Original Article

Serum Levels of Vitamin D in Nigerian Women with Uterine Fibroids: A Case-Control Study

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ABSTRACT

Introduction: Uterine fibroids (UFs) very common benign tumours of the uterine smooth muscle cells commoner in blacks and vitamin D may be a potential risk factor.

Aim: To evaluate vitamin D serum levels in women with and without UF.

Materials and Methods: This was a hospital-based case-control study. Serum levels of vitamin D were determined in adult female patients with and without UF. Pre-tested Questionnaires were also used to collect biodata, reproductive characteristics, diet and other confounders for vitamin D. SPSS version 27 was used to analyse data with a *P* value < 0.05 considered statistically significant.

Results: The mean vitamin D level for all participants was 34.96 ± 30.47 (ng/ml). There were more cases of women with uterine fibroids that had vitamin D deficiency (43, 53.1%) than when compared to the controls (38, 46.9%). The mean vitamin D levels were not statistically different (p value > 0.05) among cases 37.6 ± 33.8 (ng/ml) and controls 32.3 ± 26.5 (ng/ml) (table 4), both being within sufficient levels. There were significant associations between marital status, infertility, skin colour, exposed body parts, exercise, intake of dairy and oily fish and vitamin D levels (p value < 0.05).

Conclusion: There was no statistically significant difference in vitamin D levels between women with uterine fibroids and controls in this study population.

Keywords: Uterine fibroids, Serum vitamin D, Women, Nigeria

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INTRODUCTION

Uterine fibroids (UFs) or leiomyomas are monoclonal, benign tumours of the uterine smooth muscle cells. They are very common among women of the reproductive age group with a variable prevalence of 5–70%, depending on the population and context.[1] In Nigeria, it is associated with infertility in many cases, and is one of the commonest reasons for gynaecologic consultations and hysterectomies. Most patients do not present early, increasing their morbidity, and associated adverse psychosocial and economic effects.

Several risk factors have been proposed and include black race, elevated body mass index (BMI), hypertension, positive family history, nulliparity and longer duration since last delivery, consumption of food additives and soybean milk. [1] Recently, studies have suggested that hypovitaminosis D may also play a role in the development of UFs. [1,2,3,4,5]

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Several mechanisms have been proposed to explain the possible association between Vitamin D is has been shown to decrease cell proliferation and differentiation, increase apoptosis, regulate angiogenesis and extracellular matrix production. [6,7,8] Early studies done in Ekar rats demonstrated the antiproliferative effects of vitamin D level by reducing the proliferative cell nuclear antigen (PCNR) and some cell cycle regulatory proteins.[9] Vitamin D also has significant antagonizing effects to oestrogen and progesterone.[10] Furthermore, other studies reported that vitamin D deficiency was associated with more severe disease, and vitamin D supplementation may reduce the progression of UF to an extensive disease.[2,7]

Exposure to sunlight affects vitamin D synthesis. While black women may tolerate the increased exposure to sunlight in the tropics better, their higher skin melanin content alters vitamin D synthesis and reduces expression of the vitamin D receptor (VDR) in the myometrium.[2,7]

This study aims to evaluate vitamin D levels in a black population, since black women have a higher burden and severity of UF, which may be associated with their vitamin D status. Results previous studies have been inconsistent, and only very few studies have been done in this regard in our environment.[11] Also, vitamin D has a potential to be a simple and cheap cure for UF. Thus, more studies are still needed.

MATERIALS AND METHODS

Ethical approval for the study was gotten from the Health Research and Ethics Committee of the Barau Dikko Teaching Hospital (HREC No: 20-0072). Informed written consent was also obtained from participants.

The study was carried out at the Barau Dikko Teaching hospital (BDTH), which is the teaching hospital of the Kaduna State University. It caters for the people of Kaduna metropolis and its environs, estimated at over 8 million people. Its gynaecology clinics run twice a week with an average of 30 new patients seen on every week, and numerous follow up cases. This was a hospital-based case-control study.

