

# Vitamin D Status among Type-2 Diabetic Patients and Healthy Controls and Its Association with Age, Gender and Level of Adiposity

Babatunde Ishola Gabriel Adejumo<sup>\*1</sup>, Fidelis Ohiremen Oyakhire,<sup>1</sup> Benson Benjamen Osayetin Ebhohimhen,<sup>2</sup> Olufunke Victoria Aiyegbusi,<sup>3</sup> Uchechukwu Dimkpa,<sup>4</sup> Oladimeji Nasiru Abdulrahman,<sup>5</sup> Grace Umahi-Ottah,<sup>6</sup> Simon Uzor<sup>7</sup>

<sup>1</sup>Department of Medical Laboratory Science, College of Health Sciences, Joseph Ayo Babalola University, Ikeji Arakeji, Osun state, Nigeria <sup>2</sup> Sanctus Medical Laboratory, Warri, Delta State. <sup>3</sup>Department of Nursing Science, College of Health Sciences, Joseph Ayo Babalola University, Ikeji Arakeji, Osun state, Nigeria <sup>4</sup>Physiology Department, Nnewi Campus, Nnamdi Azikiwe University, Awka, Nigeria <sup>5</sup> Department of Medical Laboratory Science, College of Health Technology, Offa, Kwara state, Nigeria. <sup>6</sup> Department of Physiology, Ebonyi State University, Abakaliki, Nigeria. <sup>7</sup>Department of Medical Laboratory Science, Ebonyi State University, Abakaliki, Abonyi state, Nigeria.

## ABSTRACT

**Background:** There is paucity of information on Vitamin D status and its association with risk factors of type-2 diabetes mellitus (T2DM) among people living with type-2 diabetes in Nigeria. **Objectives:** To assess the vitamin D status of adult T2DM patients, and to demonstrate if there are associations between vitamin D levels and socio-demographic factors such as age, gender, and body mass index. **Materials and Methods:** A total of 128 adults (T2DM patients, n = 64; non-diabetic controls (NT2DM), n = 64) participated in this study. Fasting blood glucose and vitamin D levels were determined using standard methods. **Results:** Lower levels of vitamin D were observed in T2DM patients compared with non-diabetic control (p < 0.001). A greater level of vitamin D deficiency was found among T2DM patients (57.8%) compared with the controls (29.7%). Participants with vitamin D deficiency were at greater risk of T2DM compared with those with sufficient vitamin D (OR = 3.24; 95% CI = 1.56 – 6.73; p = 0.002). An increase in serum vitamin D level was positively associated with age and negatively associated with the level of adiposity. No correlation was found between vitamin D levels and sex of the participants. A greater percentage of patients with vitamin D deficiency was observed in women compared to men, adults of age above 40 years compared to younger adults, and obese people compared to non-obese people. **Conclusion:** Our findings suggest that vitamin D screening and supplementation should be included in the management plan for all T2DM patients.

**Keywords:** Adiposity, Age, Body Mass Index, Diabetes, Gender, Vitamin D

## INTRODUCTION

Type-2 diabetes mellitus (T2DM) is the most common type of diabetes affecting millions of people globally and is characterized by hyperglycemia, insulin resistance, and relative insulin deficiency [1]. It comprises about 90% – 95% of all diabetes cases [2, 3], and has been steadily increasing in prevalence, especially in low-income countries of Sub-Saharan Africa including Nigeria [4, 5]. The increase in the prevalence of T2DM is

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### \*Correspondence:

Adejumo B.I.G., Department of Medical Laboratory Science, College of Health Sciences, Joseph Ayo Babalola University, Ikeji Arakeji, Osun state, Nigeria.

### E-mail:

babatunde.adejumo@uniben.edu

Tel: +234816508080.

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attributable to an increase in modern lifestyle, characterized by excessive caloric intake coupled with an increased sedentary lifestyle, which is associated with weight gain, and obesity is the major risk factor for T2DM [6]. It is established that diet is a risk factor associated with T2DM and previous studies have also tried to associate nutrient consumption and/or dietary patterns with the occurrence of T2DM [7, 8, 9].

