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ORIGINAL RESEARCH

Association Between Serum Vitamin D Levels and Metformin Efficacy in Obese Type 2 Diabetes Patients: A Retrospective Cohort Study Based on HbA1c Reduction

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Purpose: To investigate the association between baseline serum 25-hydroxyvitamin D [25(OH)D] levels and glycemic response to metformin monotherapy in obese adults with type 2 diabetes mellitus (T2DM).

Patients and Methods: This single-center retrospective cohort study analyzed the electronic medical records (January 2021–December 2023) of obese T2DM patients initiating metformin monotherapy. Participants were stratified by baseline 25(OH)D levels: deficiency (<20 ng/mL, n = 256) or sufficiency (≥20 ng/mL, n = 171). Propensity score matching (1:1) balanced covariates (age, sex, BMI, HbA1c, diabetes duration, comorbidities, season), yielding 142 matched pairs (n = 284). The primary outcome was absolute HbA1c reduction (ΔHbA1c) at 3 months. Multivariable linear regression, subgroup, and sensitivity analyses were performed.

Results: In the matched cohort, vitamin D-sufficient patients achieved a clinically meaningful and statistically significant greater HbA1c reduction versus vitamin D-deficient patients (mean difference: 0.34%; 95% CI: 0.16–0.52%; $p < 0.001$). Baseline 25(OH)D positively correlated with ΔHbA1c ($r = 0.32$, $p < 0.001$). Multivariable regression confirmed that vitamin D sufficiency independently predicted greater ΔHbA1c (adjusted β = 0.41%, 95% CI: 0.22–0.60%, $p < 0.001$). Subgroup analyses revealed enhanced effects in females (p-interaction = 0.018), patients >60 years (β = 0.49% vs ≤60 years 0.33%, p-interaction = 0.009), and baseline HbA1c ≥8.5% (β = 0.56% vs <8.5% 0.21%, p-interaction = 0.003). Adverse events were comparable between groups.

Conclusion: Higher baseline vitamin D levels (≥20 ng/mL) are associated with significantly improved metformin efficacy in obese T2DM patients, particularly among females, older adults, and those with poorer glycemic control. Vitamin D status may serve as a predictive biomarker for metformin response.

Plain Language Summary:

Why was this Study Done?

Many people with type 2 diabetes also have low vitamin D levels, especially if they are living with obesity. Vitamin D helps the body use insulin properly. Metformin is a common diabetes medicine, but it does not work the same for everyone. We wanted to determine whether having enough vitamin D helps metformin work better.

What did the Researchers do?

We looked back at health records of 427 obese adults with type 2 diabetes who started taking metformin alone. We split them into two groups: those with low vitamin D (less than 20 ng/mL) and those with enough vitamin D (20 ng/mL or more). We compared how much their blood sugar levels (HbA1c) improved after three months.

What did the Researchers Find?

People with enough vitamin D had a significantly greater improvement in blood sugar levels than those with low vitamin D. This effect was especially strong in women, people over 60, and those with higher starting blood sugar levels. Vitamin D levels were positively correlated with a better response to metformin. Side effects were similar in both groups.

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What do these Results Mean?

Having enough vitamin D may help metformin work better in people with type 2 diabetes and obesity. Checking vitamin D levels when starting metformin could help doctors predict how well the treatment will work. Future studies should test whether giving vitamin D supplements can actually improve diabetes control in those who are deficient.

Keywords: vitamin D, metformin, HbA1c, obesity, type 2 diabetes, biomarker

Introduction

Type 2 diabetes mellitus (T2DM) represents a critical global health challenge, with an estimated 537 million adults affected worldwide as of 2021, a figure projected to rise to 783 million by 2045, making it one of the fastest-growing public health crises of the 21st century.[1,2] The coexistence of obesity significantly exacerbates disease progression and complicates therapeutic management. Within this population, vitamin D deficiency is remarkably prevalent, affecting up to 80% of obese individuals with T2DM, attributable to factors such as volumetric dilution in larger body fat mass, reduced sunlight exposure due to mobility issues, and adipose sequestration of this fat-soluble vitamin. This high prevalence is particularly concerning, as compelling evidence from both basic and clinical research has illuminated vitamin D's integral role in metabolic health.[3,4] This deficiency is physiologically consequential given vitamin D's multifaceted role in glucose homeostasis, including its capacity to directly modulate pancreatic β-cell insulin secretion through vitamin D response elements (VDREs) in the insulin gene promoter, enhancement of insulin sensitivity in peripheral tissues such as muscle and adipose tissue, and suppression of the chronic low-grade inflammation that is a hallmark of T2DM pathogenesis.[2,5]

Metformin remains the cornerstone first-line pharmacotherapy for T2DM, primarily acting through AMP-activated protein kinase (AMPK) activation to reduce hepatic gluconeogenesis and improve peripheral glucose uptake.[6] Nevertheless, substantial interindividual variability exists in the glycemic response to metformin. This heterogeneity underscores the need for predictive biomarkers to optimize treatment personalization. Increasingly, preclinical and mechanistic evidence suggests plausible and synergistic biological interactions between vitamin D signaling and metformin pathways.[5,7] Vitamin D receptor (VDR) activation has been shown to directly influence AMPK signaling and mitochondrial bioenergetics, pathways central to metformin's mechanism of action. Specifically, 1,25-dihydroxyvitamin D3 has been found to potentiate metformin's activation of AMPK, possibly through the inhibition of the mTOR/S6K1 pathway, thereby enhancing insulin sensitivity. Conversely, hypovitaminosis D may impair β-cell function, exacerbate insulin resistance by promoting inflammatory cytokine production (eg, IL-6, TNF-α), and blunt the cellular response to metformin, potentially diminishing its efficacy.[5]

Despite this strong biological rationale, clinical evidence remains inconclusive and fraught with methodological limitations. Previous observational studies reported correlations between baseline vitamin D status and metformin response but were constrained by small sample sizes that rendered them statistically underpowered, heterogeneous populations, or inadequate control for critical confounders such as renal function (which affects metformin clearance), precise measures of adiposity (eg, visceral vs subcutaneous fat), polypharmacy, and crucially, seasonal variation in vitamin D levels.[8,9] The failure to account for seasonality, which can cause fluctuations of up to 10 ng/mL in serum 25 (OH)D between winter and summer, is a major flaw that can obscure or create spurious associations.[10] Notably, the large D2d (Vitamin D and Type 2 Diabetes) randomized trial found no significant benefit of vitamin D supplementation on diabetes prevention in a general prediabetic population (many of whom were metformin users), although it did not specifically examine baseline vitamin D status as an effect modifier on glycemic control in obese T2DM patients already on established metformin therapy.[11] Furthermore, existing studies have rarely addressed the high-risk obese T2DM phenotype, where the interplay of vitamin D deficiency and severe insulin resistance is most pronounced.