The study participants were adult female patients seen at the gynaecology clinic. Inclusion criteria included all aged 18-50 years irrespective of parity, diagnosed with at least one or more UF by ultrasound for cases, and controls of those without uterine fibroids. Exclusion criteria included cases where sonographic evaluation of the uterus was difficult, co-existing adenomyosis, malignancy, chronic medical disorders (hypertension, diabetes mellitus, multiple sclerosis, autoimmune disorders, coronary, thyroid, hepatic, or renal diseases), history of drug/treatment with oral contraceptives, vitamin D supplementation and chronic ingestion of medications in the preceding 3 months, pregnant/lactating or postmenopausal women, chronic alcohol abuse or malabsorption. Controls had no history of a previous myomectomy.

The sample size was determined using Fisher's statistical formula.[12]

$n=Z^2pq/d^2$

n= Minimum sample size

Z=1.96 (confidence interval) which is a constant.

P= prevalence rate from a previous study (6.3 % from a previous study by Isah et al, 2018)[13]

Therefore, P=6.3% = 6.3/100 = 0.063

q=1-P=complimentary probability= 1- 0.063=0.937

d=precision (margin of error) at 95% confidence limit=0.05

$n= (1.96)^2 \times 0.063 \times 0.937/ (0.05)^2 = 90.7$

Taking a decline rate of 9 % and attrition rate of 10%, minimal sample size will be 108.

The study would therefore recruit a minimum of 110 participants as cases, and 110 apparently healthy individuals as controls. This will bring the total sample size to two hundred and twenty (220).

Purposive sampling and recruitment of consecutive eligible patients was done until the sample size was reached. Pre-tested Questionnaires were used to collect biodata, reproductive characteristics, diet, and other factors that may influence vitamin D synthesis in the body.

Blood samples for vitamin D analysis was collected after proper counseling of the patient by the attending physician or lab scientist. A tourniquet was applied to the upper arm above the cubital fossa which was cleaned with alcohol-soaked cotton wool. After drying, the most prominent peripheral vein was chosen and punctured with a vacutainer needle. A total of 5 milliliters of blood was collected into a gel/clot activator bottle. The tourniquet was then removed, the needle withdrawn, and haemostasis secured by direct application of pressure. The samples were spinned immediately in a centrifuge at a relative centrifugal force (RCF) of 1200X g for ten minutes to obtain serum which was frozen at -20°C. Sample analysis was done in batches until completion.

Quantitative measurements of 25(OH)D, was done using Enzyme Linked Immuno-Sorbent Assay (ELISA) technique. The method uses an indicator label to detect and quantify immunological reactions. Prior to assay, frozen samples would be brought to room temperature and centrifuged, if necessary, to isolate residual debris. Analysis was done using the Vitamin D kit (manufactured by CTK BIOTECH, 13855 Stowe Drive, Poway, CA 92064 United States of America), as per manufacturer's instructions. The microtiter plate provided was pre-coated with an antibody specific to Vitamin D. During the reaction, Vitamin D in the sample or standard competes

