



## ASSOCIATION BETWEEN VITAMIN D LEVELS AND DIABETIC FOOT COMPLICATIONS IN INDIVIDUALS DIAGNOSED WITH TYPE 2 DIABETES MELLITUS

Mian Mamoon Gul<sup>1</sup>, Safi Ullah Khan<sup>2\*</sup>, Tayyba Malik<sup>3</sup>, Wasfa Aijaz<sup>4</sup>, Maryum Imran<sup>5</sup>, Ahmed Bendari<sup>6</sup>

<sup>1</sup>Medical Officer, Khyber Pakhtunkhwa Employee Social Security Institution, Pakistan.

<sup>2\*</sup>Medical Officer, District Health Office, Bannu, Health Department, Khyber PakhtunKhwa, Pakistan.

<sup>3</sup>Department of Nursing, Allama Iqbal Medical College, Jinnah Hospital Lahore, Pakistan

<sup>4</sup>Senior Registrar, Medical Unit II, JPMC, Karachi, Pakistan

<sup>5</sup>Lecturer Biochemistry, Ziauddin Medical University Karachi, Pakistan

<sup>6</sup>MBBS, Department of Pathology and Laboratory Medicine, Lenox Hill Hospital, New York, USA.

**\*Corresponding Author:** Safi Ullah Khan,  
Email: safiullah03341@gmail.com

### Abstract:

**Objectives:** To assess the association between Vitamin D levels and diabetic foot in patients with Type 2 Diabetes Mellitus.

**Materials and Methods:** This Case-control study was conducted at multiples centres including Khyber Pakhtunkhwa Employee Social Security Institution, Pakistan and Health Department, Khyber PakhtunKhwa, Pakistan in the duration from July, 2023 to December, 2023 in which a total of 230 patients were enrolled and were divided into two groups: Group A, comprising individuals with diabetic foot, and Group B, consisting of those without diabetic foot. The total serum concentration of 25-OH-vitamin D was assessed using the electrochemiluminescence immunoassay method, specifically with the Roche Cobas e601 analyzer.

**Results:** The study involved a total of 230 patients, with a mean age of 54.18±10.817 years across all participants. In Group A, which consisted of individuals with diabetic foot, there were 66 (57.4%) males and 49 (42.6%) females, while in Group B, comprising patients without diabetic foot, there were 60 (52.2%) males and 55 (47.8%) females. The mean serum concentration of 25-(OH)-VD (nmol/L) differed significantly between the two groups, with Group A recording 31.62±3.97 and Group B recording 38.38±6.06, with a p-value of 0.00. In Group A, the frequency of vitamin D sufficiency, insufficiency, and deficiency were 30, 49, and 36, respectively, while in Group B, these frequencies were 46, 48, and 21, respectively. The study found that the serum level of 25-OH vitamin D was independently associated with diabetic foot, with a p-value of 0.00 and an odds ratio of 0.973.

**Conclusion:** It was concluded that low serum vitamin D levels were significantly associated with a higher prevalence of diabetic foot among patients with type 2 diabetes mellitus.

**Keywords:** Diabetic foot, Type 2 diabetes, Vitamin D deficiency

## **INTRODUCTION:**

Globally, both industrialized and developing nations are seeing an increase in the prevalence of diabetes.(1) Diabetic foot (DF) is indeed a serious complication of diabetes mellitus and can lead to significant pain, discomfort, and even more severe consequences if not managed properly.(2, 3) It typically arises from a combination of factors including peripheral neuropathy, poor circulation, and susceptibility to infections.(4) Prevention through proper foot care and management of blood sugar levels is crucial in reducing the risk of diabetic foot complications. Poor wound healing in diabetic patients can have devastating consequences.(5) It not only increases the chances of hospitalization but also raises the risk of lower extremity amputation, which can greatly impact a person's quality of life. Moreover, complications from diabetic foot ulcers can lead to disability and even mortality if left untreated.(6, 7) Throughout their lives, 15–25% of diabetic patients may get foot ulcers.(8, 9) Patients with diabetes are projected to have an annual risk of 2% for developing diabetic foot ulcers; however, over the next three years, this risk is expected to grow to 17–60% in patients with a history of foot ulceration.(10) Several studies have reported a prevalence of 1.3–12% for diabetic foot ulcers.(10, 11) Vitamin D is vital for bone health, regulating calcium and phosphorus metabolism and enhancing calcium absorption from the intestine.

