Nosratabadi et al. identified a significant decrease in serum HbA1c, FIN, and FBG levels in vitamin C-treated T2DM patients compared to untreated controls. The authors suggest that long-term (≥12 weeks) and high-dose vitamin C supplementation (≥1000 mg/d) could improve glycemic control in T2DM patients. The authors also note that additional high-quality RCTs are required to confirm their findings.

Vitamin D

The network meta-analysis of Xia et al. revealed that vitamin D supplements (MD: -0.51 mmol/L; 95% CI: -0.89 to -0.12) were more efficacious than placebo/no treatment in lowering fasting blood glucose and FIN (MD: 2.14 μ IU/mL; 95% CI: -3.70 to -0.58) (Table 3).

We identified and used 6 meta-studies of vitamin D RCTs for this review, and all 6 reported significant results for the use of vitamin D supplementation in T2DM populations. Here we will focus on reviewing the most recent SRNMA of Zhang et al. that evaluated 40 primary RCTs of 4181 T2DM adult patients. Before doing that we briefly review the main findings of the other 5 studies.

The pooled analysis of Lei et al. showed that vitamin D supplementation could significantly reduce insulin, glucose, and HOMA-IR, resulting in the author's concluding that vitamin D supplementation can be integrated into conventional medical approaches as a promising adjuvant therapy for T2DM patients [16]. Likewise, Farahmand et al showed that vitamin D supplementation produced statistically significant decreases in FPG, HbA1c, and HOMA-IR, noting that the effect was especially prominent when vitamin D was given in large doses [17]. In their SRMA, Afrie and co-workers showed that vitamin D supplementation resulted in significant reductions in FBS and HbA1c in treated T2DM patients relative to controls and concluded that vitamin D could be considered for addition into treatment guidelines for patients with T2DM. Subgroup analysis investigated the effects of study continent, age, BMI, disease duration, intervention dose, and follow up duration, yielding interesting and sometimes conflicting results. Here, the focus is on reporting the effect of the intervention dose, with < 50,000 IU/week having a greater effect on lowering HbA1c and FBS [18].

In their SRMA, Chen et al. reported overall statistically significant reductions in in serum vitamin D levels and all tested glycemic control parameters ((FBG; WMD: -0.49; 95% CI: -0.69 to -0.28] mmol/L), (HbA1c; WMD: -0.30%; 95% CI: -0.43 to -0.18), (HOMA-IR; WMD: -0.39; 95% CI: -0.64 to -0.14]), (fasting insulin; WMD -1.31; 95% CI: -2.06 to -0.56 μIU/mL)). Chen et al. also reported a somewhat complicated picture when it comes to dosing with ≤ 2,000 IU/day being better for FBG and HbA1c control but dosing ≥ 2,000 IU/day being better for reducing HOMA-IR and fasting insulin, while noting that too high a dose of vitamin D can be detrimental to health [19]. Finally, in their SRMA of placebo-controlled RCTs, Probosari et al. found that vitamin D supplementation resulted in significant differences at 12-week follow-up in insulin level, HOMA-B, and HbA1c level and at 24-week follow-up in HOMA-IR [20]. Probosari and colleagues concluded that vitamin D shows potential but modest benefits in the management of T2DM but that they may be short lived. The 5 meta-studies called attention to significant variability in the designs and results of the primary RCTs, suggesting the need for considering such factors as individual patient characteristics, vitamin D dose regime, specific outcome measures, and trial durations when interpreting results.

Zhang et al. performed a systematic review and network meta-analysis (SRNMA) of 40 RCTs that investigated the effects of vitamin D supplementation on adults with T2DM [21]. The risk of bias in the included RCTs using the revised Cochrane Risk of Bias Tool (RoB2).