Table 1: Baseline characteristics of women with and without uterine fibroids

Characteristic (n=231)	Case 116 (50.2%)	Control 115(49.8%)	Statistics
Age			
⩽20	2 (22.2)	7 (77.8)	
21-30	25 (43.1)	33(56.9)	Likelihood ratio=8.260, df=3, p
31-40	50 (49.0)	52 (51.2)	value=**0.045**
41-50	39 (62.9)	23 (37.1)	
Education			
None/Quaranic only	2 (100.0)	0 (0)	
Primary	2 (33.3)	4 (66.7)	Likelihood ratio=4.758, df=4, p
Secondary	35 (45.5)	42 (54.5)	value=0.313
Tertiary	66 (52.0)	61 (48.0)	
Occupation			
Unemployed/housewife	31 (42.5)	42 (57.5)	
Self-employed/business	43 (55.8)	34 (44.2)	
Student/corper	8 (50)	8 (50)	X^2=3.534, df=5, p value=0.618
Teacher	13 (48.1)	14 (51.9)	
Civil servant	17 (53.1)	15 (46.9)	
Others	4 (66.7)	2 (33.3)	
Marital status			
Single	18 (81.8)	4(18.2)	X^2=14.319, df=2, p value= **0.001**
Married	90 (45.2)	109(54.8)	
Divorced/widowed	8 (80)	2 (20)	
Age at menarche			
9-13	38 (60.3)	25 (39.7)	X^2=3.002, df=1, p value=0.060
⩾ 14	78 (46.4)	90 (53.6)	
Parity			
0	55 (55)	45 (45)	X^2=4.517, df=2, p value=0.104
1-4	54 (50)	54 (50)	
⩾ 5	7 (30.4)	16 (69.6)	
Previous miscarriage			
0	62 (54.9)	51(45.1)	X^2=2.635, df=2, p value=0.268
1-3	47 (47.5)	52 (52.5)	
⩾ 4	7 (36.8)	12 (63.2)	
Last Childbirth			
None	63 (55.8)	50 (44.2)	Likelihood ratio=8.860, df=2, p
< 1year	0 (0)	5 (100)	value=0.012
⩾ 1year	53 (46.9)	60 (53.1)	
Amenorrhoea			
No	93 (52.5)	84 (47.5)	X^2=1.639, df=1, p value=0.201
Yes	23 (42.6)	31 (57.4)	
Infertility			
No	58 (62.4)	35 (37.6)	X^2=9.191, df=1, p value= **0.002**
Yes	58 (42.0)	80 (58.0)	
Skin colour			
Very light	4 (100)	0 (0)	X^2=7.930, df=2, p value= **0.019**
Light	49 (44.1)	62 (55.9)	
Dark	63 (54.3)	53 (45.7)	
Body parts exposed			
Face, neck, hands	90 (46.2)	105 (53.8)	X^2=8.261, df=1, p value= **0.004**
Additional body parts	26 (72.2)	10 (27.8)	
Duration sun exposure			
<15 minutes/day	41 (43.2)	54 (56.8)	
15-60 minutes/day	48 (52.2)	44 (47.8)	X^2=4.221, df=2, p value=0.121
>60 minutes/day	27 (61.4)	17 (38.6)	

Table 1: Baseline characteristics of women with and without uterine fibroids (Cont'd)

Characteristic (n=231)	Case 116 (50.2%)	Control 115(49.8%)	Statistics
Use of sunscreen			
No	45 (59.2)	31 (40.8)	X^2=3.665, df=1, p value=0.055
Yes	71 (45.8)	84 (54.2)	
Exercise			
No	16 (88.9)	2 (11.1)	X^2=11.678, df=1, p value= **0.001**
Yes	100 (46.9)	113 (53.1)	
Oily fish intake			
None/<2 servings/week	104 (48.4)	111 (51.6)	X^2=4.224, df=1, p value= **0.040**
⩾ 2 servings/week	12 (75.0)	4 (25.00	
Dairy intake			
None/<daily intake	95 (54.3)	80 (45.7)	X^2=4.781, df=1, p value= **0.029**
⩾ daily intake	21 (37.5)	35 (62.5)	
Butter/margarine intake			
None	95 (51.4)	90 (48.6)	X^2=0.517, df=2, p value=0.772
1-7 servings/ week	12 (44.4)	15 (55.6)	
1 serving/month or more	9 (47.4)	10 (52.6)	
Body Mass Index			
<18.5	3 (37.5)	5 (62.5)	Likelihood ratio=4.003, df=3, p value=0.261
18.5-24.9	40 (56.3)	31 (43.7)	
⩾25	62 (45.9)	73 (54.1)	
Missing	11 (64.7)	6 (35.3)	

