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Comparative Plasma Levels of Vitamin D in Women with or without Uterine Fibriods in Lagos State University Teaching Hospital, Ikeja, Lagos, Nigeria

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ABSTRACT

Background: Fibroids are commonest benign tumour of the uterus in reproductive age women. Surgical treatment has been the mainstay of treatment for symptomatic fibroids. Recently, hypovitamin D has been associated with fibroid. The aim of the study was to compare the level of vitamin D in women with fibroids and women without fibroids.

Aim: To determine and compare plasma levels of Vitamin D in women with uterine fibroids and those without uterine fibroids

Method: An institution based case control study comprising of 274 women. It compared the serum levels of 25 hydroxy vitamin D in 137 women with uterine fibroids and 137 women without uterine fibroids as controls.

Result: The level of vitamin D in the women with and without uterine fibroids were $\{13.5ng/ml, (IQR 3.8 - 22.1)\}$ and $\{52.1 ng/ml, (IQR 30.6 - 75.0)\}$ (P = < 0.001) respectively.

Conclusion: The plasma level of 25-Hydoxy vitamin D was significantly lower in women with uterine fibroids and higher in women without fibroids. Subsequently, prompt detection of vitamin D deficiency by screening with effective treatment may reduce the incidence of fibroids and its sequelae in these group of women.

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Introduction

Uterine fibroid which is also referred to as ''leiomyoma" or just simply as ''myoma" is the most common benign tumor in women of reproductive age group [1]. It occurs in 25- 50% of women in reproductive age but could be as high as 70% in women of over 50 years of age [2].

Uterine leiomyoma is the most common benign tumour in women of reproductive age group and second commonest gynaecology clinic presentation in Nigeria accounting for 3.2 - 7.6% of new gynaecological cases [1-6]. The precise cause of uterine fibroids is unknown. They may be associated with devastating consequences. The mainstay of treatment for uterine fibroid is hysterectomy which is not a favorable option, especially in women who desire to preserve their future fertility [5,7,9,10].

The Incidence ranges from 40-70% in Caucasians to 60-80% in African-American women, at the age ranges of 35-50years

[2,3]. Uterine fibroids accounts for 68.1 % of hysterectomies in Nigeria [4].

Uterine fibroids are largely asymptomatic, but they may also cause a wide range of severe and chronic symptoms in approximately one-quarter to one-third of the affected women [5].

The most common symptoms include abnormal and excessive uterine bleeding, abdominal and pelvic pain, gastric disorders like bloating and constipation, voiding symptoms, infertility and obstetric complications [3-5].

The common risk factors for uterine fibroids include black race, elevated body mass index (BMI), age, premenopausal status, hypertension, positive family history, consumption of food additives, and soybean milk [2-5]. It is a major source of health challenges to women of reproductive age group in Nigeria and around the globe [6].

Even though the exact pathophysiology of uterine leiomyomas remains unknown, the major known stimulators of uterine

fibroid growth are estrogen and progesterone [6,7]. Treatment includes medical therapy, surgical intervention, and uterine artery embolization or ablative techniques [5,8,9]. The choice of treatment depends on the patient's age, the reason for treatment, the concern for fertility preservation and the patient's preference [2,5,6,9]. Clinically symptomatic Uterine Fibroids (UF) are most often treated with surgery . Surgical methods are available, both open and endoscopic (hysterectomies, myomectomies, hysteroscopic resections). UFs are the leading reason for hysterectomy worldwide and this is its definitive treatment [9].

In recent years, emphasis has been placed on the role of vitamin D in areas beyond bone metabolism and calcium haemostasis [10]. Vitamin D is also a prohormone which has been found to be associated with uterine fibroids [11]. It decreases cellular proliferation of both normal and cancer cells, induces terminal differentiation, increases apoptosis, regulation of angiogenesis and extracellular matrix production [10-14]. All these properties has lead to the recent discovery of the role of vitamin D in inhibiting the growth of uterine leiomyomas in vitro and in vivo [14].

