*Original Research Article*

**HYDROXYVITAMIN D INSUFFICIENCY IN DIABETIC FOOT ULCER AND ASSOCIATED FACTORS IN RIVERS STATE, NIGERIA**

**ABSTRACT**

**Background:** Hypovitaminosis D is considerably prevalent among individuals with Type 2 Diabetes Mellitus (T2DM), with vascular complications, and delayed wound healing. This study aims to assess the pattern of this of hydroxyvitamin D levels and associated factors among diabetics and diabetics with diabetic foot ulcers (DFU) in Southern Nigeria.

**Method:** The study population comprised of 176 individuals (88 individuals diagnosed with diabetic foot ulcers (DFUs) and 88 individuals diagnosed of type II diabetes but do not have DFU). Hydroxyvitamin D levels were assessed using blood samples according to standard ELISA methods.

**Results:**  There was a total of 176 participants. About 76 (43.2%) of all study participants (persons with and without DFU) had sufficient Vitamin D levels and 69 (39.2%) of all study participants had deficient Vitamin D levels and 31 (17.6%) had insufficient vitamin D levels. Individuals aged 50 years and above exhibited a notably higher likelihood of the condition compared to their younger counterparts, with a crude Odds Ratio (O.R.) of 7.7 (95% C.I: 3.6 – 16.4). After adjusting for other factors, this association remained significant, although the strength of the association decreased, with an adjusted O.R. of 2.2 (95% C.I: 1.1 – 4.6), suggesting age as a significant predictor.

 **Conclusion:** The study reveals strong links between demographic/biochemical factors and insufficient hydroxyvitamin D levels. People aged 50+ are more prone to deficiency, even when other factors are considered. While abnormal waist-to-hip ratios initially reduce risk, this effect weakens with adjustment, suggesting other influences. Abnormal albumin levels remain a significant predictor, emphasizing the necessity of targeted interventions in high-risk groups.

**Keywords:** *Hydroxyvitamin D, Diabetes Mellitus, Diabetic foot ulcer, Risk factors*

**INTRODUCTION**

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. It has become a major public health concern globally, with its prevalence steadily increasing, particularly in low- and middle-income countries like Nigeria.1–3 Among the complications associated with diabetes, diabetic foot ulcer (DFU) stands out as one of the most debilitating and costly, often leading to severe morbidity, limb amputation, and increased mortality rates.4,5

Hydroxyvitamin D, a precursor to the active form of vitamin D, plays a crucial role in calcium homeostasis, bone health, and immune function. Recent research has suggested a potential link between vitamin D insufficiency and the development and progression of various chronic diseases, including diabetes and its complications.6 Hypovitaminosis D is considerably prevalent among individuals with Type 2 Diabetes Mellitus (T2DM), and having a considerable relationship with impaired glycemic control, vascular complications, and delayed wound healing.3,7,8

Various factors influence vitamin D status, including sunlight exposure, geographical location, and skin characteristics. Sunlight exposure, particularly at wavelengths around 297nm, is crucial for optimal vitamin D synthesis, with regions closer to the equator experiencing consistent sunlight throughout the year.9,10 Factors such as sunscreen use and melanin levels in the skin can affect UV radiation absorption and subsequently impact vitamin D production. Additionally, age-related declines in 7-dehydrocholesterol levels may decrease vitamin D synthesis efficiency.11,12 Clothing density also plays a role, with lighter fabrics allowing for more UV light absorption and vitamin D synthesis. Gastrointestinal conditions like malabsorption syndromes can impair vitamin D absorption, while obesity is associated with lower serum vitamin D levels due to altered storage and bioavailability.1,13 Certain medications, chronic kidney disease, liver disease, and granulomatous disorders further influence vitamin D metabolism and levels in the body.14–16 Understanding these factors is vital for effectively managing vitamin D status, particularly in vulnerable populations. However, the precise relationship between hydroxyvitamin D levels and DFUs remains a subject of ongoing investigation especially in Nigeria. Studies exploring the pattern of hydroxyvitamin D in individuals with DFUs have yielded intriguing findings, suggesting both deficiency and insufficiency in a significant proportion of patients. This study aims to fill this gap in knowledge by examining the prevalence of hydroxyvitamin D insufficiency among individuals with DFU in Rivers State, Nigeria, and exploring potential demographic, clinical, and environmental factors associated with low vitamin D levels.

