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COMBINING VITAMIN D AND ORAL ANTIDIABETICS: EFFECTS ON GLYCATED HEMOGLOBIN A IN TYPE 2 DIABETES

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Abstract: Background: *A chronic metabolic condition known as type 2 diabetes mellitus (T2DM) develops when the body becomes less sensitive to insulin and the pancreatic β-cells are unable to adjust, resulting in elevated blood glucose concentrations. Oral antidiabetic agents (OADs) remain the mainstay of pharmacological treatment, yet many patients fail to achieve their glycemic goals. Through anti-inflammatory processes, vitamin D helps regulate gene expression, improve insulin responsiveness, and improve β-cell function. The purpose of this evidence-based case study was to assess the efficacy of OAD therapy alone against OAD therapy plus vitamin D supplementation in lowering HbA1c levels in T2DM patients. The literature search strategy was applied through PubMed, EBSCO, and the Cochrane Library using the keywords ("type 2 diabetes mellitus" AND "vitamin D" AND "glycemic control"). Eligible studies included systematic reviews or meta-analyses comparing OAD plus vitamin D with OAD alone and reporting HbA1c outcomes. Of 485 identified articles, after applying the inclusion criteria, five systematic reviews and meta-analyses qualified for analysis and were evaluated according to the CEBM appraisal criteria.* ***Results:*** *Four of the five included trials reported a statistically significant drop in HbA1c after using vitamin D supplements, whereas one found no impact. Overall, the findings favored vitamin D in increasing glycemic control, although the magnitude of reduction was modest. The benefit appeared greater in subjects with low vitamin D levels who underwent extended supplementation.* ***Conclusion:*** *Supplementing with vitamin D may help T2DM patients using OADs achieve better glycemic control. Although the reduction in HbA1c was small and not clinically significant, longer treatment duration may enhance outcomes*

PENDAHULUAN

Type 2 DM is a protracted metabolic disorder arising from diminished sensitivity to insulin alongside a continual deterioration of β-cell activity, which results in sustained hyperglycemia and scatter systems disorders.[1] The International Diabetes Federation estimates that 463 million people had diabetes in 2019, and if more effective preventative measures aren't implemented, that number is expected to increase to almost 700 million by 2045.[2] The growing global burden of T2DM, primarily driven by obesity, sedentary lifestyles, and population aging, underscores the urgent need for optimal glycemic control.[3]

Glycated hemoglobin A (HbA1c) remains the primary marker used to assess long-term blood glucose regulation.[4] It has been demonstrated that common oral glucose-lowering medications such as metformin, sulfonylureas, DPP-4 inhibitors, and SGLT-2 inhibitors can drop HbA1c by 0.3–1.1%; however, adherence and lifestyle factors may have an impact on effectiveness.[5] Besides the pharmacological therapy, vitamin D is playing an increasing role as a modulator of glucose homeostasis through its effects on enhancing insulin release and responsiveness, showing anti-inflammatory properties, and attenuation of β-cell dysfunction.[6] This is corroborated by evidence linking low vitamin D levels to increased insulin resistance and poor glucose regulation.[7]

Beyond its traditional involvement in calcium and skeletal regulation, vitamin D also contributes to glucose and energy homeostasis.[8] VDRs are present in various metabolic organs, including the pancreas, liver, muscle tissue, and fat cells, where VDR activation modulates gene expression related to insulin secretion, glucose uptake, and inflammatory processes.[9] According to mechanistic research, vitamin D improves insulin sensitivity by inhibiting pro-inflammatory mediators, including NF-κB and MAPK, regulating calcium flux in β-cells, and activating SIRT1/IRS1/GLUT4 pathways.[10] Furthermore, decreased insulin responsiveness, increased systemic inflammatory activity, and impaired β-cell function have all been associated with low vitamin D status. These variables are crucial in the development of type 2 diabetes and other metabolic disorders.[11]