This study therefore addresses a critical evidence gap by investigating the relationship between baseline serum 25-hydroxyvitamin D [25(OH)D] levels and glycemic response to metformin monotherapy in a well-characterized cohort of obese adults with T2DM. Utilizing rigorous methodology, including propensity score matching to minimize confounding from a wide array of demographic and clinical variables, and comprehensive sensitivity analyses to test the robustness of our findings, we evaluate whether baseline vitamin D status may serve as a clinically useful and readily available predictor of metformin efficacy in this specific, high-risk population.

Materials and Methods

Study Design

This single-center retrospective cohort study utilized electronic medical records (EMR) to evaluate the association between baseline serum 25(OH)D levels and the glycemic response to metformin monotherapy in obese adults with T2DM. Data spanned from January 1, 2021, to December 31, 2023. The study protocol was approved by the Hanzhong Central Hospital Institutional Review Board (No: [2024]-18). A waiver of informed consent was granted, as the research involved anonymized retrospective data analysis without intervention, adhering to local regulations and the Declaration of Helsinki. All data were handled confidentially with strict adherence to privacy protection protocols.

Participant Selection

Inclusion Criteria

(1) Age ≥18 years; (2) Diagnosis of T2DM according to American Diabetes Association criteria (HbA1c ≥6.5% [48 mmol/mol], fasting plasma glucose ≥126 mg/dL [7.0 mmol/L], or 2-h plasma glucose ≥200 mg/dL [11.1 mmol/L] during oral glucose tolerance test);[12] (3) Obesity defined as body mass index (BMI) ≥28 kg/m^2, consistent with Chinese population-specific cutoffs;[13] (4) Initiation of metformin monotherapy as first-line glucose-lowering agent; (5) Documented baseline serum 25(OH)D measurement within 30 days prior to metformin initiation; (6) Paired HbA1c measurements available at baseline and 3 months (±2 weeks) posttreatment initiation.

Exclusion Criteria

(1) Hepatic impairment (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >3× upper limit of normal);[14] (2) Renal dysfunction (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2 calculated using the CKD-EPI equation);[15] (3) History of other glucose-lowering agents within 6 months prior to enrollment; (4) Vitamin D supplementation (≥800 IU/day) within 90 days prior to baseline measurement;[16] (5) Malabsorption syndromes (eg, inflammatory bowel disease, bariatric surgery) or medications affecting vitamin D metabolism (glucocorticoids, anticonvulsants); (6) Pregnancy or lactation documented in medical records; (7) Missing date.

Cohort Assembly and Sample Size

Eligible patients were identified through systematic query of the hospital's EMR system using structured data extraction: ICD-10 codes for T2DM (E11), anthropometric data (BMI ≥28 kg/m^2), laboratory parameters (25(OH)D, HbA1c), and pharmacy dispensing records for metformin monotherapy. The initial screening identified 1842 potential candidates. After applying the inclusion/exclusion criteria, 427 patients comprised the analytical cohort. Sample size was calculated a priori using G*Power 3.1 software, estimating 386 participants required to detect a medium effect size (Cohen's d = 0.5) in ΔHbA1c between vitamin D groups (α=0.05, power=90%), accounting for 10% potential data attrition.

Group Stratification

Participants were stratified by baseline serum 25(OH)D levels: (1) vitamin D deficiency group: <20 ng/mL (<50 nmol/L) (n = 256); (2) vitamin D sufficiency group: ≥20 ng/mL (≥50 nmol/L) (n = 171). Using Endocrine Society clinical practice guidelines.[16] To account for the known seasonal fluctuation in serum 25(OH)D levels due to variations in sunlight exposure, we performed a season-adjusted analysis. The month of blood draw was categorized into a high-ultraviolet (UV) period (April–September) and a low-UV period (October–March) based on the solar zenith angle and typical insolation patterns in Hanzhong City, Shaanxi Province, China.[17]

Propensity Score Matching (PSM) Rationale and Implementation

Given the observational nature of this study and potential baseline imbalances between vitamin D groups (eg, age, BMI, diabetes duration), PSM was employed to minimize confounding bias. Propensity scores were generated using multivariable logistic regression with vitamin D sufficiency (≥20 ng/mL) as the outcome and the following covariates: age; sex; baseline BMI; baseline HbA1c; diabetes duration; hypertension status (icd-10 i10); dyslipidemia status (icd-10 e78.5); and season of vitamin D measurement.

A 1:1 nearest-neighbor matching algorithm with caliper width = 0.2 SD of the logit propensity score was performed without replacement. This yielded 142 matched pairs (n = 284) for primary analysis (Figure 1). Balance was assessed using standardized mean differences (SMD <0.1 for all covariates).

Variable Definitions

Exposure Variable

The key exposure assessed was the baseline serum concentration of 25-hydroxyvitamin D [25(OH)D], quantified within 30 days before metformin initiation. Vitamin D status was dichotomized based on Endocrine Society clinical practice guidelines:[16] deficiency (<20 ng/mL or <50 nmol/L) and sufficiency (≥20 ng/mL or ≥50 nmol/L). Serum 25(OH)D levels were measured quantitatively using a chemiluminescent immunoassay (CLIA) on the Abbott ARCHITECT i2000SR analyzer (Abbott Laboratories, Chicago, IL, USA). Analytical consistency throughout the study was ensured by interassay coefficients of variation (CV) consistently below 8%.[18]

Primary Outcomes

The efficacy endpoint was defined as the absolute reduction in glycated hemoglobin (ΔHbA1c), calculated as baseline HbA1c minus the value obtained after 3 months (±2 weeks) of metformin monotherapy. HbA1c measurements were performed using high-performance liquid chromatography (HPLC) with Bio-Rad VARIANT II Turbo analyzers (Bio-Rad Laboratories, Hercules, CA, USA), standardized against the National Glycohemoglobin Standardization Program (NGSP) and reported in % units (IFCC mmol/mol values were converted using the master equation: NGSP (%) = 0.0915 × IFCC (mmol/mol) + 2.15).[19]

The primary glycemic outcome was assessed at 3 months after metformin initiation. This time point was selected based on established clinical evidence and guidelines. Metformin exerts its glucose-lowering effect within weeks of initiation,[20] and a period of 3 months is considered clinically adequate to observe a near-maximal response in HbA1c, which reflects average blood glucose over the preceding 2–3 months.[21] Furthermore, a 3-month follow-up minimizes the potential for attrition bias and confounding from treatment modifications that are more likely to occur in longer-term