**METHODS**

The study population comprised of 176 individuals (88 individuals diagnosed with diabetic foot ulcers (DFUs) and 88 individuals diagnosed of type II diabetes but do not have DFU) who are receiving treatment at Rivers State University Teaching Hospital between October 2021 and May 2022. Participants were selected based on specific inclusion criteria, including a confirmed diagnosis of Type 2 Diabetes Mellitus (T2DM) and the presence of DFUs. Exclusion criteria were individuals with other significant comorbidities affecting vitamin D metabolism, such as chronic kidney disease or liver disorders.

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and relevant national regulations. Ethical approval was obtained from the Institutional Review Board (IRB) of Rivers State University Teaching Hospital prior to the commencement of the study. All participants provided informed consent before enrollment, emphasizing their right to withdraw from the study at any time without repercussions. Confidentiality of participant information was strictly maintained throughout the study, with data anonymization protocols implemented during analysis and reporting.

Five milliliters of Blood samples were collected from consenting participants for the assessment of hydroxyvitamin D levels as previously stated.12,17 The glycated haemoglobin was estimated using fluorescence immunoassay using the fine care TM FIA system.17 In addition to blood samples, relevant clinical data was collected from participants, including demographic information, medical history, duration of diabetes, presence of diabetic complications, and details pertaining to DFUs from the patients folders.

All the data was analyzed using the SPSS v25 software at a 95% confidence interval and a p-value less than 0.05 was considered statistically significant. The difference in the level of Vitamin D among T2DM with DFU and those without DFU was tested using an independent t-test analysis. and logistic regression analysis done to explore factors associated with Vitamin D levels in all the patients.

**RESULTS**

There was a total of 176 participants of which 60 (34.1%) were males and 116 (65.9%) were females, giving a male to female ratio of 1:1.9. Table 1 gives the demographic distribution of the study participants.

Table 1: Demographic Distribution of Patients

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Units** | **Frequency, n** | **Percent (%)** |
|  | 30 - 39 | 11 | 6.25 |
| Age groups (years) | 40 - 49 | 40 | 22.73 |
|  | 50 - 59 | 55 | 31.25 |
|  | 60 - 69 | 59 | 33.52 |
|  | 70 and above | 11 | 6.25 |
|  Gender | Male | 60 | 34.09 |
|  | Female | 116 | 65.91 |
|  Occupation | Civil Servant | 41 | 23.30 |
|  | Trader | 69 | 39.20 |
|  | Artisan | 18 | 10.23 |
|  | Farmer | 13 | 7.39 |
|  | Student | 4 | 2.27 |
|  | Unemployed | 31 | 17.61 |
|  Marital Status | Married | 126 | 71.59 |
|  | Single | 15 | 8.52 |
|  | Separated | 6 | 3.41 |
|  | Widow/Widower | 29 | 16.48 |

*\*Statistically significant (p<0.05), t: Student’s T-test statistic*

Table 2 compares various variables between individuals with diabetic foot ulcers (cases) and those without (controls). It reveals a significant difference in serum vitamin D levels, indicating lower levels in cases (mean of 19.6 ng/ml ± 13.6) compared to controls (mean of 36.2 ng/ml ± 11.4) with a p-value of 0.014. Conversely, serum HbA1c levels showed no significant difference between cases (mean of 8.5% ± 2.6) and controls (mean of 9.5% ± 3) with a p-value of 0.106, suggesting similar glycemic control status in both groups. Similarly, fasting plasma glucose levels did not significantly differ between cases (mean of 10.6 mmol/l ± 4.2) and controls (mean of 9.8 mmol/l ± 4.4) with a p-value of 0.793, indicating comparable fasting glucose levels in individuals with and without diabetic foot ulcers. These findings suggest a potential association between lower serum vitamin D levels and the presence of diabetic foot ulcers, while glycemic control status, as measured by HbA1c and fasting plasma glucose levels, remained similar between the two groups.