(12) Vitamin D extends its impact beyond bone health, displaying pleiotropic effects, suggesting diverse biological functions beyond its classic role in calcium and bone metabolism.(13) Studies indicate that vitamin D might contribute to immune system modulation, inflammation reduction, cell growth and differentiation regulation, and cardiovascular health influence, among other functions.(14, 15) Approximately one billion individuals worldwide are experiencing vitamin D deficiency, with the highest prevalence observed in regions such as the Middle East, China, Mongolia, and India.(16) Notably, this deficiency tends to be more pronounced during the winter months.(17) Several preclinical studies and observational research have indicated a positive impact of vitamin D on wound healing. However, the connection between vitamin D and the onset and advancement of DF remains a topic of debate and contention.

## **Objective:**

To assess the association between Vitamin D levels and diabetic foot in patients with Type 2 Diabetes Mellitus.

## **MATERIALS AND METHODS:**

**Study Design:** Case-control study.

**Study setting:** multiples centres including Khyber Pakhtunkhwa Employee Social Security Institution, Pakistan and Health Department, Khyber PakhtunKhwa, Pakistan.

**Duration of the study:** The study duration was 6 month from (from July, 2023 to December, 2023).

## **Inclusion Criteria:**

- Patients diagnosed with T2DM of age 18 to 65 year.
- Participants with diabetic foot complications.
- Both gender.

## **Exclusion Criteria:**

- Individuals diagnosed with T2DM.
- Pregnant and breastfeeding women.
- Individuals receiving immunosuppressive therapy or diagnosed with conditions causing immunosuppression.
- Individuals with severe comorbidities such as end-stage renal disease, advanced liver disease, rheumatologic, cardiac, malignancy, and endocrine diseases.
- Participants with significant foot trauma.

**Methods:**

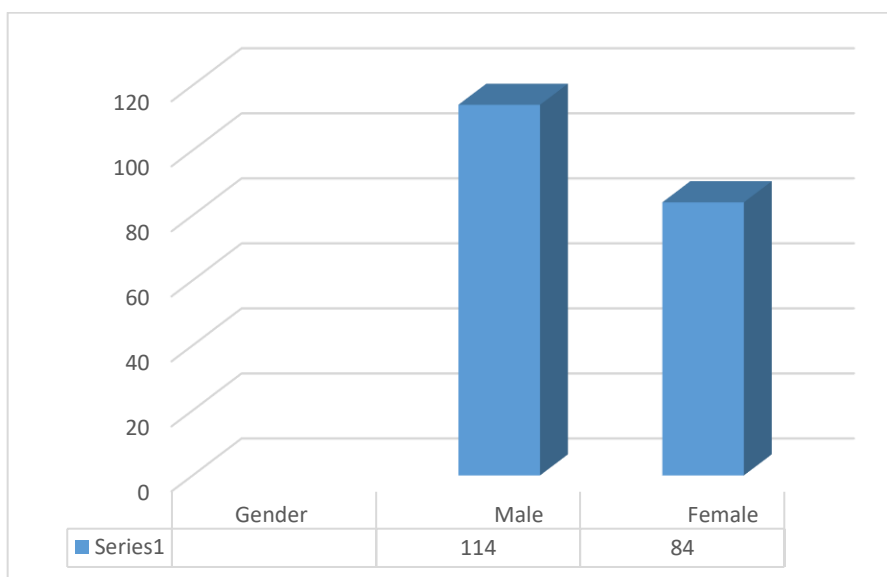
This Cross sectional study was conducted at multiples centres including Khyber Pakhtunkhwa Employee Social Security Institution, Pakistan and Health Department, Khyber PakhtunKhwa, Pakistan in the duration from July, 2023 to December, 2023. An ethical approval was obtained from the participants or their guardian. We enrolled a total of 230 patients. The enrolled patients were divided into two groups. Group A include patients with Diabetic foot while Group B include patients with non-Diabetic foot. The baseline demographics data, medical history, duration of diabetes, HbA1c levels, medications, and other relevant factors were collected. The total serum concentration of 25-OH-vitamin D was determined using the electrochemiluminescence immunoassay (Roche Cobas e601 analyzer). In the present study, normal serum levels of 25OH-vitamin D were defined as  $\geq 50$  nmol/L, while vitamin D insufficiency (VDI) was characterized by  $30 \text{ nmol/L} \leq 25\text{-OH-vitamin D} < 50 \text{ nmol/L}$ , and vitamin D deficiency (VDD) was indicated by serum 25-OH-vitamin D  $< 30 \text{ nmol/L}$ . Statistical analysis was conducted using SPSS Version 25.