with a fixed amount of biotin-labeled vitamin D for sites on a pre-coated Monoclonal antibody specific to Vitamin D. Excess conjugate and unbound sample or standard are washed from the plate. Avidin conjugated to Horseradish Peroxidase (HRP) is added to each microplate well and incubated. A TMB substrate solution was added to each well. The enzyme-substrate reaction was terminated by the addition of a sulphuric acid solution and the colour change is measured using a spectrophotometer at a wavelength of 450 nm ± 2 nm. The concentration of Vitamin D in the samples is then determined by comparing the O.D. of the samples to the standard curve.

As recommended by the Endocrine Society Practice Guidelines on vitamin D status, "deficiency" was defined as 25(OH)D level of ⩽ 20 ng/mL, "insufficiency" as 20–29 ng/mL, and "sufficiency" as at least ⩾30 ng/mL. [14,15]

Statistical software SPSS 27 (SPSS Inc, Chicago, IL) was used to analyse data. Descriptive analysis was done and chi-squared or Fisher exact test used to test for association as appropriate. Independent t test was used to compare group means. Linear regression was used to adjust for confounders when appropriate. A *P* value < 0.05 was considered statistically significant.

RESULTS

There was a total of 231 participants (116, 50.2% cases and 115, 49.8%). Their baseline characteristics are shown in table 1 and table 2. There was a statistically significant difference in their ages with mean age of cases (36.9 ± 7.2 years) being higher than that of controls (33.9 ± 8.1 years). The association between marital status, infertility, skin colour, exposed body parts, exercise, intake of dairy and oily fish and the cases/controls was statistically significant (p value < 0.05). However, logistic regression showed only exposed body parts to be significantly associated with uterine fibroids (table 3). Those who had only their face, neck and hands exposed were three times more likely to have uterine fibroids than those with additional parts exposed.

Table 2: Comparison of Some Gynaecological characteristics of women with and without uterine fibroids

Mean characteristics	Case	Control	p-value
Mean age (years)	36.9 ± 7.2	33.9 ± 8.1	**0.004**
Mean age at menarche	14.4 ± 1,8	14.5 ± 1.8	0.571
Parity	1.6 ± 2.6	1.9 ± 2.4	0.311
Mean number of miscarriages	1.0 ± 1.4	1.3 ± 1.5	0.226
BMI	28.7 ± 8.8	28.4 ± 6.3	0.788

The mean vitamin D level for all participants was 34.96 ± 30.47 (ng/ml) which is sufficient. There were more cases of women with uterine fibroids that had vitamin D deficiency (43, 53.1%) than when compared to the controls (38, 46.9%). Overall, however, the mean vitamin D levels were not statistically different (p value > 0.05) among cases 37.6 ± 33.8 (ng/ml) and controls 32.3 ± 26.5 (ng/ml) (table 4), both being within sufficient levels.

Table 3: Multiple logistic regression model for the predictors of uterine fibroids

Characteristic	Significance	Odds ratio	95% Confidence interval
Marital status			
Divorced			
Married		1.344	0.190 -9.515
Single	0.116	0.360	0.101 -1.283
Infertility			
No			
Yes	0.142	1.620	0.851 -3.082
Skin colour			
Dark			
Light		0.999	0.000
Very light	0.455	0.999	0.000
Exposed body parts			
Additional body parts	**0.019**	3.168	1.210 -8.290
Face, neck, hands			
Exercise			
No			
Yes	0.060	5.025	0.932 -27.101
Oily fish intake			
⩾2 pieces			
<2 pieces	0.752	0.784	0.173 -3.550
Dairy intake			
Daily intake			
< Daily intake	0.058	0.517	0.262 -1.022

Table 4: Comparison of serum levels of vitamin d in women with and without uterine fibroids