Table 2: T-test Comparison of Mean biochemical indices of Patients

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **DFU****Mean ±SD** | **No DFU****Mean ±SD** |  **p-value** |
| Serum vitamin D3 (ng/ml) | 19.6 ±13.6 | 36.2 ±11.4 | 0.014\* |
| Serum HbAlc (%) | 8.5 ±2.6 | 9.5 ±3 | 0.106 |
| Fasting plasma glucose (mmol/l) | 10.6 ±4.2 | 9.8 ±4.4 | 0.793 |
| Serum calcium (mmol/l) | 2.2 ±0.2 | 2.3 ±0.1 | 0.077 |
| Serum albumin mg/dl | 37.4 ±4.3 | 39.9 ±3.5 | 0.012\* |
| Corrected calcium (mmol/l) | 2.3 ±0.6 | 2.3 ±0.1 | 0.284 |
| Serum phosphate mg/dl | 1.3 ±0.3 | 1.4 ±0.3 | 0.497 |
| Serum creatinine umol/L | 74.2 ±17.7 | 74.8 ±10.5 | 0.0001\* |
| Total cholesterol (mmol/l) | 4.3 ±0.9 | 4.9 ±0.6 | 0.0001\* |
| HDL Cholesterol (mmol/l) | 0.9 ±0.2 | 1 ±0.2 | 0.126 |
| LDL Cholesterol (mmol/l) | 2.7 ±0.7 | 3.2 ±0.6 | 0.279 |
| Triglycerides (mmol/l) | 1.4 ±0.6 | 1.5 ±0.4 | 0.0001\* |
| eGFR | 99.2 ±19.7 | 101.8 ±17.4 | 0.109 |

*HbA1c- Glycated haemoglobin, DFU- diabetic foot ulcer, eGFR- estimated glomerular filtration rate, HDL- high density lipoprotein, LDL- low density lipoprotein, SD- Standard deviation*

*\* statistically significant (p<0.05)*

Figure 1 below shows that 76 (43.2%) of all study participants (persons with DFU and no DFU) had sufficient Vitamin D levels and 69 (39.2%) of all study participants has deficient Vitamin D levels and 31 (17.6%) has insufficient vitamin D levels.

Figure 1: Pattern of Hydroxyvitamin D levels in type 2 DM

Table 3 indicates a notable contrast in vitamin D levels between individuals with diabetic foot ulcers (cases) and those without (controls). A significant majority of controls (70.45%) possessed sufficient levels of vitamin D, whereas only a minority of cases (15.91%) fell within this category (χ² = 71.83, p < 0.0001). Conversely, a substantial portion of cases (69.32%) were deficient in vitamin D, in stark contrast to controls (9.09%). Although there were minor variations in the prevalence of insufficient vitamin D levels, with cases at 14.77% and controls at 20.45%, the overarching trend underscores a strong association between deficient vitamin D levels and the occurrence of diabetic foot ulcers.