Maintaining healthy nutrition or diet is a key component of managing T2DM [10, 11]. Dietary management of diabetes mellitus is targeted at improving overall health by achieving and maintaining optimal nutritional status, attaining good glycemic control, and preventing or slowing down the rate of development of diabetes complications [10, 11]. Vitamins play an important role in glucose metabolism, thus understanding the impact of vitamin deficiencies is relevant to the prevention and/or management of T2DM [6]. Vitamin D, a fat-soluble vitamin obtained from sun exposure, foods, and supplements, plays a major role in physiological processes that modulate mineral metabolism and immune function with probable link to several chronic and infectious conditions [12, 13].

The increased burden of T2DM which includes increased mortality risk and significant long-term morbidity and a high health cost to individual patients, their families, and countries [14], calls for increased investment in effective diabetes prevention and management to battle this global epidemic. However, despite the increasing prevalence of diabetes and its associated disease burden in Nigeria, dietary interventions are still poor and nutritional management therapies are inadequate. To the best of our knowledge, there is limited information on the vitamin D status of Nigerian type 2 diabetic patients in Nigeria [15, 16], but these studies could not determine the association between vitamin D status and some socio-demographic risk factors of T2DM. This study, therefore, sought to provide preliminary information on vitamin D status among Nigerian type 2 diabetics and assessed its association with

some socio-demographic factors such as age, gender, and body mass index.

## MATERIALS AND METHODS

### Study Area and Study Population

A total of 128 participants (T2DM patients, n = 64; NT2DM control, n = 64), aged between 24 – 60 years, were recruited for this study from the diabetic clinic of General Hospital Warri, Delta State, Nigeria. A structured questionnaire was administered to each participant to obtain their demographic information. The medical history and the nature of the treatment of the diabetic patients were obtained from their case notes. Type-2 diabetes was diagnosed based on the medical history, participant's self-report, and clinical evaluation including fasting blood glucose  $\geq 126$  mg/dl [17]. Exclusion criteria included those that had a history of unstable cardiovascular and peripheral diseases; those with chronic illnesses; those with recent blood loss; those of age below 24 years old and those using multivitamin supplements as well as medications that are known to affect glucose metabolism. The participants signed an informed consent after we explained the gains and pains of the study to them.

### Ethical Approval

Ethical approval was obtained from the Delta State Hospitals Management Board, Warri Medical Zone with Protocol Number CHW/ECC VOL.I/140.

### Anthropometric Measurement

The height and weight of all the participants were measured using a standard scale (Seca model, UK) and a beam balance (Hackman, UK) respectively. Body mass index (BMI) was calculated from the formula  $BMI = \text{Weight (kg)} / \text{Height (m}^2\text{)}$ .

### Sample Size Determination

The sample size for this study was calculated by using the formula;

$$\text{Sample Size (n)} = \frac{(Z_{\alpha})^2 \times p(1-p)}{d^2}$$

Where  $Z_{\alpha}$  = Standard value for the level of confidence at 95% confidence interval, 1.96;  $p$  =

Estimated prevalence of type II diabetic patients in Nigeria (5.7% or 0.057), based on previous research [18];  $d$  = the degree of precision or margin of sampling error to be used, 0.05.

$$n = \frac{(1.96)^2 \times 0.057(1-0.057)}{(0.05)^2} = \frac{3.84 \times 0.0537}{0.0025} = \frac{0.206}{0.0025} = 82$$

### Sample Collection

10 ml of fasting blood sample was collected via aseptic technique from each subject and 5 ml was dispensed into a sterile non-anticoagulant container and allowed to clot for 1 hour. Thereafter, it was spun for 15 minutes at 1000 revolutions/min. The separated serum was then transferred into a plain sterile container and stored at  $-20^{\circ}\text{C}$  before assay for vitamin D (ELISA). The remaining 5 ml was dispensed into a fluoride oxalate container, spun for 15 minutes at 1000 revolutions/min, and separated, and analyzed for fasting blood glucose immediately.