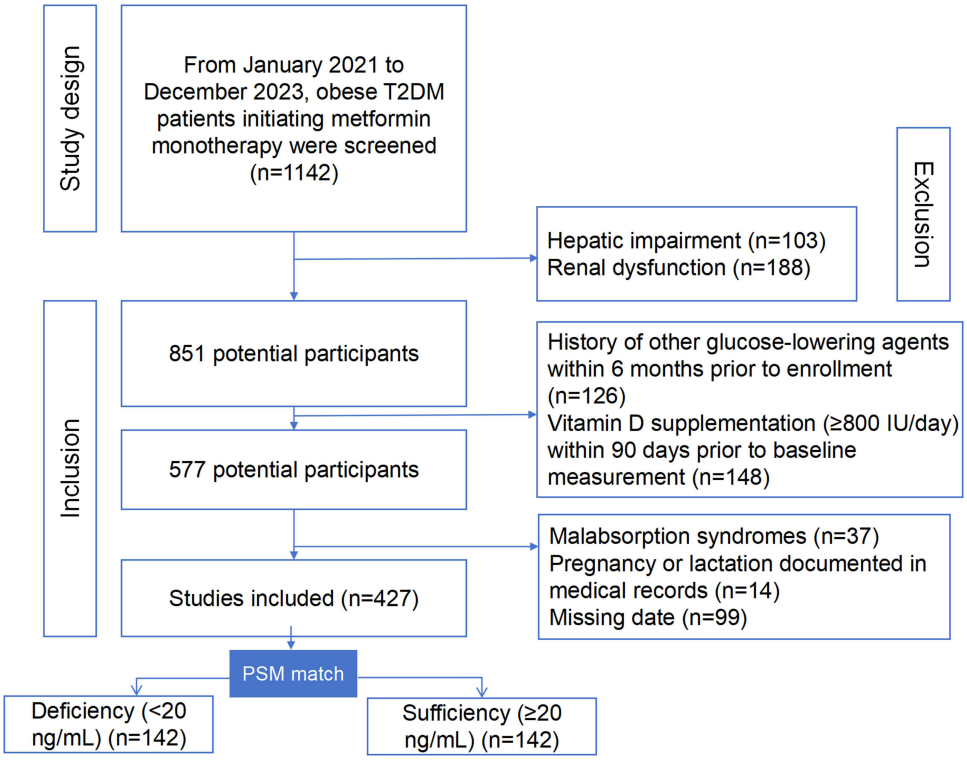

Figure 1 Inclusion and exclusion flowchart.

observational studies while still allowing a robust assessment of the initial pharmacodynamic response to metformin monotherapy.

Covariates

Clinically relevant covariates were rigorously extracted from structured EMR fields to address potential confounding: (1) Demographic factors: Age (years, continuous), sex (male/female), body mass index (BMI, kg/m^2 calculated from height/weight recorded within ±7 days of metformin initiation); (2) Diabetes-related parameters: Baseline HbA1c (%, continuous), diabetes duration (years, calculated from date of first T2DM diagnosis in EMR); (3) Comorbidities: Hypertension (defined as systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg on ≥2 occasions, or ICD-10 code I10 with concurrent antihypertensive medication),[22] dyslipidemia (ICD-10 code E78.5 plus lipid-lowering therapy, or LDL-C ≥130 mg/dL);[23] (4) Seasonality: Month of 25(OH)D blood draw categorized into high-ultraviolet (UV) period (April–September) and low-UV period (October–March) based on geographic insolation patterns in Northern China;[17] (5) Additional adjustments: Metformin daily dose (mg/day, extracted from pharmacy dispensing records), estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2 calculated using CKD-.

Statistical Analysis

Analyses were conducted on both the full unmatched cohort (n=427) and the propensity score-matched (PS-matched) cohort (n=284), with the PS-matched cohort serving as the primary dataset for hypothesis testing. Continuous data conforming to a normal distribution are presented as the mean ± standard deviation (SD); skewed data are reported as the median (interquartile range, IQR). Between-group comparisons for continuous variables employed independent Student's t tests or Mann–Whitney *U*-tests, as appropriate. Categorical variables are expressed as counts (percentages) and were compared using χ^2-tests or Fisher's exact tests. The relationship between baseline 25(OH)D levels (continuous) and ΔHbA1c was assessed using Pearson's correlation coefficient for normally distributed pairs or Spearman's rank correlation for nonparametric distributions, following confirmation of normality via Shapiro–Wilk tests (W >0.95). Multiple linear regression models were fitted to evaluate the independent association of vitamin D status (categorical: deficiency vs sufficiency) with ΔHbA1c, employing sequential covariate adjustment: Model 1 (age, sex); Model 2 (Model 1 + BMI, baseline HbA1c, diabetes duration); Model 3 (Model 2 + hypertension, dyslipidemia, season, metformin dose, eGFR). The absence of significant multicollinearity was confirmed by variance inflation factors (VIFs) <5 in the fully adjusted model. Subgroup analyses incorporating interaction terms within Model 3 were performed stratifying by sex, age (>60 vs ≤60 years), and baseline HbA1c (<8.5% vs ≥8.5%), with heterogeneity assessed using likelihood ratio tests. Sensitivity analyses included: 1) repeating primary analyses using absolute 25(OH)D concentrations (per 10 ng/mL increase) rather than categorical groups; 2) excluding outliers (ΔHbA1c beyond mean ± 3SD); 3) multiple imputation (chained equations, 20 imputations) for missing covariate data (<5%); and 4) repeating regression in the full unmatched cohort with inverse probability weighting. All analyses were conducted using R version 4.3.4 with the packages MatchIt for PSM, mice for imputation, and lmtest for regression diagnostics; two-sided p values <0.05 were considered statistically significant.

Results

Baseline Characteristics

From January 2021 to December 2023, 1842 obese T2DM patients initiating metformin monotherapy were screened. After applying the inclusion/exclusion criteria, 427 patients comprised the full cohort (vitamin D deficient: n=256 [59.9%]; sufficient: n=171 [40.1%]). Propensity score matching generated 142 matched pairs (n=284), achieving balance across all covariates (standardized mean differences [SMD] <0.1). In the full cohort, deficient patients were significantly older (62.4±10.1 vs 58.9±9.3 years, p=0.001), had higher baseline HbA1c (8.9±1.4% vs 8.5±1.2%, p=0.002), and had a longer diabetes duration (4.1[2.0–7.0] vs 3.0[1.0–5.0] years, p<0.001). After matching, no significant differences persisted between groups (all p>0.05), confirming effective confounding control (Table 1).