Table 3: Pattern of Hydroxyvitamin D levels in Study Participants

|  |  |  |  |
| --- | --- | --- | --- |
| **Vitamin D Level** | **DFU****n, (%)** | **No DFU****n, (%)** | **Chi-square (p-value)** |
| Sufficient | 14(15.91) | 62(70.45) | 71.83 (0.0001)\* |
| Deficient | 61(69.32) | 8(9.09) |
| Insufficient | 13(14.77) | 18(20.45) |
| **Total** | **88 (100.0)** | **88 (100.0)** |  |

*DFU- diabetic foot ulcer*

*\* statistically significant (p<0.05)*

The table below shows the association of demographic and biochemical factors with hyrdoxyvitamin D levels. Statistically significant findings from the table indicate that individuals aged 50 and above were notably more likely to have deficient or insufficient levels compared to those below 50 years old (Chi-square = 5.69, p = 0.001, Odds Ratio (O.R.) = 7.7). Additionally, individuals with abnormal waist-hip ratios exhibited a significantly lower likelihood of having deficient or insufficient levels compared to those with normal ratios (Chi-square = 8.93, p = 0.003, O.R. = 0.3). Moreover, those with abnormal calcium levels were significantly more prone to deficient or insufficient levels compared to those with normal calcium levels (Chi-square = 7.03, p = 0.007, O.R. = 4.9). Likewise, individuals with abnormal albumin levels demonstrated a significantly higher likelihood of having deficient or insufficient levels compared to those with normal albumin levels (Chi-square = 16.95, p = 0.0001, O.R. = 7.7). Conversely, individuals with abnormal cholesterol levels were significantly less likely to have deficient or insufficient levels compared to those with normal cholesterol levels (Chi-square = 10.0, p = 0.002, O.R. = 0.3). Similarly, individuals with abnormal LDL levels exhibited a significantly lower likelihood of deficient or insufficient levels compared to those with normal LDL levels (Chi-square = 16.2, p = 0.0001, O.R. = 0.2). These findings underscore associations between specific demographic and physiological factors and the likelihood of deficient or insufficient levels.

Table 4: Association of Demographic and Biochemical factors with hydroxyvitamin D levels.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Deficient/Insufficient** | **Total** | **Chi-square** | **O.R** |
|  | **n=100, (%)** | **n=176, (%)** | **(p-value)** | **(95% C.I)** |
| **Gender**  |  |  |  |  |
| Male | 32(32.00) | **60(100.0)** | 0.45 (0.502) | 0.8 (0.4 - 1.5) |
| Female  | 68(68.00) | **116(100.0)** |  |  |
| **Age groups** |  |  |  |  |
| 50 and above | 88(71.00) | **125(100.0)** | 5.69 (0.001)\* | 7.7 (3.6 – 16.4) |
| Below 50  | 12(29.00) | **51(100.0)** |  |  |
| **Marital Status** |  |  |  |  |
| Single/Separated/Widowed | 29(29.00) | **50(100.0)** | 0.04 (0.842) | 1.0 (0.5 - 2.0) |
| Married  | 71(71.00) | **126(100.0)** |  |  |
| **Waist-Hip-Ratio** |  |  |  |  |
| Abnormal | 17(37.8) | **45(100.0)** | 8.93 (0.003)\* | 0.3 (0.1 - 0.7) |
| Normal  | 83(63.4) | **131(100.0)** |  |  |
| **BMI Class** |  |  |  |  |
| Abnormal (obese/overweight/obese) | 75(58.6) | **128(100.0)** | 0.6 (0.437) | 1.3 (0.6 - 2.5) |
| Normal  | 25(52.1) | **48(100.0)** |  |  |
| **Triglycerides** |  |  |  |  |
| Abnormal | 34(57.6) | **59(100.0)** | 0.24 (0.878) | 1.0 (0.5 - 1.9) |
| Normal  | 66(56.4) | **117(100.0)** |  |  |
| **Fasting Blood Glucose** |  |  |  |  |
| Abnormal | 83(58.9) | **141(100.0)** | 1.21 (0.271) | 1.5 (0.7 - 3.1)  |
| Normal  | 17(48.6) | **35(100.0)** |  |  |
| **Calcium** |  |  |  |  |
| Abnormal | 17(85.0) | **20(100.0)** | 7.03 (0.007)\* | 4.9 (1.4 - 17.6)  |
| Normal  | 83(53.2) | **156(100.0)** |  |  |
| **Albumin** |  |  |  |  |
| Abnormal | 30(88.2) | **34(100.0)** | 16.95 (0.0001)\* | 7.7 (2.5 - 23.0)  |
| Normal  | 70(49.3) | **142(100.0)** |  |  |
| **Cholesterol** |  |  |  |  |
| Abnormal | 14(35.0) | **40(100.0)** | 10.0 (0.002)\* | 0.3 (0.1 - 0.6) |
| Normal  | 86(63.2) | **136(100.0)** |  |  |
| **HDL** |  |  |  |  |
| Abnormal | 74(59.7) | **124(100.0)** | 1.38 (0.237) | 1.4 (0.7 - 2.8)  |
| Normal  | 26(50.0) | **52(100.0)** |  |  |
| **LDL** |  |  |  |  |
| Abnormal | 15(31.9) | **47(100.0)** | 16.2 (0.0001)\* | 0.2 (0.1 - 0.4) |
| Normal  | 85(65.9) | **129(100.0)** |  |  |
| **Phosphate** |  |  |  |  |
| Abnormal | 20(50.0) | **40(100.0)** | 0.91 (0.340) | 0.7 (0.3 – 1.4) |
| Normal  | 79(58.5) | **135(100.0)** |  |  |

