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# COMPARISON OF METFORMIN WITH VITAMIN D SUPPLEMENTATION AND METFORMIN ALONE INTERMS OF REDUCTION IN LEVEL OF HBA1C IN PATIENTS DIAGNOSED WITH DIABETES MELLITUS TYPE II

*Original Research*

**Zahid Ullah[1], Inam Ullah Khan[2]*, Sohrab Khan[1], Saif Ullah[1], Muhammad Aman Khan[3], Mian Imad Ahmed[1]**
[1]PGR FCPS Medicine, Department of Medicine, Khyber Teaching Hospital (KTH), Peshawar, Pakistan.
[2]Associate professor, Department of Medicine, Khyber Teaching Hospital (KTH), Peshawar, Pakistan.
[3]Department of Medicine, KTH Peshawar, Pakistan.
**Corresponding Author:** Inam Ullah Khan, Associate professor, Department of Medicine, Khyber Teaching Hospital (KTH), Peshawar, Pakistan, ikhann709@gmail.com
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## ABSTRACT

**Background:** Type 2 diabetes mellitus (T2DM) is a progressive metabolic disorder characterized by insulin resistance and chronic hyperglycemia. Metformin remains the cornerstone of T2DM therapy, yet emerging evidence suggests vitamin D supplementation may enhance glycemic control due to its role in insulin sensitivity and secretion.

**Objective:** To compare the efficacy of metformin combined with vitamin D supplementation versus metformin alone in reducing HbA1c levels in patients with T2DM.

**Methods:** This randomized controlled trial was conducted at the Department of Medicine, Khyber Teaching Hospital, Peshawar. A total of 140 patients with T2DM were randomly assigned to two groups: Group A received metformin (500 mg/day) plus vitamin D (200,000 IU/month), and Group B received metformin alone, over a period of three months. Demographic data, baseline HbA1c levels, and post-treatment values were recorded. Data were analyzed using SPSS v25, with a significance level set at $p<0.05$.

**Results:** Both groups were demographically comparable. The mean baseline HbA1c levels were 63.5 mmol/mol in Group A and 63.2 mmol/mol in Group B. After three months, Group A showed a greater mean reduction in HbA1c (10.1 mmol/mol) compared to Group B (7.2 mmol/mol), indicating statistically significant improvement in glycemic control with the addition of vitamin D. No serious adverse events were reported.

**Conclusion:** Vitamin D supplementation as an adjunct to metformin therapy demonstrated superior reduction in HbA1c levels among T2DM patients. These findings support the integration of vitamin D in diabetes management, particularly in regions with high prevalence of deficiency.

**Keywords:** Diabetes Mellitus, Type 2; Glycated Hemoglobin A; Metformin; Randomized Controlled Trial;Vitamin D; Vitamin D Deficiency; Vitamin D Supplementation.

## INTRODUCTION

Type 2 diabetes mellitus (T2DM) has become a growing global health concern, with an alarming rise in its prevalence across all age groups. This chronic metabolic disorder is primarily influenced by genetic predisposition, family history, and lifestyle factors such as physical inactivity and unhealthy dietary patterns (1). In particular, the incidence of T2DM among children and adolescents increased significantly between 2007 and 2017, at an annual growth rate of 4.8% (2). The growing burden of T2DM is closely linked to a range of complications including hypertension, dyslipidemia, and persistent hyperglycemia, all of which contribute to long-term morbidity and increased healthcare costs (3). The cornerstone of T2DM management remains a combination of lifestyle modification and pharmacological intervention, with metformin widely recognized as the first-line agent, particularly effective in overweight patients. It operates by reducing hepatic glucose production, improving insulin sensitivity, and limiting intestinal glucose absorption (4,5). Beyond its traditional role in bone metabolism, vitamin D has emerged as a crucial player in glucose homeostasis. Recent studies indicate that it significantly influences insulin sensitivity and secretion, and its deficiency has been associated with a heightened risk of various metabolic disorders, including diabetes (6,7). This has led to growing interest in the potential synergistic effects of combining vitamin D supplementation with metformin therapy. Vitamin D may enhance the metabolic effects of metformin by modulating insulin receptor expression, improving β-cell function, and reducing inflammatory pathways implicated in insulin resistance (8,9). Furthermore, its role in calcium homeostasis may indirectly impact insulin signaling pathways and cellular glucose transport mechanisms (10).