**RESULTS:**

The mean age of all 230 patients was  $54.18 \pm 10.817$  years (Table 1). In Group A, 66 (57.4%) were male and 49 (42.6%) were female, while in Group B, 60 (52.2%) were male and 55 (47.8%) were female. Among the patients in Group A, 22 (19.1%) had a duration of T2DM of less than 5 years, whereas in Group B, 21 (18.3%) had a duration of T2DM of less than 5 years. Additionally, in Group A, 46 (40.0%) patients had a duration of T2DM between 6 to 10 years, compared to 50 (43.5%) in Group B. Furthermore, 47 (40.9%) patients in Group A had a duration of T2DM of less than 15 years, while in Group B, 44 (38.3%) had a duration of T2DM of less than 15 years. The mean 25-(OH)-VD (nmol/L) in Group A and Group B was  $31.62 \pm 3.97$  and  $38.38 \pm 6.06$  respectively with significant p-value of 0.00. The diabetic complications of the both groups were given in table 4 with significant p-value of 0.00 in all types of complication. Table 5 presents the results of multivariate logistic regression analysis, identifying risk factors for diabetic foot in patients with T2DM. Frequency of Vitamin D sufficiency, insufficiency and deficiency were shown in fig 2. In group A, frequency of Vitamin D sufficiency, insufficiency and deficiency were 30, 49 and 36 respectively in in group B, it was 46,48 and 21 respectively.

**Table 1:** Mean age of all enrolled Patient ( $n=230$ )

Variables	Mean±SD
Age (Years)	$54.18 \pm 10.817$



**Fig 1:** Bar graph showing gender distribution

**Table 2:** characteristic of all the enrolled patients (*n*=230)

Variables	Group A (DF)	Group B (DF)	P-value
<b>Gender</b>			
Male	66(57.4%)	60(52.2%)	0.42
Female	49(42.6%)	55(47.8%)	
Age	53.41±10.1	54.94±10.1	0.25
<b>Duration of T2DM</b>			
≤5 Years	22(19.1%)	21(18.3%)	0.86
6 to 10 Years	46(40.0%)	50(43.5%)	
11 to 15 Years	47(40.9%)	44(38.3%)	
<b>Smoking</b>			
Yes	20(17.4%)	21(27.0%)	0.05
No	95(82.6%)	84(73.0%)	

**Table 3:** Laboratory characteristics of all the enrolled patients of groups (*n*=230)

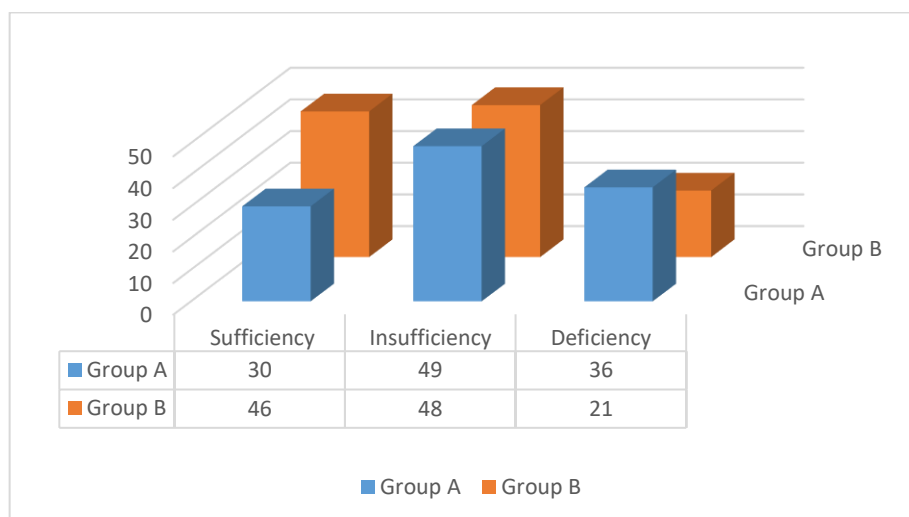
Variables	Group A (DF)	Group B (DF)	P-value
25-(OH)-VD (nmol/L)	31.62±3.97	38.38±6.06	0.00
HbA1c (%)	7.80±1.06	8.05±1.09	0.07
TG (mmol/L)	1.41±0.47	1.46±0.48	0.43

**Table 4:** The diabetic complications in the two groups (*n*=230)

Variables	Group A (DF)	Group B (DF)	P-value
Diabetic nephropathy	74(64.3%)	28(24.3%)	0.00
Diabetic retinopathy	59(51.3%)	8(24.3%)	0.04
Diabetic peripheral neuropathy	80(80.9%)	42(42.6%)	0.00
Peripheral arterial disease	55(47.8%)	23(20.0%)	0.00
Diabetic autonomic neuropathy	90(78.3%)	37(32.2%)	0.00