Table 1 Demographic and Clinical Characteristics Before and After Propensity Score Matching

Characteristic	Full Cohort				PSM-Matched Cohort			
	Deficiency (<20 ng/mL) (n=256)	Sufficiency (≥20 ng/mL) (n=171)	p value	SMD	Deficiency (<20 ng/mL) (n=142)	Sufficiency (≥20 ng/mL) (n=142)	p value	SMD
Demographics								
Age, years	62.4 ± 10.1	58.9 ± 9.3	0.001	0.35	60.2 ± 9.8	59.7 ± 9.1	0.64	0.05
Male, n (%)	132 (51.6%)	92 (53.8%)	0.68	0.04	74 (52.1%)	76 (53.5%)	0.81	0.03
Anthropometrics								
BMI, kg/m^2	31.7 ± 3.2	31.2 ± 2.9	0.12	0.16	31.4 ± 3.0	31.3 ± 2.8	0.78	0.03
Diabetes Parameters								
Baseline HbA1c, %	8.9 ± 1.4	8.5 ± 1.2	0.002	0.31	8.6 ± 1.3	8.7 ± 1.2	0.52	0.08
Diabetes duration, years	4.1 [2.0–7.0]	3.0 [1.0–5.0]	<0.001	0.42	3.5 [1.8–6.0]	3.3 [1.5–5.5]	0.31	0.09
Comorbidities								
Hypertension, n (%)	178 (69.5%)	107 (62.6%)	0.14	0.15	96 (67.6%)	94 (66.2%)	0.79	0.03
Dyslipidemia, n (%)	149 (58.2%)	95 (55.6%)	0.60	0.05	81 (57.0%)	80 (56.3%)	0.90	0.01
Laboratory Values								
25(OH)D, ng/mL	14.3 ± 3.8	27.6 ± 5.9	<0.001	2.65	14.5 ± 3.6	26.8 ± 5.5	<0.001	2.58
eGFR, mL/min/1.73 m^2	88.2 ± 16.7	92.4 ± 15.3	0.01	0.26	89.8 ± 15.9	90.5 ± 16.2	0.69	0.04
Treatment								
Metformin dose, mg/day	1270 ± 320	1320 ± 290	0.10	0.16	1290 ± 310	1280 ± 300	0.77	0.03
Season								
Low-UV period, n (%)	172 (67.2%)	98 (57.3%)	0.04	0.21	92 (64.8%)	90 (63.4%)	0.80	0.03

Notes: Data are presented as the mean ± standard deviation, median [interquartile range], or frequency (percentage). Comparisons: *t* test for normally distributed continuous variables, Mann–Whitney *U*-test for skewed data (diabetes duration), χ^2-test for categorical variables. Matching covariates: age, sex, BMI, baseline HbA1c, diabetes duration, hypertension, dyslipidemia, season. All SMD <0.1 in the matched cohort indicates successful balance.
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; SMD, standardized mean difference; PSM, propensity score matching.

Primary Outcomes

In the propensity score-matched cohort (n=284), patients with vitamin D sufficiency (≥20 ng/mL) achieved significantly greater HbA1c reduction after 3 months of metformin monotherapy than those with vitamin D deficiency (<20 ng/mL) (ΔHbA1c: −1.52% ± 0.82% vs −1.18% ± 0.76%; mean difference 0.34%, 95% CI: 0.16–0.52%, p<0.001) (Table 2). Baseline serum 25(OH)D levels demonstrated a significant positive correlation with ΔHbA1c (r=0.32, 95% CI: 0.21–0.43, p<0.001), and the reduction in HbA1c was significantly greater in the vitamin D-adequate group than in the vitamin D-deficient group (average difference: 0.34%, 95% CI: 0.16–0.52%, p<0.001), indicating that higher vitamin D levels were associated with greater glycemic improvement (Figure 2).

Table 2 Glycemic Response to Metformin Monotherapy by Vitamin D Status

Variable	Vitamin D Deficiency (<20 ng/mL) (n=142)	Vitamin D Sufficiency (≥20 ng/mL) (n=142)	Mean Difference (95% CI)	p value
HbA1c, %				
Baseline	8.64 ± 1.31	8.71 ± 1.22	−0.07 (−0.35 to 0.21)	0.621
3-month follow-up	7.46 ± 1.15	7.19 ± 0.98	0.27 (0.01 to 0.53)	0.042
ΔHbA1c (reduction)	−1.18 ± 0.76	−1.52 ± 0.82	0.34 (0.16 to 0.52)	<0.001
Response categories, n (%)				
Good response (ΔHbA1c ≥1.0%)	89 (62.7%)	118 (83.1%)	-	<0.001*
Poor response (ΔHbA1c <1.0%)	53 (37.3%)	24 (16.9%)	-	

Notes: Data are presented as the mean ± standard deviation or frequency (percentage). ΔHbA1c = baseline HbA1c - 3-month HbA1c. The mean difference was calculated as deficiency minus sufficiency (a positive value favors the sufficiency group). *Comparison of response categories performed using χ^2-test.