There exist a relationship (inverse correlation) between high prevalence of uterine fibroids and low vitamin D level in African American women [5,13]. They found a significantly lower serum concentration of 25 hydroxyvitamin D in women having uterine fibroids compared with women without uterine fibroids [15]. Some studies done in United State, Egypt, Finland suggested that vitamin D inhibits growth and induces apoptosis in cultured human leiomyomas cells, Eker rats and in humans [12-16].

Ours is a predominantly black environment with high prevalence of uterine fibroids. A demonstration of deficiency of vitamin D in patients with uterine fibroids could suggest a way of prevention of uterine fibroids through Vitamin D supplementation.

This study aims at comparing plasma vitamin D levels in patients having uterine fibroids and those without in the gynaecological clinic of our institution.

Material and Methods

The study was conducted at the Obstetrics and Gynaecology Department of the Lagos State University Teaching Hospital (LASUTH), Ikeja, Lagos State, Nigeria. The study lasted for 6 months. A case control study designed to determine the relationship between the plasma vitamin D level and uterine fibroids in women between the age of 25-40 years attending gynaecology clinic in the department of Obstetrics and Gynaecology.

Inclusion criteria were premenopausal women age 25–40years old, symptomatic for uterine fibroids. A transvaginal or transabdominal ultrasonography diagnosis of uterine fibroids of any size. Exclusion criteria are women currently lactating, ingesting calcium/ vitamin supplements or hormonal treatments, calcium antagonist medications, antipsychotics, anti-kochs (rifampicin) and anti-retroviral drugs. Also women with parathyroid dysfunction.

Sample size calculation of case control studies for difference was used.

n= (r+1/r) $\frac{\sigma 2 (Z_{\beta} + Z_{\alpha})^2}{(\mu 1 - \mu 0)2}$

A case control study, comparing serum levels of 25 hydroxyvitamin D in 137 women with uterine fibroids and 137 women without

uterine fibriods as controls. A total of 274 consecutive consenting women were matched for age, age at menarche and parity.

Ethical Consideration

The study protocol was approved by the Health Research and Ethics Committee of the Lagos State University Teaching Hospital. Samples were collected from subjects who had given their written consent for inclusion in the study.

Data and Sample Collection

Data was collected from eligible participants using well-structured questionnaires administered by the investigator to obtain participants' personal information.

5ml of venous blood was collected from the antecubital vein of the participant by means of venipuncture into vacutainer tubes containing lithium heparin, from both the study and control groups. The laboratory method used for measurement / analysis of 25(OH) D in this study was High Performance Liquid Chromatography (HPLC). The test was run by an experienced and trained laboratory scientist on the use of the equipment. The value of 25(OH)D used to determine insufficient level is < 20ng/ml which is the value considered to be the minimum concentration in 2007 workshop consensus report Using high performance liquid chromatography (hplc) for Vitamin D analysis Clin Rep[®] complete kit for 25 hydroxy-vitamin D2/D3 in plasma/ serum and Clinchek^R Controls [17].

Data was entered and analyzed with the statistical package for social sciences (SPSS, v 19.0).

Mean and standard deviation were calculated for numerical variables while percentages were calculated for both numerical and categorical variables. Test of normality was conducted to determine if the outcome variables are normally distributed. Chisquare and fisher's exact test was used to compare categorical variables. Mann Whitney U test was used to compare the median of numerical variables. Linear regression was used to find the relationship between dependent and independent numerical variables. Spearman Rho correlation was used to find the correlation between numerical variables.

The confidence interval was set at 95% for all statistical tests. For all statistical tests, a p value < 0.05 was considered significant. Microsoft excel was used to draw charts.

Result

A total of 274 participants who met the inclusion criteria were selected into the study, 137 premenopausal women with ultrasound diagnosis of uterine fibroids (study group) and 137 premenopausal women without uterine fibroid (control group).

The age of the women ranged between 25 - 40 yrs. The mean age of the study group was higher (33.8 ± 4.4 years) compared to the control group (32.1 ± 4.5 years) (p = 0.809). Over three quarters of the respondents were Christians and majority (65.7%) of the study and control groups participants had tertiary education (p = 0.258). There was no significant difference in the age at menarche, parity, BMI, use of combine oral contraceptives (COCP) and cigarette smoking between the study and control group (p >0.05)

However significant higher proportion of those in the study group had family history of fibroid (15.3%) compared with those in the control group (2.9%) (p = 0.001) as shown in Table-1.