### Sample Analysis

Fasting Blood Glucose level was determined using the Randox kit purchased from Randox Company, United Kingdom, and utilizing the glucose oxidase method according to the manufacturer's instructions. Vitamin D level was assayed using commercially purchased ELISA kits from Cabiotech USA (REF VD220B LOT VDS5260) according to the manufacturer's instructions.

### Data analysis

Descriptive data were expressed as mean  $\pm$  standard deviation for continuous variables and percentages for categorical variables. Comparative analysis was done using an independent sample t-test. The test of significance was set at  $p < 0.05$ . All statistics were done using SPSS/IBM software, version 20.

## RESULTS

The demographic and baseline characteristics of subjects are shown in Table 1. Data indicates that

type 2 diabetic subjects were older ( $p = 0.008$ ) compared with the non-diabetic controls. A higher proportion of the participants were within the age range of 41–60 years in both control (42.2%) and the diabetic group (54.7%). The majority of the participants were females (NT2DM, 73.4%; T2DM, 93.8%). Compared with the non-diabetic controls, the diabetic subjects had statistically higher BMI ( $p < 0.001$ ). All type 2 diabetics were obese (obesity I, 56.3%; obesity II, 12.5%; obesity III, 31.3%). On the other hand, all NT2DM participants were non-obese ( $\text{BMI} \leq 25\text{kg/m}^2$ ). The FBG level was higher in T2DM patients compared with the NT2DM group ( $p < 0.001$ ). The majority (75%) of the non-diabetic participants had FBG levels within the normal range (70–99.9 mg/dl), followed by those with a pre-diabetic FBG range of 100–125.9 mg/dl (25%). All the type 2 diabetics had abnormal FBG levels  $\geq 126$  mg/dL.

The independent sample t-test indicated that the non-diabetic T2DM control group presented statistically higher mean serum vitamin D concentration (ng/ml) compared with the T2DM patients ( $25.5 \pm 12.3$  vs  $18.9 \pm 9.6$ ,  $p < 0.001$ ) as shown in Figure 1.

Table 2 shows the mean serum concentrations of vitamin D according to the age, sex, and body mass index of the study participants. In the overall data, analysis of variance (ANOVA) indicated significantly ( $p < 0.01$ ) higher vitamin D serum concentration in those aged 60 years and above ( $26.4 \pm 14.1$ ) compared with 41–60 years ( $18.9 \pm 8.6$ ) and 20–40 years ( $21.2 \pm 7.6$ ) age groups. Serum vitamin D concentration did not show any gender differences. Participants with normal BMI indicated significantly ( $p < 0.05$ ) higher vitamin D level compared with those that have class I obesity (25.5 vs. 18.9 ng/ml) and class II obesity (25.5 vs. 18.3 ng/ml) respectively. Among non-diabetic controls, vitamin D levels significantly increased with increasing age ( $p = 0.006$ ). However, no significant differences were observed in vitamin D among the age groups for T2DM patients. Independent sample t-test indicated no significant gender differences in

vitamin D levels (ng/ml) for both the NT2DM controls ( $21.54 \pm 8.41$  vs.  $26.89 \pm 13.22$ ;  $p = 0.125$ ) and T2DM patients ( $19.7 \pm 8.84$  vs.  $18.85 \pm 9.76$ ;  $p = 0.867$ ). Furthermore, the ANOVA test indicated no significant differences among the BMI categories in type 2 diabetic patients. All the non-diabetic control were non-obese with a mean vitamin D level of  $25.54 \pm 12.29$  ng/ml.