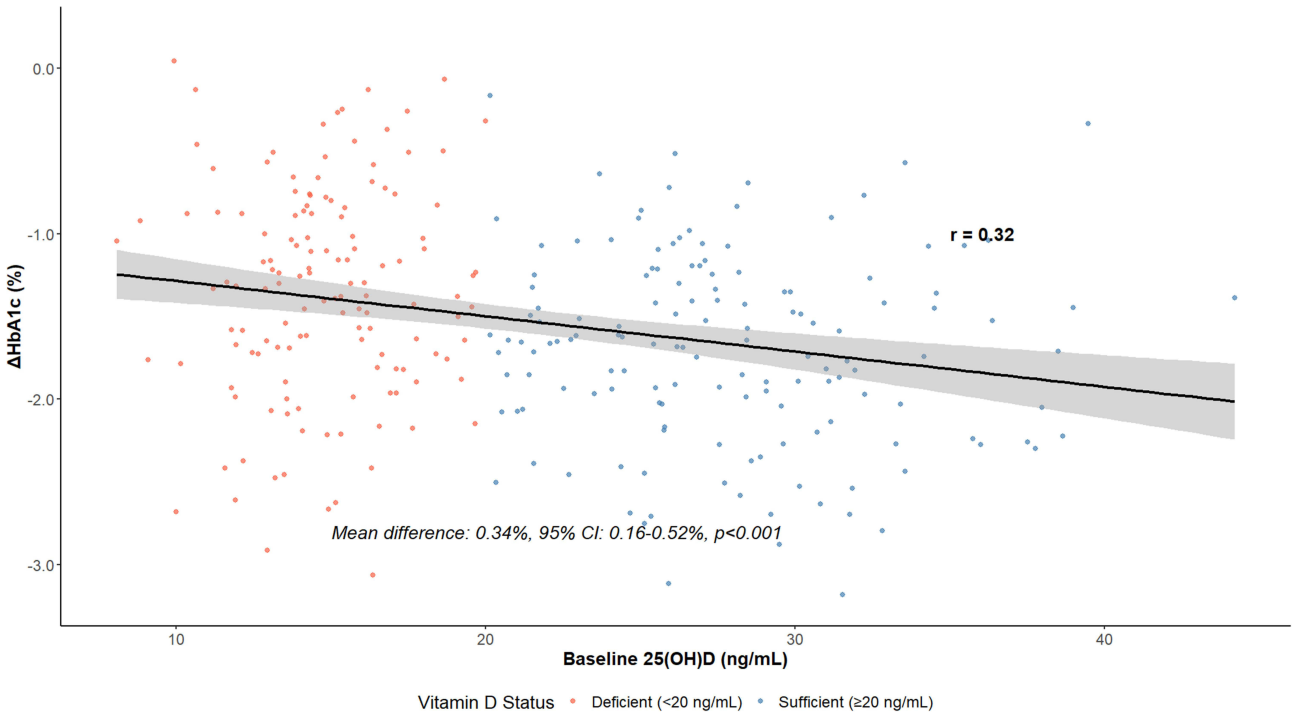

Figure 2 Association Between Baseline 25(OH)D Levels and HbA1c Reduction. Scatter plot showing the relationship between baseline vitamin D levels [25(OH)D] and reduction in HbA1c (ΔHbA1c) after three months of metformin monotherapy. Red dots represent vitamin D-deficient patients (<20 ng/mL), and blue dots represent vitamin D-sufficient patients (≥20 ng/mL). The black regression line shows the correlation between the two variables, with the shaded area representing the 95% confidence interval.

Multivariable Regression

Multivariable linear regression analyses confirmed the independent association between vitamin D sufficiency and enhanced glycemic response after comprehensive adjustment for potential confounders. In the fully adjusted model (Model 3), vitamin D sufficiency remained significantly associated with greater HbA1c reduction (β=0.41%, 95% CI: 0.22–0.60%, p<0.001) compared to deficiency, indicating a 0.41% absolute increase in HbA1c reduction. This effect was robust across sequential adjustment stages: unadjusted model (β=0.34%, p<0.001), age- and sex-adjusted model (β=0.37%, p<0.001), and fully adjusted model accounting for BMI, baseline HbA1c, diabetes duration, comorbidities, season, metformin dose, and renal function (β=0.41%, p<0.001). Among covariates, higher baseline HbA1c (β=0.21% per 1% increase, p<0.001) and greater metformin dosage (β=0.07% per 500 mg increase, p=0.024) were independent predictors of HbA1c reduction, while other factors, including age, sex, and comorbidities, showed no significant associations. The final model explained 38% of the variance in HbA1c response (R^2=0.38), with variance inflation factors <3.0 confirming the absence of multicollinearity (Table 3).

Subgroup Analyses

Stratified analyses revealed significant heterogeneity in the association between vitamin D status and metformin efficacy across clinically relevant subgroups. The beneficial effect of vitamin D sufficiency was consistently observed in all subgroups but significantly enhanced in specific populations: females demonstrated a 108% greater HbA1c reduction benefit than males (β=0.52% vs 0.25%, p-interaction=0.018), patients >60 years showed 48% stronger effects than younger individuals (β=0.49% vs 0.33%, p-interaction=0.009), and those with baseline HbA1c ≥8.5% exhibited a 167% greater benefit versus lower HbA1c counterparts (β=0.56% vs 0.21%, p-interaction=0.003). No significant effect modification was observed for hypertension status (p-interaction=0.215) or dyslipidemia (p-interaction=0.437). In all subgroup analyses, the point estimates favored vitamin D sufficiency with β coefficients ranging from 0.21% to 0.56%, and statistical significance was maintained in all strata except the baseline HbA1c <8.5% subgroup (p=0.059) (Table 4, Figure 3).

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Table 3 Multivariate Linear Regression Analysis of Factors Associated with HbA1c Reduction (ΔHbA1c)

Variable	Model 1: Unadjusted β (95% CI)	p value	Model 2: Partially Adjusted* β (95% CI)	p value	Model 3: Fully Adjusted† β (95% CI)	p value
Vitamin D status						
Deficiency (<20 ng/mL)	Ref	–	Ref	–	Ref	–
Sufficiency (≥20 ng/mL)	0.34 (0.16 to 0.52)	<0.001	0.37 (0.19 to 0.55)	<0.001	0.41 (0.22 to 0.60)	<0.001
Covariates						
Age (per 5-year increase)	-	-	0.01 (−0.05 to 0.07)	0.714	0.03 (−0.04 to 0.10)	0.402
Male sex	-	-	−0.08 (−0.25 to 0.09)	0.361	−0.06 (−0.24 to 0.12)	0.514
BMI (per kg/m^2 increase)	-	-	-	-	−0.02 (−0.05 to 0.01)	0.198
Baseline HbA1c (per 1% increase)	-	-	-	-	0.21 (0.14 to 0.28)	<0.001
Diabetes duration (per year)	-	-	-	-	−0.02 (−0.04 to 0.00)	0.076
Hypertension	-	-	-	-	−0.09 (−0.27 to 0.09)	0.325
Dyslipidemia	-	-	-	-	−0.05 (−0.22 to 0.12)	0.573
Low-UV season	-	-	-	-	−0.11 (−0.28 to 0.06)	0.204
Metformin dose (per 500 mg)	-	-	-	-	0.07 (0.01 to 0.13)	0.024
eGFR (per 10 mL/min/1.73 m^2)	-	-	-	-	0.01 (−0.05 to 0.07)	0.799

Notes: β coefficients represent absolute changes in ΔHbA1c (%). Positive β indicates greater HbA1c reduction. Model 1: Unadjusted. *Model 2: Adjusted for age and sex. †Model 3: Adjusted for all listed covariates. Analysis based on propensity score-matched cohort (n=284). Model 3 R^2 = 0.38; Variance inflation factors <3.0 for all variables.

Table 4 Subgroup Analysis of Vitamin D Effect on HbA1c Reduction

Subgroup	n	Deficiency Group ΔHbA1c (%, Mean±SD)	Sufficiency Group ΔHbA1c (%, Mean±SD)	Adjusted β* (95% CI)	p value	p-Interaction
Overall	284	−1.18 ± 0.76	−1.52 ± 0.82	0.41 (0.22 to 0.60)	<0.001	-
Sex						0.018
Male	150	−1.22 ± 0.81	−1.42 ± 0.79	0.25 (0.01 to 0.49)	0.042	
Female	134	−1.14 ± 0.70	−1.64 ± 0.83	0.52 (0.28 to 0.76)	<0.001	
Age						0.009
≤60 years	156	−1.25 ± 0.80	−1.57 ± 0.85	0.33 (0.09 to 0.57)	0.007	
>60 years	128	−1.09 ± 0.69	−1.46 ± 0.77	0.49 (0.25 to 0.73)	<0.001	
Baseline HbA1c						0.003
<8.5%	148	−0.95 ± 0.61	−1.18 ± 0.65	0.21 (−0.01 to 0.43)	0.059	
≥8.5%	136	−1.43 ± 0.80	−1.89 ± 0.82	0.56 (0.32 to 0.80)	<0.001	
Hypertension						0.215
No	94	−1.29 ± 0.82	−1.61 ± 0.88	0.38 (0.08 to 0.68)	0.013	
Yes	190	−1.13 ± 0.72	−1.48 ± 0.79	0.42 (0.18 to 0.66)	<0.001	
Dyslipidemia						0.437
No	123	−1.15 ± 0.77	−1.48 ± 0.80	0.35 (0.08 to 0.62)	0.011	
Yes	161	−1.20 ± 0.76	−1.55 ± 0.84	0.45 (0.21 to 0.69)	<0.001	

Notes: *β coefficients derived from Model 3 (fully adjusted) excluding the stratification variable; P-interaction from likelihood ratio test comparing models with/without interaction term.