Table 1: Socio Demographic and Clinical Parameters of the Study and Control Group								
Variables	Study n = 137 (%)	Control n = 137 (%)	x2	р				
Age group								
25 - 30	46 (33.6)	44 (32.1)	0.43	0.809				
30 - 34	41 (29.9)	46 (34.3)						
35-40	50 (36.5)	47 (34.3)						
Mean±SD	33.8±4.4	32.1±4.5						
Religion								
Christianity	107 (78.7)	100 (73.0)	1.203	0.273				
Islam	29 (21.3)	37 (27.0)						
Educational Status								
Primary	11 (8.0)	5 (3.6)	2.712	0.258				
Secondary	36 (26.3)	42 (30.7)						
Tertiary	90 (65.7)	90 (65.7)						
Occupation								
Professional	47 (34.3)	43 (31.4)	12.43	0.029				
Unemployed	12 (8.8)	26 (19.0)						
Artisan	19 (13.9)	16 (11.7)						
Clerk	7 (5.1)	16 (11.7)						
Trader/ Business	38 (27.7)	24 (17.5)						
Civil servant	14 (10.2)	12 (8.8)						
Age at Menarche								
Less than 15 years	95 (69.3)	104 (75.9)	1.487	0.223				
15 years and above	42 (30.7)	33 (24.1)						
Parity								
Nulliparous	83 (60.6)	70 (51.1)	2.501	0.114				
Multiparous	54 (39.4)	67 (48.9)						
BMI								
Underweight	11 (8.0)	8 (5.8)	4.208	0.240				
Normal	37 (27.0)	52 (38.0)						
Overweight	48 (35.0)	45 (32.8)						
Obese	41 (29.9)	32 (23.4)						
Family History								
Yes	21 (15.3)	4 (2.9)	12.72	< 0.001				
No	116 (84.7)	133 (97.1)						
Use of COCP								
Yes	13 (9.5)	6 (4.4)	2.771	0.096				
No	124 (90.5)	131 (95.6)						
Previous Myomectomy		1						
Yes	16 (11.7)	0 (0.0)	16.992	< 0.001				
No	121 (88.3)	137 (100.0)						
Vit D levels	1	,						
Deficient (<20ng/ml)	91 (70.0)	0 (0.0)	156.02	< 0.001				
Insufficient (20 – 29 ng/ml)	23 (17.7)	28 (21.2)						
Normal (≥30ng/l)	16 (12.3)	104 (78.8)						

About two third of the premenopausal women in the study group had lower abdominal swelling, prolong menstrual bleeding and dysmenorrhea as the commonest associated morbidity of uterine fibroids while about a third had history of non cyclic pelvic pain, frequency in urination and dyspareunia

The median value for the level of vitamin D in the premenopausal women with and without uterine fibroids were $\{13.5ng/ml, (IQR 3.8 - 22.1)\}$ and $\{52.1 ng/ml, (IQR 30.6 - 75.0)\}$ (P = < 0.001) respectively. As shown in Table -2 below

Table 2: Median	Vit D Levels in	Study and	Controls
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Group	Ν	Median	IQR	U	р
Study	137	13.5	3.8 - 22.1	1240.5	< 0.001
Control	137	52.1	30.6 - 75.0		

Note: IQR = Interquartile range U = Mann Whitney U test

The median vitamin D level in women in the control group was significantly higher than those in the study group regardless of age group, parity, age at menarche and BMI (p < 0.001)

The median Vitamin D of women aged 25-30 years for the study and control groups was 9.7 ng/ml and 70. 6 ng/ml (p= <0.001) while women aged 30-34 years had vitamin D levels 16.1ng/ml and 43.ng/ml p = 0.001 and 35-40 years were 13.7 and 47.1 ng/ ml (p = 0.001) respectively. Similarly, plasma level of vitamin D in nulliparous women in the study and control group was 13.4ng/ ml and 63.6 ng/ml (p = 0.001) while among primiparous 13.9 ng/ ml and 39.1ng/ml (p = < 0.001) respectively. Similar pattern was observed between the different BMI groups

Graph-2 shows the correlation between Vitamin D and fibroid status in volume(cm³). There was an inverse relationship between uterine fibroid mass and Vitamin D level. The larger the fibroid volume, the lower the Vitamin D level (Spearman Rho = -0.113, p = 0.189).