Table 3 shows the correlation tests between Vitamin D level and age, gender, and BMI in type 2 diabetic patients and non-diabetic controls. In type 2 diabetic patients, no significant associations were observed between age, gender, BMI and vitamin D. In non-type 2 diabetic controls, significant positive correlations ( $p < 0.01$ ) were observed between age, and vitamin D. In contrast, vitamin D did not indicate significant correlations with either gender

or BMI. In the overall data, a significant positive correlation was observed between vitamin D and age ( $p = 0.009$ ). There was a significant negative correlation ( $p < 0.01$ ) between BMI, and vitamin D in the combined data. However, no significant association was observed between vitamin D and gender in all subjects' data. Vitamin D deficiency (%) was significantly more prevalent among the T2DM patients than the non-diabetic patients ( $57.8$  vs  $29.7$ ,  $p = 0.001$ ) (Figure 2). Vitamin D sufficiency (%) was more prevalent among non-diabetic patients compared with T2DM patients ( $70.3$  vs  $42.2$ ;  $p < 0.001$ )

In Table 4, logistic regression analysis indicated that subjects with T2DM were 3.2 times more likely to have Vitamin deficiency compared to their non-diabetic counterparts [OR = 3.24, 95% CI (1.56 –

**Table 1: Demographic and Baseline Characteristics of Subjects**

Characteristics	NT2DM, n = 64	T2DM, n = 64	Statistics	
			Coefficients	P - Value
	Mean $\pm$ SD or n (%)	Mean $\pm$ SD or n (%)		
Mean Age (years)	$54.0 \pm 14.02$	$59.25 \pm 11.41$	t, - 2.72	0.008
Age Groups (years)			$\chi^2$ , 14.0	0.001
20 – 40	15 (23.4)	1 (1.6)		
41 – 60	27 (42.2)	35 (54.7)		
$\geq 61$	22 (34.4)	28 (43.8)		
Gender			$\chi^2$ , 9.62	0.002
Males	17 (26.6)	4 (6.2)		
Females	47 (73.4)	60 (93.8)		
Mean BMI (kg/m <sup>2</sup> )	$21.98 \pm 2.08$	$37.0 \pm 6.32$	t, 18.14	<0.001
BMI Categories (kg/m <sup>2</sup> )			$\chi^2$ , 128.0	<0.001
Non-Obese ( $\leq 25$ )	64 (100)	0 (0)		
Obese I (30 – 34.9)	0 (0)	36 (56.3)		
Obese II (35 – 39.9)	0 (0)	8 (12.5)		
Obese III ( $\geq 40$ )	0 (0)	20 (31.3)		
Mean FBG (mg/dL)	$87.01 \pm 13.84$	$197.70 \pm 48.28$	t, -17.62	<0.001
FBG Categories (mg/dL)			$\chi^2$ , 128.0	<0.001
Normal (70– 99.9)	48 (75.0)	0 (0)		
Pre-diabetes (100 – 125.9)	16 (25.0)	0 (0)		
Diabetes ( $\geq 126$ )	0 (0)	64 (100)		

Abbreviations: NT2DM, Non-Type 2 Diabetes Mellitus; T2DM, Type 2 Diabetes Mellitus; BMI, Body Mass Index; FBG, Fasting Blood Glucose; SD, Standard Deviation;  $\chi^2$ , Chi Square coefficient; t, Independent sample t-test coefficient.

6.73), p=0.002)].

Vitamin D deficiency was more common among the age group >40 years in NT2DM (68.4% vs. 31.6% p < 0.001), T2DM (100% vs. 0), and all subjects (89.3% vs. 10.7%) compared to the age group ≤40 years. Females indicated a greater percentage of

vitamin D deficiency compared to males in NT2DM (63.2% vs. 36.8%; p = 0.009), T2DM (94.6 vs. 5.4%; p < 0.001), and all subjects data (83.9 vs. 16.1%; p < 0.001). The obese participants indicated a greater proportion of vitamin D deficiency compared with the non-obese (66.1 vs. 33.9%; p = 0.001) (Table 5).