Abbreviations: SD, standard deviation; CI, confidence interval.

Sensitivity Analyses

Robustness of the primary findings was confirmed through comprehensive sensitivity analyses. When vitamin D was analyzed as a continuous variable, each 10 ng/mL increase in baseline 25(OH)D was associated with a 0.27% greater HbA1c reduction (95% CI: 0.14–0.40%, p<0.001) in the fully adjusted model, aligning with categorical analysis results. Exclusion of 13 outliers (ΔHbA1c beyond the mean ± 3SD) strengthened the association (β=0.43% for sufficiency vs

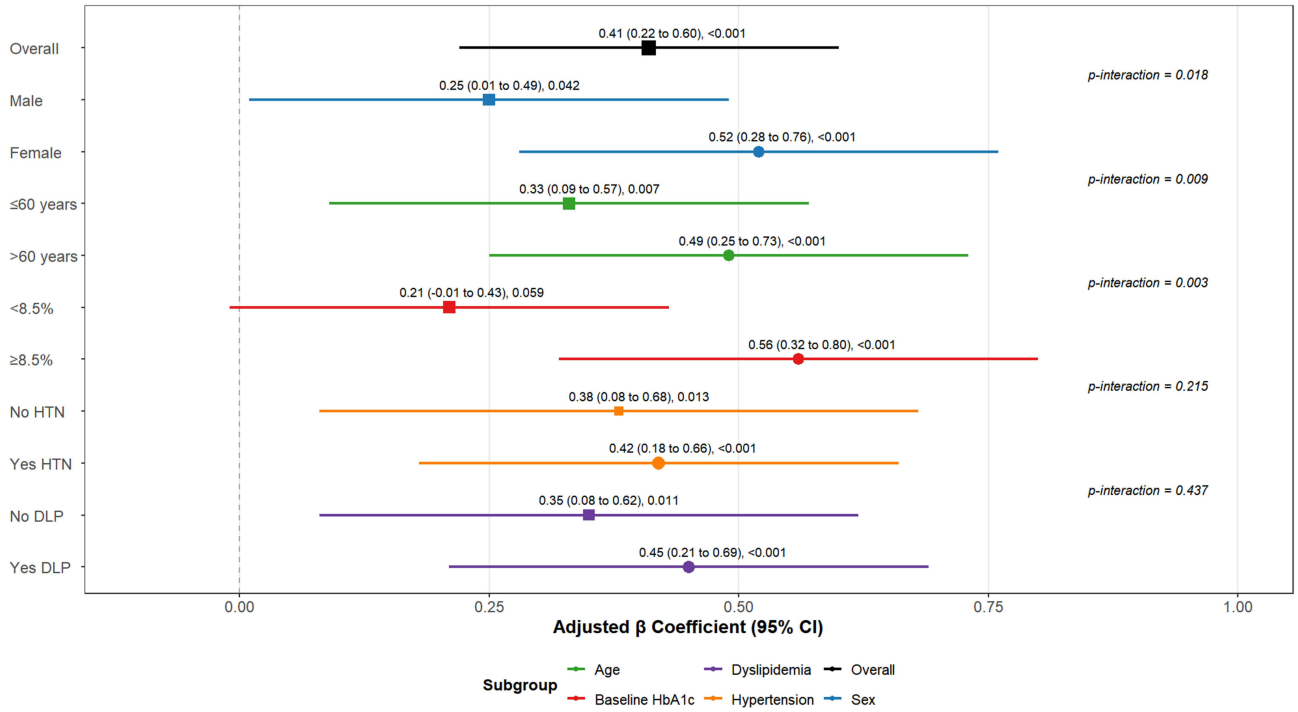

Figure 3 Effect of Vitamin D Sufficiency on HbA1c Reduction by Subgroup. Forest plot showing the adjusted β coefficients and 95% confidence intervals for the effect of vitamin D sufficiency (≥20 ng/mL) versus deficiency (<20 ng/mL) on HbA1c reduction across different subgroups. Point estimates to the right of the dashed vertical line indicate greater HbA1c reduction in the vitamin D-sufficient group. The size of each point is proportional to the subgroup sample size. P-interaction values indicate whether the effect of vitamin D status significantly differs between subgroup strata.

deficiency, 95% CI: 0.23–0.63, p<0.001). Multiple imputation for missing covariates (4.2% missingness) yielded nearly identical results (β=0.40%, 95% CI: 0.21–0.59, p<0.001). Critically, analysis of the full unmatched cohort (n=427) using inverse probability weighting reproduced the significant benefit of vitamin D sufficiency (β=0.35%, 95% CI: 0.16–0.54, p<0.001), confirming consistency across analytical approaches (Table 5).

Adverse Events

Safety profiles were comparable between vitamin D groups. Gastrointestinal adverse events (diarrhea, nausea) occurred in 26.1% of deficient patients vs 22.5% of sufficient patients (p=0.42). Documented hypoglycemia (<70 mg/dL) was rare and similar between groups (3.5% vs 2.8%, p=0.73). No severe adverse events (eg, lactic acidosis, vitamin D toxicity) were recorded in either group during the 3-month observation period (Table 6).

Table 5 Sensitivity Analyses of Vitamin D and Metformin Efficacy Association

Analysis Approach	Vitamin D Effect Measure	β (95% CI)	p value	Model Details
Primary Analysis (PSM cohort)	Sufficiency (≥20 ng/mL) vs Deficiency	0.41 (0.22 to 0.60)	<0.001	Fully adjusted
Continuous Vitamin D	Per 10 ng/mL increase in 25(OH)D	0.27 (0.14 to 0.40)	<0.001	Fully adjusted
Excluding outliers	Sufficiency vs Deficiency	0.43 (0.23 to 0.63)	<0.001	Fully adjusted (n=271)
Multiple imputation	Sufficiency vs Deficiency	0.40 (0.21 to 0.59)	<0.001	Fully adjusted (20 imputations)
Full cohort (IPW)	Sufficiency vs Deficiency	0.35 (0.16 to 0.54)	<0.001	IPW with propensity scores

Notes: β coefficients represent absolute differences in ΔHbA1c (%). All models were adjusted for age, sex, BMI, baseline HbA1c, diabetes duration, hypertension, dyslipidemia, season, metformin dose, and eGFR.
Abbreviations: PSM, propensity score matching; IPW, inverse probability weighting; CI, confidence interval.