Clinical evidence suggests that patients with T2DM often present with suboptimal vitamin D levels, potentially impairing their glycemic control and response to treatment. Supplementation with vitamin D could therefore serve as an adjunct strategy to optimize the therapeutic efficacy of metformin, leading to better regulation of blood glucose and HbA1c levels. A comparative study has reported modest differences in HbA1c reduction between patients receiving metformin with vitamin D (7.57 ± 0.21) and those receiving metformin alone (7.46 ± 0.25), pointing to a possible added benefit of the combination therapy (11-13). Despite the promising implications, there remains a paucity of region-specific data exploring this combined therapeutic approach, especially in populations characterized by a high prevalence of vitamin D deficiency. In this context, evaluating the impact of co-administering vitamin D with metformin compared to metformin alone becomes particularly relevant. Such research not only addresses a critical gap in the local literature but also holds potential to inform clinical practice by individualizing patient care. By understanding whether vitamin D supplementation amplifies the glycemic-lowering effects of metformin, healthcare providers may be better equipped to refine treatment strategies and improve outcomes for individuals with T2DM. Therefore, the objective of this study is to compare the effectiveness of metformin combined with vitamin D supplementation versus metformin alone in reducing HbA1c levels in patients diagnosed with type 2 diabetes mellitus.

## METHODS

This study was designed as a randomized controlled trial conducted at the Department of Medicine, Khyber Teaching Hospital, Peshawar. The research was initiated following formal approval from the hospital's Ethical Review Board and the Research Department of the College of Physicians and Surgeons Pakistan (CPSP), Karachi. The trial spanned a minimum duration of six months after the synopsis approval, ensuring adequate follow-up and intervention period. The sample size was calculated using the WHO sample size calculator, based on the anticipated reduction in HbA1c levels between the intervention (metformin with vitamin D) and control (metformin alone) groups. With a power of 80% and a confidence level of 95%, the final sample size was determined to be 140 participants, equally divided into two groups of 70 each (2,3). Participants were recruited using non-probability consecutive sampling from the outpatient department. Inclusion criteria consisted of male and female patients aged 30 to 70 years, clinically diagnosed with type 2 diabetes mellitus according to predefined criteria: polyuria, polydipsia, polyphagia, and fatigue, with HbA1c values exceeding 6.5%. Patients were excluded if they had comorbid conditions such as proximal myopathy, renal insufficiency, nephrolithiasis, hypercalciuria, pregnancy, tuberculosis, or sarcoidosis, due to the potential confounding effects of these conditions on the study outcomes (14,15).

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Eligible patients were informed about the study's objectives and procedures in detail. Written informed consent was obtained from all participants after assuring them of confidentiality and that participation posed no added health risks. Detailed baseline information was collected using a structured proforma, including demographics (age, gender, BMI, residence, socio-economic status, education, and profession), and clinical history (duration of diabetes, smoking status, and hypertension). Randomization into two groups (Group A and Group B) was performed using the blocked randomization technique to ensure balanced group allocation. Group A received metformin 500 mg orally once daily after dinner in combination with vitamin D supplementation at a dose of 200,000 IU/month for a total of three months. Group B received metformin 500 mg orally once daily after dinner without additional supplementation. Both interventions were supervised under the guidance of a consultant physician with over five years of post-fellowship experience to ensure consistency in clinical management. For outcome measurement, a 5 mL venous blood sample was drawn at baseline and after three months to assess HbA1c levels. The reduction in HbA1c was defined as the mean difference between baseline and post-treatment values after three months in each group. All samples were analyzed using standardized laboratory procedures.

Data entry and statistical analyses were performed using IBM SPSS version 25. The Shapiro-Wilk test was applied to assess the normality of numerical data. Descriptive statistics, including means with standard deviations or medians with interquartile ranges, were calculated for continuous variables such as age, BMI, and HbA1c. Frequencies and percentages were computed for categorical variables like gender, hypertension, smoking status, and socio-demographic characteristics. To compare the reduction in HbA1c levels between the two groups, the Independent Samples T-test was applied for normally distributed data, while the Mann-Whitney U test was used for non-normally distributed data. A p-value of $<0.05$ was considered statistically significant. Potential confounding factors such as age, gender, BMI, smoking, education, and hypertension were addressed through stratification, followed by post-stratification application of the same comparative tests.