**Table 2. Mean serum concentrations of vitamin D according to the age, sex and body mass index of the study participants**

Characteristics	NT2DM			T2DM			ALL		
	N	Mean ± SD	P - Value	N	Mean ± SD	P - Value	N	Mean ± SD	P - Value
Age (years)									
20 – 40	15	21.2±7.8		1	22.0 ± 0		16	21.2±7.6	
41 – 60	27	22.4±7.9	0.006	35	16.3±8.2	0.059	62	18.9±8.6	0.002
≥ 60	22	32.1±16.2		28	22.0±10.6		50	26.4±14.1	
Gender									
Males	17	21.5±8.4		4	19.7±8.8		21	21.2±8.3	
Females	47	26.9±13.2	0.125	60	18.8±9.7	0.867	107	22.4±12.0	0.665
BMI Groups									
Non-Obese	64	25.5±12.3		0	-		64	25.5±12.3	
Obese I	0	-		36	18.9±11.2		36	18.9±11.3	
Obese II	0	-	-	8	20.2±7.9	0.894	8	20.3±7.9	0.013
Obese III	0	-		20	18.3±7.1		20	18.3±7.1	

Abbreviations: NT2DM, Non-Type 2 Diabetes Mellitus; T2DM, Type 2 Diabetes Mellitus; BMI, Body Mass Index; N, number of participants.

**Table 3. Pearson’s bivariate correlation between Vitamin D as dependent variable and age, gender, BMI and FBG as independent variables in type 2 diabetic patients and non diabetic controls**

Vitamin D vs.	NT2DM		T2DM		ALL	
	R	P	R	P	R	P
Age (years)	0.400	0.001	0.170	0.179	0.229	0.009
Gender (M/F)	0.194	0.125	-0.021	0.867	0.039	0.665
BMI (kg/m <sup>2</sup> )	0.002	0.989	0.042	0.744	-0.231	0.009

**Table 4. Logistic regression analysis between vitamin D status and diabetes status of participants**

Vitamin D Status	X <sup>2</sup> (P-value)	Odds Ratio	95% Confidence Interval	P - Value
Deficiency	10.28 (0.001)	3.24	1.56 – 6.73	0.002
Sufficiency		1 (Reference)		

**Table 5. Presence of vitamin D deficiency according to characteristics of study participants and the effects of age, gender and body mass index on the development of vitamin D deficiency**

Variables	NT2DM		T2DM		ALL	
	N (%)	P - Value	N (%)	P - Value	N (%)	P - Value
Age (years)						
≤ 40	6 (31.6)	<0.001	0 (0)	-	6 (10.7)	<0.001
> 40	13 (68.4)		37 (100)		50 (89.3)	
Gender						
Males	7 (36.8)	0.009	2 (5.4)	<0.001	9 (16.1)	<0.001
Females	12 (63.2)		35 (94.6)		47 (83.9)	
BMI Categories						
Non-Obese	19 (100)	-	0 (0)	-	19 (33.9)	0.001
Obese	0 (0)		37 (0)		37 (66.1)	

Abbreviation: BMI, Body mass index; All vitamin D values of <20 ng/ml were considered as vitamin D deficient.



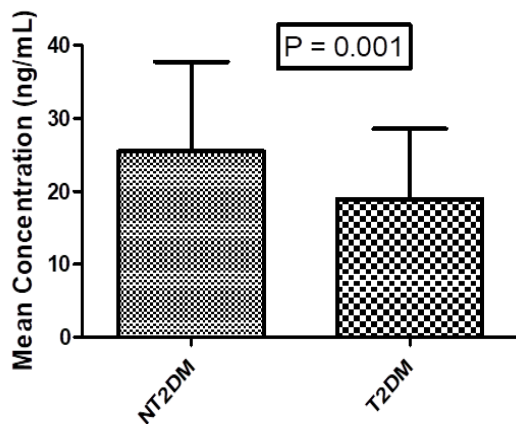


Figure 1. Vitamin D concentrations of the study participants (Abbreviation: NT2DM, Non-type 2 diabetes mellitus; T2DM, Type 2 diabetes mellitus)

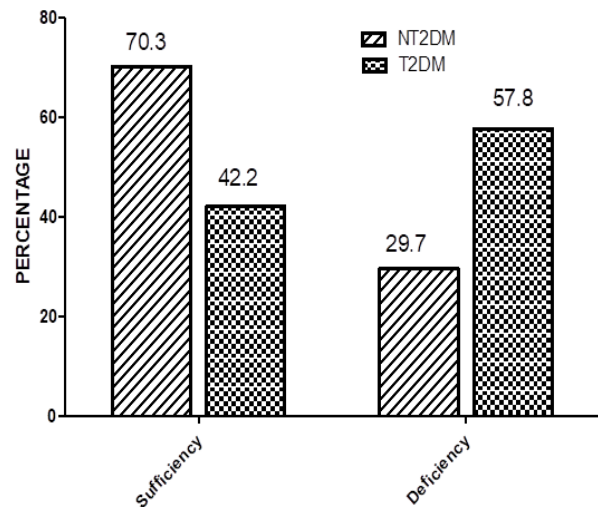


Figure 2. Vitamin D status among type 2 diabetes mellitus patients and non-diabetic subjects.