Characteristic (n=231)	Case 116 (50.2%)	Control 115(49.8%)	Statistics
Vit D (ng/ml)			
< 20	43 (53.1)	38 (46.9)	X^2=2.824, df=2, p value = 0.244
20-29	18 (39.1)	28 (60.9)	
⩾ 30	55 (52.9)	49 (47.1)	
Mean Vit D level (ng/ml)	37.6 ± 33.8	32.3 ± 26.5	p value= 0.194

DISCUSSION

Our study aimed to determine and compare levels of vitamin D among women with, and without uterine fibroids. Skin colour, exposed body parts, exercise, intake of dairy and oily fish were significantly different among cases of uterine fibroids and controls, and this is not surprising as these are well known factors that can affect vitamin D synthesis and levels.

Overall however, our results were unexpected as we were unable to collaborate any possible association between vitamin D deficiency and uterine fibroids. The mean vitamin D levels were not statistically different among cases and controls. The reason for this is not quite clear and is in contrast to other similar international and national studies [2,3,4,16] which support the association of insufficient/deficient levels of vitamin D and uterine fibroids.

Tunau et al in Sokoto[17] (Nigeria) studied 100 women and found a statistically significant difference in vitamin D levels among women with uterine fibroids (mean plasma level of 10.16 ± 7.78 ng/ml) and that of controls (mean plasma level of 14.35 ± 6.8 ng/ml). However, in that study the mean plasma level of Vitamin D for all the study participants was already deficient (12.47 ± 7.53 ng/ml),[17] while the plasma level of Vitamin D for all the study participants in our study was sufficient (34.96 ± 30.47 ng/ml). The reason for this is again unclear since both study settings are in the northwest of Nigeria and have similar geography, sunlight, and cultural patterns. Both were also hospital-based studies, though our study was slightly larger. Perhaps there may be some other possible confounders including higher poverty rates in Sokoto as Kaduna is more cosmopolitan, and this may impact on diet. In a study of 166 pregnant women in Lagos (southern Nigeria), [18] vitamin D deficiency was seen in only 4.8% of the mothers and in 29.5% of the neonates, with a mean maternal serum concentration 35.0 ± 0.8 ng/ml. Gbadegesin et al (2021) [19] in Lagos also looked 274 premenopausal women and found significantly reduced levels of serum vitamin D in women with uterine fibroids (median value 13.5ng /ml, IQR 3.8 – 22.1) than in controls (52.1 ng/ml, IQR 30.6 – 75.0).

Makwe et al (2021) [20] in Lagos studied micronutrients in 88 women and showed not only significantly lower levels of vitamin D among cases with uterine fibroids versus controls (34.23 ±10.67 vs 37.06 ±11.46 ng/ml), but also lower serum levels of vitamin C (1.20 ± 0.59 vs 1.62 ± 1.75 mg/dl) and calcium (2.27 ± 0.19 vs 2.32 ± 0.09 mmol/L).[20] This shows that micronutrient status may be another potential confounder for the development of uterine fibroids which we did not look at in our study.

One meta-analysis reported a positive correlation between low serum vitamin D levels and UF.[21] There was however some heterogeneity based on study area with African studies showing that the correlation was insignificant, unlike Asian and European studies.[21] This is more in keeping with our findings and was attributed to differences in sunlight exposure, racial and individual differences.[7,21]

LIMITATIONS

This was a hospital-based study which may not reflect what obtains in the community. As with some other studies done, only point serum vitamin D levels were determined while it may take a while for fibroids to develop and be detected clinically. Non validated subjective measures were used to determine confounders such as diet, sun exposure and skin

colour. There may be several other confounders that could affect vitamin D which were beyond the scope of this study.

CONCLUSION

In our study, there was no statistically significant difference in vitamin D levels between women with uterine fibroids and controls. This may be because there are several other confounders not accounted for. Larger multicentre and community studies are recommended considering baseline vitamin D levels.

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