In the last few years, the effect of vitamin D administration on glycemic control in T2DM patients, with or without OAD medication, has been investigated in a number of randomized controlled trials (RCTs) and systematic reviews.[12] Several studies have shown moderate to rather substantial decreases in HbA1c following vitamin D supplementation, particularly among those who had low levels of vitamin D at baseline or used higher doses of vitamin D, while others found marginal or inconsistent effects of treatment with it, potentially because of the difference in study design, dosage regimen, and duration of intervention.[13]

Given these inconsistencies, further evidence-based evaluation is warranted. Therefore, this evidence-based case report (EBCR) aims to determine the effectiveness of combining oral antidiabetic therapy with vitamin D supplementation compared to OAD only in reducing HbA1c levels among patients with T2DM, and to determine whether this combination yields clinically meaningful improvements in glycemic control.[14]

In this case, a 54-year-old woman came to the clinic reporting easy fatigue, excessive thirst, and frequent urination. She had a history of T2DM for the past three years and had been regularly taking sulfonylurea medication. Her most recent HbA1c level was 8.5%. The patient reported spending most of her time indoors and rarely being exposed to sunlight. The physician considered adding vitamin D supplementation to her regimen in hopes of improving blood glucose levels. However, the physician wanted to determine whether vitamin D supplementation in patients receiving oral antidiabetic drugs (OAD) provides better glycemic control compared to OAD therapy alone.

METHODS

Search Strategy

This evidence-based case report was developed to address the clinical question: "Is the combination of OAD and vitamin D supplementation more effective in reducing HbA1c levels compared to OAD only in patients with T2DM?" Three major internet databases—PubMed, EBSCO, and the Cochrane Library—were used to conduct a thorough investigation of published research. The search process used a mix of keywords and MeSH terms, including: ("Type 2 Diabetes Mellitus" OR "T2DM") AND ("Vitamin D" OR "cholecalciferol" OR "calcitriol") AND ("Glycemic control" OR "Blood glucose"). Initial search yielded 485 potentially relevant studies (PubMed = 23, EBSCO = 72, Cochrane = 390). After duplicate removal, 483 articles remained and underwent assessment guided by titles and abstracts according to PRISMA guidelines.

Adults with type 2 diabetes mellitus (Population) who are receiving OAD are the subject of this evidence-based case study. OAD therapy plus vitamin D supplementation is the intervention, as opposed to OAD therapy alone or a placebo (Comparison). HbA1c change as a glycemic control indicator was the primary outcome examined. In order to ascertain if adding vitamin D supplementation to regular OAD therapy leads to a larger improvement in HbA1c in patients with type 2 diabetes, this PICO framework was developed.

Table 1. Search Strategy

Database	Keywords
Pubmed	#1 Type 2 diabetes OR diabetes mellitus type 2 OR diabetes mellitus
	#2 Vitamin D OR calcitriol OR cholecalciferol OR vitamin D3
	#3 Glycemic control OR hba1c OR blood sugar OR blood glucose
	#4 #1 AND #2 AND #3
EBSCO	#1 Type 2 diabetes OR diabetes mellitus type 2 OR diabetes mellitus
	#2 Vitamin D OR calcitriol OR cholecalciferol OR vitamin D3
	#3 Glycemic control OR hba1c OR blood sugar OR blood glucose
	#4 #1 AND #2 AND #3
Cochrane	(TITLE-ABS-KEY (diabetes OR mellitus OR type 2 diabetes) AND TITLE-ABS-KEY (vitamin D OR Cholecalciferol) AND TITLE-ABS-KEY (Glycemic control OR hba1c OR blood glucose)