## DISCUSSION

In this study, lower levels of vitamin D as well as a greater percentage of vitamin D deficiency were found among those living with T2DM compared with the non-diabetic controls. We observed a vitamin D deficiency of 57.8% among T2DM cases and 29.7% among the non-diabetic controls. Participants with vitamin D deficiency were at greater risk of T2DM compared with those with sufficient vitamin D. Increase in the level of serum vitamin D is related to aging, and a decrease in the level of adiposity. Vitamin D level was not affected by the sex of the participants. Vitamin D deficiency was more common in adults of age >40 years compared to younger age, in females compared to males and in obese compared with non-obese.

The present study which reported lower levels of vitamin D and a higher proportion of vitamin D deficiency in diabetic patients compared with non-diabetic subjects agrees with some studies [16 - 21] which reported similar findings. The mechanisms behind the lower vitamin D level and the increased incidence of vitamin D deficiency in this study are not very clear, but it is speculated that excess adiposity, advanced age, and inhibition of megalin may have played a role. Increased adiposity as seen

in obesity is associated with vitamin D deficiency [22, 23]. This is because vitamin D is known to be sequestered or stored in adipose tissues and due to the limited storage ability of the adipocytes, obese individuals tend to have lower circulating 25-hydroxyvitamin D concentrations [22, 23]. Advanced age has also been associated with vitamin D deficiency [24, 25]. The effects of aging on vitamin D metabolism include decreased intestinal concentration of vitamin D receptors [26, 27]; decreased renal production of 1,25-dihydroxy vitamin D [1,25(OH)<sub>2</sub>D] in the aging kidney due to a decrease in the activity of the renal enzyme 1 $\alpha$  hydroxylase that converts 25-hydroxy vitamin D (25OHD) into 1,25(OH)<sub>2</sub>D [25]. Other effects of aging on vitamin D metabolism include, decreased skin production of vitamin D due to a decrease in the concentration of 7-dehydrocholesterol in the epidermis in old compared with young individuals and a reduced response to UV light, resulting in a 50% decrease in the formation of vitamin D<sub>3</sub> [24]; and substrate deficiency of vitamin D, which is a common problem in the elderly [28]. Furthermore, high glucose concentration has been shown to inhibit megalin expression [29, 30]. Megalin, a multi-ligand scavenger receptor in the proximal

tubules helps in converting 25hydroxyvitamin D to its active form 1,25dihydroxyvitamin (OH)2D [31]. A decrease in megalin expression, therefore, results in decreased vitamin D levels. Interestingly, in the present study, the type 2 diabetic patients indicated significantly higher mean age, BMI, and FBG levels compared with the non-diabetic control.

There is increasing evidence that vitamin D deficiency may be a risk factor for T2DM. Our finding showed that participants with vitamin D deficiency were at greater risk of T2DM compared with those with sufficient vitamin D. This is in agreement with previous studies which have demonstrated a significant association between Vitamin D deficiency and type 2 diabetes [25, 32, 33]. In contrast, other studies have reported no association between vitamin D deficiency and type-2 diabetes [34]. The association between T2DM and vitamin D deficiency is attributable to decreased insulin secretion, increased insulin resistance, and  $\beta$ -cell dysfunction in the pancreas [35]. Vitamin D deficiency decreases insulin secretion via decreased calcium concentration and flux through B-cells [36]; increased parathyroid hormone, which inhibits insulin synthesis and secretion in the pancreas according to Fadda *et al.* [37]; Increased renal renin production and angiotensin II formation, which inhibits the action of insulin thus impairing glucose uptake [38]. There has also been a report of decreased activation of insulin genes due to a decline in vitamin D receptor activity in pancreatic beta cells [39]. A decrease in calbindin, a systolic calcium-binding protein found in pancreatic beta cells, has also been shown to inhibit insulin secretion through the regulation of intracellular calcium [40]. However, a recent study has also reported that there is no association between vitamin D deficiency and insulin resistance or beta cell function in our study population [25]. Vitamin D deficiency is associated with increased insulin resistance by inhibiting the expression of insulin receptors found in the pancreatic beta cells, which leads to decreased insulin sensitivity [41, 42]; increased PTH, and decreased expression of peroxisome proliferator-activated receptor delta,