*BMI- Body mass index, HDL- high density lipoprotein, LDL- low density lipoprotein*

*O.R: Odds ratio; C.I: Confidence interval; \*Statistically significant (p<0.05)*

The table below reveals significant associations between various variables and the likelihood of a particular condition. Firstly, individuals aged 50 years and above exhibited a notably higher likelihood of the condition compared to their younger counterparts, with a crude Odds Ratio (O.R.) of 7.7 (95% C.I: 3.6 – 16.4). After adjusting for other factors, this association remained significant, although the strength of the association decreased, with an adjusted O.R. of 2.2 (95% C.I: 1.1 – 4.6), suggesting age as a significant predictor. Conversely, individuals with abnormal waist-to-hip ratios demonstrated a lower likelihood of the condition, as indicated by a crude O.R. of 0.3 (95% C.I: 0.1 - 0.7). However, after adjusting for other variables, although the association persisted, it was not statistically significant, with an adjusted O.R. of 0.4 (95% C.I: 0.2 – 1.0). This suggests a potential association that becomes less significant when considering other factors. Additionally, individuals with abnormal albumin levels showed a significantly higher likelihood of the condition, with a crude O.R. of 7.7 (95% C.I: 2.5 - 23.0). After adjustment, this association remained significant, with an adjusted O.R. of 4.6 (95% C.I: 1.3 – 16.2), indicating abnormal albumin levels as a significant predictor of the condition.

Table 5: Risk factors associated with Deficient/insufficient hydroxy vitamin D

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Crude O.R****(95% C.I)** | **Adjusted O.R****(95% C.I)** | **p-value** |
| Age (50 years and above) | 7.7 (3.6 – 16.4) | 2.2 (1.1 – 4.6)R | 0.021\* |
| Abnormal waist to hip ratio  | 0.3 (0.1 - 0.7) | 0.4 (0.2 – 1.0) | 0.065 |
| Abnormal Calcium  | 4.9 (1.4 - 17.6) | 1.3 (0.3 – 6.1)R | 0.660 |
| Abnormal Albumin | 7.7 (2.5 - 23.0) | 4.6 (1.3 – 16.2)R | 0.017\* |
| Abnormal Cholesterol  | 0.3 (0.1 - 0.6) | 1.2 (0.3 – 4.5) | 0.771 |
| Abnormal LDL | 0.2 (0.1 - 0.4) | 0.2 (0.08 – 1.0) | 0.051 |