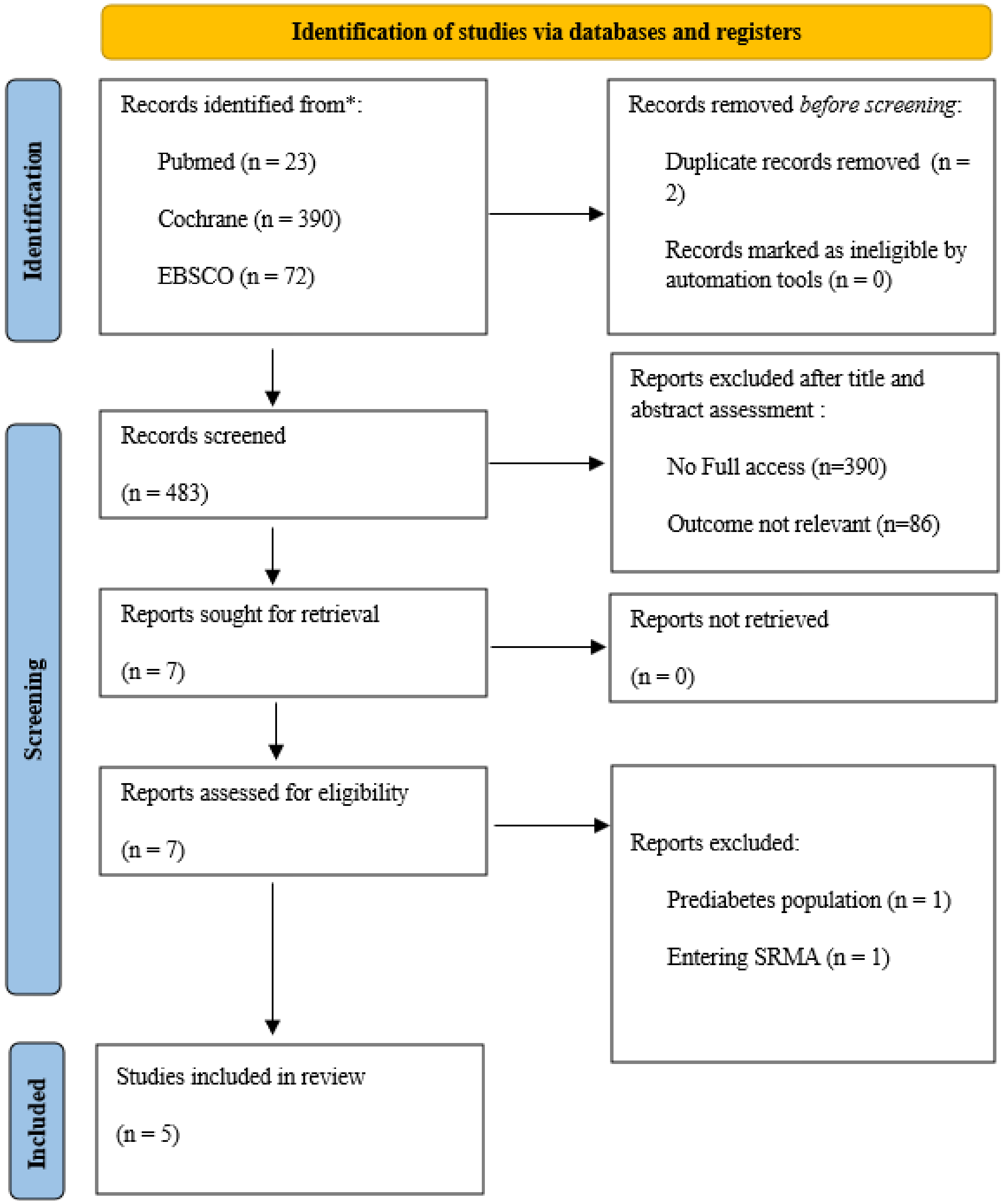

Figure 1. PRISMA

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Eligibility Criteria
The following conditions were used to determine which studies were eligible: (1) randomized controlled trial or systematic review/meta-analysis design; (2) adult population diagnosed with T2DM; (3) intervention involving combined OAD therapy and vitamin D supplementation; (4) primary outcome assessing changes in HbA1c levels before and after intervention; and (5) availability of full-text articles in English or Indonesian. Studies were excluded when they did not present HbA1c as an outcome, combined vitamin D with other micronutrients without separate analysis, involved populations aside from T2DM (e.g., type 1 diabetes, gestational diabetes, or prediabetes), or were published only as abstracts. The selection process took place in two steps: first, a preliminary appraisal of the titles and abstracts was carried out, and then the in-depth appraisal of the complete articles was conducted to determine qualification.