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Table 6 Adverse Events by Vitamin D Status

Event Category	Vitamin D Deficiency (n=142)	Vitamin D Sufficiency (n=142)	Risk Difference (95% CI)	p value
Gastrointestinal, n (%)				
Diarrhea	25 (17.6%)	21 (14.8%)	2.8% (−5.6 to 11.2)	0.52
Nausea/Vomiting	12 (8.5%)	11 (7.7%)	0.7% (−6.1 to 7.6)	0.83
Abdominal discomfort	9 (6.3%)	7 (4.9%)	1.4% (−4.2 to 7.0)	0.61
Total GI events	37 (26.1%)	32 (22.5%)	3.5% (−6.9 to 13.9)	0.42
Hypoglycemia				
Documented <70 mg/dL	5 (3.5%)	4 (2.8%)	0.7% (−3.6 to 5.0)	0.73
Severe (<54 mg/dL)	1 (0.7%)	0 (0.0%)	0.7% (−0.7 to 2.1)	0.32
Other events				
Headache	8 (5.6%)	6 (4.2%)	1.4% (−4.0 to 6.8)	0.59
Fatigue	11 (7.7%)	9 (6.3%)	1.4% (−5.1 to 7.9)	0.67

Notes: Data are presented as frequencies (percentages). Risk difference calculated as Deficiency minus Sufficiency. Comparisons by χ^2-test or Fisher's exact test.

Discussion

This retrospective cohort study demonstrates a significant association between serum 25(OH)D levels and the glycemic response to metformin monotherapy in obese patients with T2DM. The primary finding indicates that patients with sufficient baseline vitamin D levels (≥20 ng/mL) achieved a significantly greater reduction in HbA1c after 3 months of metformin treatment compared to those with vitamin D deficiency (<20 ng/mL) (mean ΔHbA1c difference: 0.34%, 95% CI: 0.16–0.52%, p<0.001). This magnitude of HbA1c reduction is considered clinically relevant, as landmark studies such as the UK Prospective Diabetes Study (UKPDS) have established that even a modest 0.5% decrease in HbA1c is associated with a significant reduction in the risk of long-term diabetic complications.[24] This association remained robust in multivariable linear regression analysis, where vitamin D sufficiency was independently associated with a 0.41% greater HbA1c reduction (95% CI: 0.22–0.60%, p<0.001) after comprehensive adjustment for potential confounders, including age, sex, BMI, baseline HbA1c, diabetes duration, comorbidities, season, metformin dose, and renal function. This finding suggests that baseline vitamin D status may serve as a predictive biomarker for metformin efficacy in this specific population, aligning with the established biological roles of vitamin D in modulating insulin sensitivity, beta-cell function, and inflammation.[2,4] Vitamin D exerts its effects through the VDR, widely expressed in pancreatic beta cells, adipose tissue, and skeletal muscle, influencing insulin secretion, glucose transporter (GLUT4) expression, and inflammatory pathways.[25] Vitamin D deficiency may impair these pathways, exacerbating insulin resistance and potentially diminishing the response to insulin-sensitizing agents such as metformin.[26]

It is well established that serum 25(OH)D levels exhibit significant seasonal fluctuations driven by variations in sunlight exposure. This phenomenon is particularly relevant in the Chinese population, as demonstrated by a large-scale study across 30 provinces involving over 1.5 million individuals, which reported that median 25(OH)D concentrations reached a nadir in winter (18.5 ng/mL) and peaked in summer (25.3 ng/mL).[27] This national trend is corroborated by findings specific to the study region of Hanzhong, where children's mean 25(OH)D levels were significantly lower and the prevalence of vitamin D deficiency was highest during winter compared to other seasons.[17] To control for the potential confounding effect of this seasonality on both baseline vitamin D status and the assessment of glycemic response, we therefore performed a season-adjusted analysis. Specifically, the month of blood draw was categorized into a high-UV period (April–September) and a low-UV period (October–March) based on the solar zenith angle and typical insolation patterns in Hanzhong City, Shaanxi Province. This binary "season" variable was subsequently included as a covariate in both the propensity score model and the multivariable regression analyses. This methodological adjustment enhances the robustness of our findings by ensuring that the observed association between baseline 25(OH)D levels and metformin response is independent of seasonal variation in vitamin D status.

Our results corroborate some, but not all, findings from previous observational studies. A small descriptive study in newly diagnosed T2DM patients reported a positive correlation between baseline vitamin D levels and HbA1c reduction after 12 weeks, consistent with the correlation observed here, but this study did not evaluate the relationship of

metformin.[28] However, the results of a large D2d trial showed that after a median follow-up of 2.5 years, the incidence of new-onset diabetes was 9.4 and 10.7 per 100 person-years in the vitamin D group and placebo group, respectively, with no statistically significant difference (HR = 0.88, 95% CI 0.75–1.04, P = 0.12).[7] This discrepancy may stem from differences in study design (supplementation intervention vs observation of baseline status) and participant characteristics (eg, lower prevalence of baseline deficiency and inclusion of nonobese individuals in D2d). Another cross-sectional study in obese diabetic patients reported an association between vitamin D deficiency and poorer metformin response, supporting our core finding.[29] The novelty of the present study lies in its focus on obese T2DM patients, a subgroup with a high prevalence of vitamin D deficiency and pronounced insulin resistance; the strict inclusion of metformin monotherapy initiators to eliminate confounding by other glucose-lowering agents; the systematic application of propensity score matching to address baseline imbalances; and the extensive sensitivity and subgroup analyses confirming result robustness.