*LDL- low density lipoprotein, O.R: Odds ratio*

 *\*Statistically significant (p<0.05)*

**DISCUSSION**

The findings of the biochemical characteristics of the patients with and without DFU were similar to that of Zubair et al where T2DM patients without DFU had a higher mean LDL and total cholesterol despite having higher vitamin D levels, compared to T2DM patients with DFU. In contract, Rolim et al had a different result where a higher proportion of persons with deranged lipid profile had hypovitaminosis D.18 The results of this study showing a higher rate of dyslipidemia among patients with sufficient vitamin D levels can be explained by higher mean cholesterol levels among the control group subjects who also have predominantly normal vitamin D levels. Another reason is possible statin therapy which is common among most middle aged persons with DM.19,20 Research from a similar study also noted that statin use reduced the levels of LDL, total cholesterol and triglycerides, but had no effect on vitamin D status, thus the difference in lipidemia among study participants may be affected more by statin use than by the effect of vitamin D on cholesterol.21–23 HDL was noted to be reduced in 70.5% of study participants especially in those with hypovitaminosis D though this difference is not statistically significant . The current study showed that a patient with reduced calcium levels was 4.9 times more likely to have hypovitaminosis D. This attests to the crucial relationship between vitamin D and calcium, emphasizing the role played by vitamin D in calcium homeostasis.24

This finding is consistent with reports of a previous study where HDL was noted to be lower in T2DM patients with vitamin D deficiency compared to those with sufficient vitamin D.25 A higher proportion of persons with reduced calcium levels had vitamin D deficiency/insufficiency. This study found that the prevalence of vitamin D deficiency among all study participants was 39.2% while the prevalence of vitamin D insufficiency was 17.6%, thus hypovitaminosis D present among 56.8% of study participants. Karau et al in Kenya noted similar findings in a study analysing vitamin D levels in patients with T2DM and found vitamin D deficiency in 38.4% of patients and insufficiency in 21.9% of patients.26 Anyanwu et al in Lagos noted a higher prevalence of vitamin d deficiency, 63.2%.20 The lower prevalence in our study48 can be explained by dietary factors, as residents in Port Harcourt, a town whose dietary habits are influenced by the riverine culture are known to regularly consume oily fish, a rich source of vitamin D.23,27 Another reason could be that the highly commercialized and industrialized theme of Lagos would imply more indoor official and commercial activity thus reducing the amount of time exposed to sunlight.28

Findings of the current study indicates that individuals aged 50 years and above were 7.7 times more likely to have hypovitaminosis D, consistent with previous research indicating decreased vitamin D levels in older individuals. Factors such as reduced skin 7-dehydrocholesterol, declining renal function, and decreased sunlight exposure contribute to this phenomenon.29,30 Nutritional factors were also examined, with a high intake of fish noted among participants, typical of residents in coastal cities like Port Harcourt.20 Regarding adiposity, most participants had abnormal BMI, with no underweight individuals observed. While a higher proportion of subjects with hypovitaminosis D had a higher BMI, this difference was not statistically significant. However, previous studies have shown a significant association between obesity and vitamin D deficiency.21,22,31 The waist-hip ratio displayed a different trend, with a higher proportion of abnormal ratios found among the vitamin D-sufficient group, indicating that factors other than adiposity may influence vitamin D levels in this population.

**CONCLUSION**

The current study highlights significant associations between demographic and biochemical factors and the likelihood of deficient or insufficient hydroxyvitamin D levels. Individuals aged 50 and above exhibited a notably higher likelihood of deficiency or insufficiency, suggesting age as a significant predictor even after adjusting for other factors. Conversely, while individuals with abnormal waist-to-hip ratios initially showed a lower likelihood, this association became less significant after adjustment, implying a potential association influenced by other variables. Moreover, abnormal albumin levels emerged as a robust predictor of deficient or insufficient levels, maintaining significance even after adjusting for confounding factors. These findings underscore the importance of considering both demographic and physiological factors when assessing vitamin D status and highlight the need for targeted interventions in high-risk populations to mitigate deficiency or insufficiency.

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