Table 2. Characteristics of studies that meet the selection criteria

Author	No. of Studies	Vitamin D Supplementation	Result
Probosari E et al., 2025	9 RCT	Dosage: 1000 IU/day to 100,000 IU bolus + daily dose. Duration: 12-24 weeks	Not Significant HbA1c reduction after 12 weeks; not significant at 24 week WMD -0.17; 95% CI: -0.35 to 0.00
Bruna-Mejías A et al., 2025	13 RCT	Dosage: Varies (4000 IU/day, 50,000 IU/week, high bolus). Duration: 6 weeks to 9 years	Significant HbA1c decrease WMD -0.19; 95% CI: -0.31 to -0.07
Afraie M et al., 2024	61 RCT	Dosage: Varies (400 IU/day to 400,000 IU bolus). Duration: 4-48 weeks	Significant HbA1c reduction WMD -0.15; 95% CI: -0.29, -0.20
Musazadeh V et al., 2023	37 Meta-analysis	Dosage: Varies (545 to 21,000 IU/day). Duration: 7-47 weeks	Small but significant HbA1c reduction WMD -0.05; 95% CI: -0.10, -0.01
Farahmand MA et al., 2023	46 RCT	Dosage: Varies (e.g., 1000 IU/day, 50,000 IU/week, high bolus). Duration: 8-48 weeks	Significant HbA1c decrease WMD -0.2; 95% CI: -0.29, -0.11

Critical Appraisal
Each included study underwent critical appraisal using the CEBM appraisal tools

(Oxford University, 2023) to evaluate three domains: validity, importance, and applicability. Validity assessed methodological rigor and bias control; importance evaluated effect size expressed as mean difference, standardized or weighted mean differences accompanied by 95% confidence intervals deviation; and applicability examined the relevance of findings to clinical practice, particularly within the Indonesian T2DM population context. Data extracted from eligible studies included study characteristics, intervention details, and quantitative outcomes related to HbA1c reduction. Statistical interpretation emphasized effect size and precision of estimates rather than sole reliance on p-values. Microsoft Word 2021 was used to create descriptive summaries and show the data as weighted or standardized mean differences with accompanying 95% CIs.

Table 3. CEBM

			FAAT				Result	
Author	Clear PICO	Appropriate searching	Appropriate inclusion criteria	Study validity	Result similarity	Weighted Mean Difference	Heterogenity	Overall effect
Probosari E et al., 2025	+	+	+	+	-	-0.17; 95% CI: -0.35 to 0.00	I^2 = 44%	Z = 1.93 (P = 0.05)
Bruna-Mejías A et al., 2025	+	+	+	+	-	-0.19; 95% CI: -0.31 to -0.07	I^2 = 36%	Z = 3.01 (P = 0.003)
Afraie M et al., 2024	+	+	+	+	-	-0.15; 95% CI: -0.29, -0.20	I^2 = 79.76%	p value < 0.001
Musazadeh V et al., 2023	+	+	+	+	-	-0.05; 95% CI: -0.10, -0.01	I^2 = 74.0%	p = 0.004
Farahmand MA et al., 2023	+	+	+	+	-	-0.2; 95% CI: -0.29, -0.11	I^2 = 98.2%	p < 0.001

DISCUSSION

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Four of the five systematic reviews and meta-analyses (SRMAs) found that adding vitamin D resulted in a statistically significant drop in HbA1c, whereas one found no change. The study by Farahmand et al. (2023), which included 46 randomized controlled trials (RCTs) with various dosing regimens (Dosage: 1000 IU/day to 100,000 IU bolus + daily dose. Duration: 12-24 weeks), reported a mean HbA1c decrease of 0.20% (WMD 95% CI: −0.29, −0.11), with the greatest effect observed in high-dose and short-duration supplementation.[15] Similarly, Musazadeh et al. (2023), a comprehensive analysis of 37 meta-analyses (e.g., large bolus, 50,000 IU/week, 1000 IU/day). HbA1c decrease was observed to be -0.05 (WMD 95% CI: -0.10, -0.01) during a period of 8–48 weeks.[16]