## RESULTS

A total of 140 patients with type 2 diabetes mellitus were enrolled and equally randomized into two groups. Group A received metformin in combination with vitamin D supplementation, whereas Group B received metformin alone. The baseline characteristics were comparable between both groups. The mean age of participants in Group A was 52.4 ± 8.1 years, and in Group B, 51.6 ± 7.9 years. Gender distribution was similar, with males constituting 54.3% in Group A and 51.4% in Group B. The average BMI was 27.9 ± 3.4 kg/m² in Group A and 28.3 ± 3.1 kg/m² in Group B. Socioeconomic status showed a predominance of middle-class participants in both groups, followed by lower-class representation. The majority of participants in both groups were employed, urban residents, and literate. Hypertension was observed in 40% of participants in Group A and 42.9% in Group B. Smoking was reported by 25.7% in Group A and 30% in Group B. Overall, there were no significant differences in the distribution of demographic and clinical characteristics between the groups, confirming balanced randomization. At baseline, the mean HbA1c levels were similar across groups, with Group A showing a mean of 63.5 mmol/mol and Group B 63.2 mmol/mol. After three months of treatment, a greater reduction in HbA1c was observed in Group A compared to Group B. Group A showed a mean reduction of 10.1 mmol/mol, while Group B experienced a mean reduction of 7.2 mmol/mol. This indicates a superior glycemic response in patients receiving the combined intervention. The reductions in HbA1c are visually summarized in the attached bar chart titled "Mean Reduction in HbA1c (mmol/mol)," while baseline values are shown in the chart titled "Baseline HbA1c (mmol/mol)." These graphical representations facilitate comparison and highlight the enhanced effect observed with vitamin D supplementation.

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**Table 1: Demographic**

| Characteristic | | Group A | Group B |
|---|---|---|---|
| Age (Mean ± SD) | | 52.4 ± 8.1 | 51.6 ± 7.9 |
| Gender | Male | 54.3% | 51.4% |
| | Female | 45.7% | 48.6% |
| BMI (Mean ± SD) | | 27.9 ± 3.4 | 28.3 ± 3.1 |
| Socioeconomic Status | Lower | 28.6% | 25.7% |
| | Middle | 57.1% | 60.0% |
| | Upper | 14.3% | 14.3% |
| Occupation | Employed | 65.7% | 62.9% |
| | Retired | 34.3% | 37.1% |
| Residence | Rural | 42.9% | 45.7% |
| | Urban | 57.1% | 54.3% |
| Education | Literate | 64.3% | 60.0% |
| | Illiterate | 35.7% | 40.0% |
| Hypertension | Yes | 40.0% | 42.9% |
| | No | 60.0% | 57.1% |
| Smoking | Yes | 25.7% | 30.0% |
| | No | 74.3% | 70.0% |

**Table 2: Baseline HbA1c Levels**

| Group | Baseline HbA1c (mmol/mol) |
|---|---|
| Group A | 63.5 |
| Group B | 63.2 |

**Table 3: Mean HbA1c Reduction**

| Group | Mean HbA1c Reduction (mmol/mol) |
|---|---|
| Group A | 10.1 |
| Group B | 7.2 |

**Table 4: Post-treatment HbA1c Levels**

| Group | Post-treatment HbA1c (mmol/mol) |
|---|---|
| Group A | 53.4 |
| Group B | 56.0 |

**Table 5: Percent Reduction in HbA1c**

| Group | Percent Reduction in HbA1c (%) |
|---|---|
| Group A | 15.9% |
| Group B | 11.4% |