which regulates fatty acids in skeletal muscles and adipose tissues, thereby promoting insulin resistance [43]. Increased systemic inflammation also increases insulin resistance [44]. Vitamin D deficiency-induced beta cell dysfunction is a result of decreased modulation of the expression and activity of cytokines resulting in increased systemic inflammation. An increase in systemic inflammation causes worsening glycemic control and stimulates beta cell-cytokine-induced apoptosis according to Riachy *et al.* [45].

Similar to our finding, previous studies [46 - 48] observed that serum levels of 25-hydroxyvitamin D did not decline with age. In contrast, other studies revealed that vitamin D levels decreased with age [23 – 24]. It is noteworthy that despite the positive correlation between age and mean vitamin D concentration, the incidence of vitamin deficiency was more common among the older adults aged >40 years compared with those aged  $\leq$  40 years, not only in the NT2DM group but also in T2DM and the combined data. This is in agreement with previous studies [49, 50]. Generally, elderly people are susceptible to vitamin D deficiency due to many risk factors, such as reduced skin production of vitamin D, decreased sunlight exposure, decreased dietary intake, reduced skin thickness, impaired intestinal absorption, and diminished hydroxylation in the liver and kidney [51, 52].

Despite the lack of significant gender differences in serum concentrations of vitamin D, the females showed a higher vitamin D deficiency compared with the males in all the groups considered. Previous studies have reported significantly lower vitamin D levels in women compared to men [53] [54]. Another study indicated significantly higher vitamin D levels in males compared with females has been reported by Sanghera *et al.* [55]. A higher prevalence of vitamin D deficiency in women compared with men has been reported in several studies [53, 56, 57], but not in others [58, 59]. According to VanDam [60], it has been suggested that the excess adipose tissue of females compared

with males is responsible for the lower vitamin D concentrations in females.

In the overall data, serum vitamin D concentration was negatively correlated with BMI and vitamin D deficiency was more common among the obese compared with non-obese individuals. Our study confirms the inverse association of serum vitamin D with BMI, which has been consistently reported and well-established [61, 62]. Vitamin D is a fat-soluble hormone and its absorption is enhanced in obesity. It has been previously reported that obesity can lead to the sequestration of vitamin D in adipose tissue, thus reducing its bioavailability [22]. We encountered some limitations in the course of this study. Some patients decided to opt out of the study at the middle with reasons ranging from religion, cultural to personal. Also, some of the participants were reluctant to volunteer oral information during interview.

## CONCLUSION

Our findings demonstrated that type 2 diabetic patients presented a lower mean vitamin D concentration and a higher prevalence of vitamin D deficiency compared to non-diabetic individuals. Furthermore, vitamin D deficiency was more common in older adults of age >40 years, females, and obese individuals. The present study, therefore, suggests that vitamin D screening and supplementation should be included in the management plan for all T2DM patients.

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## Author contributions:

BBOE and BIGA conceptualized and designed the study. GO, UD, OFO, OVA, ONA, and SU contributed to the implementation of the project and revision of the manuscript. All authors were involved in the writing and revision of the manuscript. The authors read, approved the final

manuscript, and agreed to be accountable for all aspects of the work.

## Data availability

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

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**Conflict of interest:** None declared.

## Ethical approval:

The study was approved by the Institutional Ethics Committee.

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