The findings were further supported by Afraie et al. (2024), who analyzed 61 RCTs with dosage: Varies (400 IU/day to 400,000 IU bolus). Duration: 4-48 weeks WMD of −0.15 (95% CI: −0.29, −0.20). According to this study, a 50,000 IU dose was very beneficial, however, patients with higher body mass indices and longer sickness durations tended to see less of an impact from vitamin D.[17] Bruna-Mejías et al. (2025) analyzed 13 RCTs (Dosage: Varies (4000 IU/day, 50,000 IU/week, high bolus). Duration: 6 weeks to 9 years reported a mean decrease of 0.19% (MD 95% CI: −0.31, −0.07) in HbA1c.[18] Meanwhile, Probosari et al. (2025) reviewed nine RCTs (Dosage: 1000 IU/day to 100,000 IU bolus + daily dose. Duration: 12-24 weeks) found a mean HbA1c reduction of −0.17 (95% CI: −0.35 to 0.00; p = 0.05) when the studies were pooled reported a non-significant change, the non-significant HbA1c reduction at 24 weeks may relate to the short intervention duration and wide variation in vitamin D dosages, which contributed to heterogeneity across studies.[19]

All five systematic reviews and meta-analyses showed a constant tendency toward better glycemic control, although only four of them indicated a significant drop in HbA1c after taking vitamin D. The substantial heterogeneity (I^2 = 36–98.2%) likely resulted from variations in inclusion criteria, dosage, administration frequency, treatment duration, and study quality. Although all studies used oral vitamin D, the regimens ranged from daily low doses to high or bolus doses with differing durations. These methodological and clinical differences explain the inconsistent effect sizes and the lack of consensus on the most effective dosage and length of therapy, and the patient subgroup that would gain the most.

The five SRMAs included in this critical appraisal synthesized data from RCTs conducted globally, encompassing populations from Asia, Europe, the Americas, and other regions. Notably, a significant proportion of the included studies originated from Asian countries, suggesting that these findings may have strong clinical relevance for the Indonesian population.[20] Considering similarities in lifestyle patterns, dietary habits, risk factors for T2DM, and the common presence of vitamin D deficiency in many Asian groups, the results of these SRMAs could provide valuable guidance for diabetes management in Indonesia.[21]

Vitamin D is commonly available in oral formulations such as tablets, capsules, and liquid drops, consistent with the forms used in most primary studies included in these reviews.[22] However, using vitamin D as an adjunct to help regulate blood glucose in T2DM is generally not covered under the National Health Insurance (JKN) system, making cost and availability important considerations for patients.[23] Furthermore, the distribution of oral vitamin D preparations may remain uneven across regions in Indonesia. These factors should be considered when deciding on using vitamin D as an adjunct therapy.[24]

All systematic reviews included in this report involved adult patients with T2DM who had been receiving oral antidiabetic treatment as standard therapy and had varying baseline vitamin D levels. Overall, the data suggests that vitamin D treatment very slightly affects glycemic outcomes, resulting in a statistically significant but clinically negligible drop in HbA1c. The results imply that vitamin D, while offering only a limited supportive effect, its addition to OAD therapy has a limited impact on overall glycemic control in T2DM patients.[25]

CONCLUSION

Among adults with T2DM on oral antidiabetic therapy, vitamin D may provide an added supportive effect in regulating blood glucose. However, the reduction in HbA1c was smaller than expected and not clinically significant. The effect appeared more noticeable in patients with moderately raised HbA1c levels and vitamin D deficiency, whereas patients with markedly high HbA1c values remained within the diabetic range despite supplementation. Longer treatment duration may yield greater improvements in glycemic outcomes. Therefore, adding vitamin D to oral antidiabetic therapy may serve as an additional supportive strategy, particularly in people with confirmed vitamin D deficiency. Further large-scale studies using diverse dosing schedules and longer treatment durations are necessary to establish to prolonged safety and effectiveness of vitamin D in supporting glycemic regulation in individuals with T2DM.

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CONFLICT OF INTEREST

Regarding the production or distribution of this evidence-based case study, the authors disclose no pertinent conflicts of interest.

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