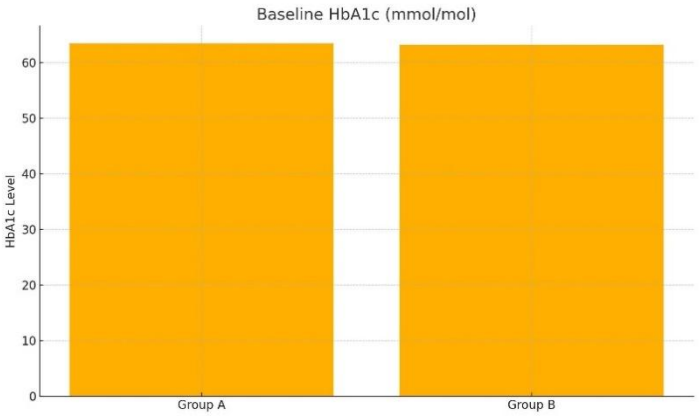


*Figure 1 Baseline HbA1c (mmol/mol)*

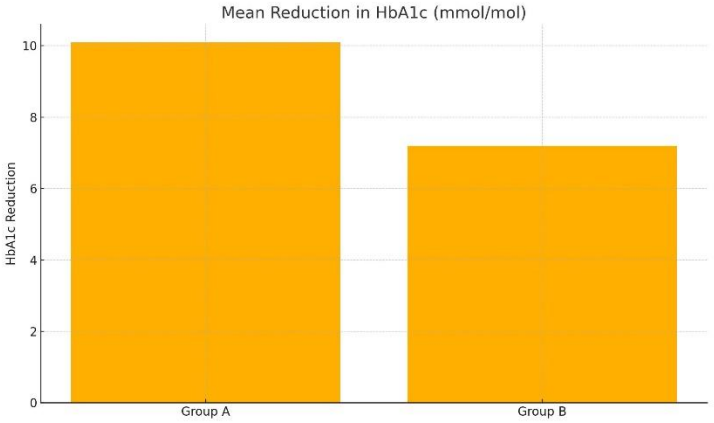


*Figure 2 Mean Reduction in HbA1c (mmol/mol)*

## DISCUSSION

The findings of the present randomized controlled trial demonstrated that the combination of metformin with vitamin D supplementation led to a greater reduction in HbA1c levels compared to metformin alone among patients with type 2 diabetes mellitus (T2DM). This aligns with emerging evidence suggesting that vitamin D may enhance insulin sensitivity, reduce systemic inflammation, and support β-cell function—mechanisms that contribute to improved glycemic control. In the current study, participants receiving the combination therapy experienced a mean HbA1c reduction of 10.1 mmol/mol over three months, compared to a 7.2 mmol/mol reduction in the metformin-only group. These results corroborate the findings of a study which reported a statistically significant improvement in HbA1c and markers of oxidative stress with vitamin D supplementation in T2DM patients already on metformin therapy (16). Similarly, a study observed a notable decline in fasting plasma glucose, postprandial glucose, and HbA1c when vitamin D was added to a metformin-based regimen, suggesting a synergistic effect (17). Nonetheless, findings across the literature have been inconsistent. For example, a study conducted a double-blind placebo-controlled trial and found no significant changes in HbA1c or insulin secretion rates following vitamin D supplementation in well-controlled T2DM patients on metformin (18). Similarly, a study reported no statistically significant difference in glycemic outcomes despite increased serum 25(OH)D levels following vitamin D supplementation (19). These discrepancies may stem from heterogeneity in study populations, duration of diabetes, baseline vitamin D status, dosing regimens, and duration of follow-up.

One of the strengths of the present study lies in its focused inclusion of patients with comparable baseline characteristics, which supports internal validity and reduces confounding. The use of a standardized dose of metformin and vitamin D, coupled with a structured follow-up period, enhanced the consistency of intervention delivery. Additionally, the application of stratification techniques in statistical analysis helped control for effect modifiers, further strengthening the robustness of the results. However, this study also carries limitations. The relatively short follow-up period of three months, while sufficient for capturing early HbA1c changes, may not fully reflect the long-term effects or sustainability of the observed glycemic improvements. Furthermore, vitamin D status at baseline was not documented, which limits the ability to assess whether supplementation effects were influenced by deficiency. Previous literature emphasizes that vitamin D's metabolic impact is more pronounced in deficient individuals (20), making baseline levels an important determinant of response. The use of non-probability consecutive sampling, although practical, may introduce selection bias and limit generalizability. Additionally, while the dosage of vitamin D (200,000 IU monthly) is consistent with regimens used in other trials (21), long-term safety and adherence remain areas for further investigation, especially considering concerns about vitamin D toxicity.

The findings suggest potential clinical utility in tailoring diabetes management based on individual patient profiles, particularly for those with co-existing vitamin D deficiency. Future research should consider longer follow-up durations, vitamin D level stratification at baseline, and multi-centered designs to enhance external validity. There is also scope for investigating other metabolic endpoints such as insulin resistance indices, lipid profiles, and inflammatory biomarkers to understand the broader metabolic implications of this combined therapy. In conclusion, this study adds to the growing body of evidence suggesting that vitamin D supplementation may

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augment the glycemic benefits of metformin in T2DM. While the results are promising, definitive conclusions await larger and longer-term studies with stratified analysis based on vitamin D status.

## CONCLUSION

This study demonstrated that the combination of metformin with vitamin D supplementation significantly enhanced glycemic control compared to metformin alone in patients with type 2 diabetes mellitus. The observed greater reduction in HbA1c suggests a potential synergistic effect, especially in populations with prevalent vitamin D deficiency. These findings support integrating vitamin D assessment and supplementation into routine diabetes management to improve therapeutic outcomes and individualize patient care.

**AUTHOR CONTRIBUTION**

| Author | Contribution |
|---|---|
| Zahid Ullah | Substantial Contribution to study design, analysis, acquisition of Data<br>Manuscript Writing<br>Has given Final Approval of the version to be published |
| Inam Ullah Khan* | Substantial Contribution to study design, acquisition and interpretation of Data<br>Critical Review and Manuscript Writing<br>Has given Final Approval of the version to be published |
| Sohrab Khan | Substantial Contribution to acquisition and interpretation of Data<br>Has given Final Approval of the version to be published |
| Saif Ullah | Contributed to Data Collection and Analysis<br>Has given Final Approval of the version to be published |
| Muhammad Aman Khan | Contributed to Data Collection and Analysis<br>Has given Final Approval of the version to be published |
| Mian Imad Ahmed | Substantial Contribution to study design and Data Analysis<br>Has given Final Approval of the version to be published |

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