Subgroup analyses revealed clinically relevant heterogeneity in the association between vitamin D status and metformin efficacy. The enhanced HbA1c reduction associated with vitamin D sufficiency was significantly more pronounced in females (β=0.52% vs 0.25% in males, p-interaction=0.018), patients older than 60 years (β=0.49% vs 0.33% in ≤60 years, p-interaction=0.009), and those with poorer baseline glycemic control (HbA1c ≥8.5%, β=0.56% vs 0.21% in HbA1c <8.5%, p-interaction=0.003). The stronger effect in females could relate to sex-specific differences in vitamin D metabolism and VDR expression, potentially influenced by estrogen regulation.[30] The greater benefit in older adults may reflect their higher prevalence of vitamin D deficiency, age-related sarcopenia exacerbating insulin resistance, and potential alterations in VDR function.[31] The pronounced effect in patients with higher baseline HbA1c suggests that vitamin D status might be particularly important when underlying beta-cell dysfunction and insulin resistance are more severe. Mechanistically, metformin primarily activates AMPK, improving hepatic and peripheral insulin sensitivity. Vitamin D has also been shown to modulate AMPK activity. Experimental studies indicate that 1,25-dihydroxyvitamin D can regulate AMPK and its upstream kinase LKB1 through calcium-dependent pathways or direct VDR binding, suggesting potential synergy in improving mitochondrial function and glucose uptake.[32] Furthermore, the anti-inflammatory properties of vitamin D, such as downregulating TNF-α and IL-6, may ameliorate chronic low-grade inflammation-induced insulin signaling impairment, thereby augmenting metformin's effects.[33]

Regarding safety, the incidence of adverse events was comparable between vitamin D-sufficient and vitamin D-deficient groups. Gastrointestinal adverse events (diarrhea, nausea) were the most common, occurring in 26.1% of deficient patients versus 22.5% of sufficient patients (p=0.42). Documented hypoglycemia (<70 mg/dL) was rare and similar between groups (3.5% vs 2.8%, p=0.73). No severe adverse events, such as lactic acidosis or vitamin D toxicity, were recorded during the 3-month observation period. This finding aligns with the established safety profile of metformin and suggests that vitamin D status itself does not significantly alter short-term metformin tolerability.[34]

Several limitations warrant cautious interpretation of our findings. First, the single-center, retrospective observational design, while appropriate for generating hypotheses, inherently limits causal inference between vitamin D status and metformin response. Although we employed rigorous inclusion/exclusion criteria and propensity score matching to control for known confounders, residual bias from unmeasured or imperfectly measured factors cannot be excluded. Specifically, parameters such as detailed physical activity levels, precise sunlight exposure habits, and dietary vitamin D/calcium intake, which may influence both serum 25(OH)D concentration and glycemic control, were not systematically available and represent potential sources of residual confounding. Second, serum 25(OH)D was measured only once at baseline, precluding assessment of its dynamic changes during follow-up and their potential influence on the observed associations. Third, the follow-up duration was limited to 3 months, which, while adequate for assessing initial HbA1c response, restricts insights into the long-term impact of vitamin D status on sustained metformin efficacy and diabetes-related complications. While our study provides a snapshot of the initial treatment phase, the durability of this effect is a critical question. Metformin's glucose-lowering effect can wane over time,[35] and whether adequate vitamin D status can help preserve or prolong this response remains unknown. However, evidence from meta-analyses of randomized controlled trials does suggest that long-term vitamin D supplementation can lead to modest but significant improvements in glycemic control in patients with T2DM,[36] lending biological plausibility to a potentially sustained beneficial interaction that warrants investigation in longer-term studies. Fourth, our cohort consisted exclusively of obese

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Chinese patients with T2DM; thus, the generalizability of our findings to other ethnicities, nonobese individuals, or populations residing in geographical regions with markedly different sunlight exposure patterns may be limited. Fifth, while the vitamin D sufficiency cutoff (≥20 ng/mL) aligns with Endocrine Society guidelines, the optimal threshold for predicting glycemic benefits remains debated, and a higher target (eg, ≥30 ng/mL) might be relevant in metabolic contexts.[37] Sixth, the lack of data on vitamin D binding protein (DBP) polymorphisms or free 25(OH)D levels limits our ability to assess the impact of vitamin D bioactivity and bioavailability on the observed associations.

Future research should address these limitations and build upon our findings: 1. Conduct large-scale prospective cohort studies with serial vitamin D measurements to evaluate the relationship between dynamic vitamin D status and long-term metformin efficacy, durability of response, and cardiovascular outcomes. 2. Design Randomized controlled trials (RCTs) specifically testing whether vitamin D supplementation, compared to placebo, enhances the glucose-lowering effect of metformin in obese T2DM patients with confirmed vitamin D deficiency, with particular attention to the subgroups (females, elderly, high baseline HbA1c) showing greater benefit here. 3. Investigate the molecular mechanisms underlying the potential interaction between vitamin D and metformin, focusing on pathways such as AMPK signaling, mitochondrial function, and gut microbiota modulation. 4. Evaluate optimal vitamin D supplementation strategies (dosing regimens, target serum levels >30 ng/mL) for maximizing glycemic benefits in metformin-treated patients. 5. Incorporate genetic analyses to identify individuals most likely to benefit from vitamin D status optimization.

Based on our findings, several clinical implications merit discussion. We suggest that screening for vitamin D status could be a valuable component of the initial assessment for obese T2DM patients initiating metformin therapy. However, it is crucial to clarify the rationale for this. Current evidence does not support correcting vitamin D deficiency primarily for metabolic improvement, as major guidelines, including those from the Endocrine Society and the US Preventive Services Task Force, do not advocate for routine vitamin D supplementation for the sole purpose of improving glycemic control.[37,38] Instead, the correction of vitamin D deficiency should continue to be guided by the primary goal of maintaining skeletal health.

Conclusion

This rigorous observational study demonstrates that higher baseline serum vitamin D levels (≥20 ng/mL) are independently associated with a significantly greater reduction in HbA1c after 3 months of metformin monotherapy in obese patients with T2DM. This association was particularly strong among females, older adults, and patients with poorer baseline glycemic control. Our results suggest that achieving vitamin D sufficiency, as recommended for general health, may confer an additional benefit by enhancing the initial glycemic response to metformin. While these observational findings are not sufficient to recommend vitamin D supplementation specifically to augment metformin's effects, they strongly support the clinical wisdom of screening for and correcting vitamin D deficiency in this high-risk population according to existing guidelines. This finding supports the potential role of vitamin D status as a biomarker for predicting the metformin response, possibly mediated through mechanisms involving enhanced insulin sensitivity, reduced inflammation, and potential modulation of AMPK signaling. While these results should inform clinical suspicion and highlight the importance of vitamin D status in metabolic management, they do not justify a direct change in practice, such as high-dose vitamin D supplementation specifically to enhance metformin efficacy. Instead, they reinforce the importance of screening for vitamin D deficiency as part of the comprehensive initial evaluation of obese T2DM patients initiating metformin, with subsequent repletion guided by established clinical guidelines. Future well-designed randomized controlled trials are essential to determine whether correction of vitamin D deficiency causally improves the therapeutic response to metformin and to establish the optimal serum 25(OH)D target level for achieving potential metabolic benefits.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author, Z. W, upon special request.

Ethics Approval and Consent to Participate

The study protocol was approved by the Hanzhong Central Hospital Institutional Review Board (No: [2024]-18). A waiver of informed consent was granted, as the research involved anonymized retrospective data analysis without intervention, adhering to local regulations and the Declaration of Helsinki. All data were handled confidentially with strict adherence to privacy protection protocols.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors confirm that there is no conflict of interest related to the paper.

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