**Table 5:** Multivariate logistic regression analysis of risk factors for diabetic foot in patients with T2DM (*n*=230)

Variables	Odd Ratio	95% (CI)		P-value
		Lower limit	Upper limit	
25-(OH)-VD	0.973	0.968	0.991	0.00
TG	0.756	0.647	0.832	0.00
HDL-C	0.275	0.184	0.451	0.00
Diabetic nephropathy	2.297	1.616	3.032	0.00
Diabetic retinopathy	1.940	1.432	2.581	0.00
Diabetic peripheral neuropathy	14.23	7.732	23.654	0.00
Peripheral arterial disease	4.434	3.411	5.824	0.00
Diabetic autonomic neuropathy	4.657	3.541	6.91	0.00



**Fig 2:** Frequency of Vitamin D sufficiency, insufficiency and deficiency

**Discussion:** The association between vit D levels and DF complications in individuals with T2DM has been a subject of interest in medical research. The exact mechanisms underlying the association between vitamin D deficiency and DF complications are not clear. However, it is believed that vitamin D is responsible for improving insulin sensitivity, reducing inflammation, and promoting wound healing, all of which are important factors in preventing and managing diabetic foot complications. So the present study was conducted in order to assess the association between Vitamin D levels and DF in patients with T2DM. In the present study the mean 25-OH-vitamin D levels in the DF group were significantly lower than that in the non-DF group. The mean 25-(OH)-VD in Group A and Group B was  $31.62 \pm 3.97$  (nmol/L) and  $38.38 \pm 6.06$  (nmol/L) respectively with significant p-value of 0.00. Our research results align with those of Wei Wei Tang et al.,(18) who similarly found that levels of 25-OH-vitamin D were notably lower in the DF group compared to the non-DF group. Several other research studies conducted by Jiezhi Dai et al.(19), Manar Fayiz Atoum et al.(20) and Ying Xiao et al.(21) also supported our study statement.

Furthermore, in Group A, the frequencies of Vitamin D sufficiency, insufficiency, and deficiency were 30, 49, and 36 respectively. In contrast, in Group B, the frequencies were 46, 48, and 21 respectively. This means that Group B has a higher proportion of individuals with sufficient levels of Vitamin D compared to Group A. Conversely, Group A appears to have a higher prevalence of Vitamin D insufficiency and deficiency compared to Group B.

Indeed, Tiwari et al.(22) were the first to evaluate the vitamin D status among patients with DF infection in India. Their study findings suggested that vitamin D deficiency was not only more prevalent but also more severe among patients with diabetic foot infection compared to those without infection. According to another cross-sectional study conducted (23) in 2019, there wasn't a statistically significant difference found in the serum levels of vitamin D between diabetic patients with and without foot infections in India. This statement was supported by S Tsitsou et al.(24) finding. In contrast to the previous statement, similar observational studies(25, 26) conducted in Europe have demonstrated that patients with DF syndrome are indeed at a heightened risk of having low levels of vitamin D.

Additionally, our analysis using multivariate logistic regression indicated that vitamin D emerged as an independent risk factor for DF and could potentially offer some caring influence against its occurrence. However, it's worth noting that the magnitude of this effect (OR = 0.973) was minimal, and there remains a possibility of false-positive results, particularly when considering vitamin D as a continuous variable. The connection between vitamin D and diabetic foot remains somewhat ambiguous, despite conflicting findings. Nevertheless, a substantial body of preclinical research suggests promising effects of vitamin D on diabetic foot, particularly regarding wound healing, as indicated by numerous studies.(27, 28) Vitamin D aids wound healing by: regulating inflammation,

promoting vascular regeneration, aiding in epidermal cell renewal, inducing antimicrobial peptides, and improving glycemic control.(29-34) Vitamin D deficiency may cause diabetic foot ulcer development, while existing diabetic foot conditions increase the risk of worsening vitamin D deficiency due to factors like prolonged bedrest, limb immobilization, reduced physical activity, poor nutrition, and other factors. The causal relationship between vitamin D and diabetic foot remains uncertain. Based on current research, it appears that diabetic foot and vitamin D levels may influence each other.

**Conclusion:** The study's conclusion was that low serum vitamin D levels were significantly associated with a higher prevalence of DF among patients with T2DM. It highlights the potential importance of maintaining adequate levels of vitamin D for individuals with T2DM to potentially lower their risk of developing diabetic foot complications. It underscores the interconnectedness of various factors in managing diabetes-related complications.

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