Data from a total of 4,181 adult T2DM participants provided the evidence base. Interventions included different types of vitamin D (D2 (ergocalciferol) or D3 (cholecalciferol)) administered at different doses, ranging from low (< 1,000 IU/day; LDS), medium (1,000-2,000 IU/day; MDS), high (2,000–4,000 IU/day; HDS), and extremely high (≥ 4,000 IU/day; EHDS). Controls included subjects who received placebos or no treatment. Outcomes included FBG, FIN, HbA1c, and HOMA-IR. By exploiting the dose data, Zhang et al. were able to perform a network analysis comparing different doses of vitamin D2/D3 with placebo/no treatment. Most studies were considered to be at low risk of bias.

As shown in Table 7, pooled results indicated that vitamin D2 significantly reduced FBG levels compared to placebo (MD: −0.81; 95% CI: −1.47 to −0.16) and no treatment (MD: −1.13; 95% CI: −1.92 to −0.33). EHDS vitamin D3 supplementation also reduced FBG levels compared to no treatment (MD: −0.56; 95% CI: −0.99 to −0.13). Vitamin D3 MDS significantly reduced FIN levels compared to placebo (MD: −4.76; 95% CI: −8.91 to −0.61) and no treatment (MD: −7.30; 95% CI: −14.44 to −0.17), and LDS vitamin D3 significantly reduced HbA1c levels compared to placebo (MD: −0.41%; 95% CI: −0.77% to −0.04%), and. Supplementation treatments consistently and significantly increased 25-hydroxyvitamin D or 25-(OH)-D levels. The SUCRA results identified vitamin D2 as the single best option for reducing FBG, vitamin D3 LDS as the single best option for lowering HbA1c, vitamin D3 MDS as the single best option for mitigating FIN,

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and vitamin D3 EHDS as the best option for boosting 25-(OH)-D levels. Importantly, vitamin D3 EHDS scored well in the three key outcomes of FBG, HbA1c, and 25-(OH)-D, and MDS vitamin D3 scored best for FIN.

Based on their results, Zhang et al. cautiously concluded (Table 8) that vitamin D supplementation significantly affects biomarkers associated with T2DM, and that supplementation with lower doses of vitamin D may be sufficient to improve glycemic markers in individuals with T2DM. Finally, Zhang et al. called for large scale RCTs to be conducted to test and confirm their findings.

Selenium, Vanadium, Zinc, Magnesium, and Calcium

The NMA of Xia et al. identified zinc supplementation as efficacious for lowering FBG (MD: -1.28 mmol/L; 95% CI: -1.83 to -0.73) and HbA1c (MD: -0.41%; 95% CI: -0.71 to -0.11) (Table 3). According to their SUCRA analysis, Zinc was ranked as the second-best compound for lowering FBG. The Xia et al. study uncovered no significant glycemic control effects for selenium, vanadium, magnesium, and calcium. No other independent SR or MA studies were found that explored the utility of using selenium, vanadium, zinc, magnesium, and calcium supplementation for glycemic control in T2DM.

Evidence synthesis and conclusions

Based on the results and author's conclusions of the 11 systematic reviews and meta-analysis considered in the present article, it can be reasonably concluded that chromium, vitamin E, vitamin C, and vitamin D supplements can be used to help lower glycemic markers in adults with T2DM. The conclusions and supporting information are summarized in Table 9.

For all 4 supplements, at least two independent SRMAs provide overlapping and reinforcing support on one or more glycemic outcome markers. Two SRMAs support the use chromium for lowering FBG, HbA1c, FIN and HOMA-IR, and two studies confirm the usefulness of vitamin E for reducing HbA1c. Three of the studies provide support for the use of vitamin C to manage FBG, FIN, and HbA1c. Finally, 7 studies verify the efficacy of vitamin D supplementation for lowering FBG, FIN, HbA1c, and HOMA-IR. While the studies considered here provide empirical guidelines for dosing and duration of use, individual patient characteristics, objectives and results should be considered when developing and implementing a personalized supplement treatment program. Future high-quality research is needed to clarify the mechanisms of action by which the compounds exert their glycemic effects, identify patients most likely to benefit from mineral/vitamin therapy, and confirm the results presented herein.

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