Discussion

This study was conducted to determine the relationship of plasma Vitamin D level in women of reproductive age with uterine fibroids and those without uterine fibroids.

Age matched for both groups, there was no statistical significance difference. A higher proportion of women in the study group had family history of uterine fibroids in first degree relatives 21(15.3%) compared to the study group of 4(2.9%) p=0.001 and -these women with positive family history and previous myomectomy 16(11.7%) were found to have lower levels of plasma vitamin D in relation to women with uterine fibroids and no family history of fibroids.

This study showed a preponderance symptom of lower abdominal swelling 81.8% which is higher than the study done in Zaria where the symptom account for 48.8% [18].

In this study, the median plasma vitamin D in women with uterine fibroids was significantly lower than in those without fibroids. This is consistent with similar studies done [13,19]. This may be because transforming growth factor (TGF -ß3) upregulates the synthesis of many of the extracellular matrix (ECM) protein involved in fibrosis with resultant extracellular matrix protein over production in human leiomyomas by stimulating the expression of collagen type 1, fibronectin, laminin and proteoglycans as found in uterine fibroids [20,21]. More so, there is a positive feedback loop between extracellular matrix production and cell proliferation in which vitamin D might act to block the positive feedback in the pathogenesis of uterine fibroids [20-22].

70% of women with uterine fibroids had a deficient level of plasma vitamin D(<20.0 ng/ml), while there was none(0%) in the study group p=0.001, while 17.7% and 21.2% had insufficient plasma level of vitamin D(20-28ng/ml) respectively and 12.3% and 78.0% had sufficient level of vitamin D(.30ng/ml) for the study and control group respectively. The median plasma vitamin D level in women with uterine fibroid in LASUTH was 13.5ng/ml which is slightly lower than the mean value by Baird et al of 14.6ng/ml and lower in blacks than Caucasians(10.4ng/ml vs 20.7ng/ml) [22]. Sabry et al found a mean value of vitamin D to be significantly lower in women with uterine fibroids 19.7ng/ml which is higher than the findings of this study and also lower in BLACKS than WHITE subjects(14.2ng/ml vs 25.5ng/ml) [13]. Paffoni et al found a slightly higher level of vitamin D in women with uterine fibroids 18.0ng/ml, while in women without uterine fibroids the median plasma vitamin D level was found to be 52.1ng/ml which is higher than what Sabry et al and Paffoni et al found in women without uterine fibroids 22.3ng/ml 20.8ng/ml respectively [13,19].

Uterine fibroids is approximately ten times more prevalent in African American (40-45%) than in Caucasian women (4%) [5,23]. Which may account for higher incidence of Uterine fibroids in Africa American women(3-4 times more) than Caucasians [5,21,22]. Studies show that there is low level of vitamin D because of higher melanin concentrations and reduced expression of the vitamin D receptor (VDR) in the adjacent myometrium compared to white women [3-23]. Comparison of both median plasma vitamin D level of women with uterine fibroids 13.5ng/ml IQR 3.8-22.1ng/ml with women without uterine fibroids 52.1ng/ml IQR 30.6-75.0ng/ml, p value = < 0.001 demonstrates inversely correlation between low level of vitamin D with presence of uterine fibroids showing statistical significant negative correlation. Similar findings were shown by Sabry M. et al and Paffoni A. et al when comparing Vitamin D levels in women with or without uterine fibroids (14.2ng/ml vs 22.3ng/ml p=0.001) (18.0ng/ml vs20.8ng/ml) respectively [13,19].

Furthermore, the study illustrates lowest level of plasma 25 (OH) vitamin D in women with largest fibroid volume dropping to as low as <10ng/ml with large fibroid size. This could probably be due to the diverse functions of vitamin D mediated predominantly through a G1/S (gap1/synthesis) phase block of the cell cycle and its inhibitory role in cell growth, proliferation related genes (proliferating cell nuclear antigen (PCNA), Cell proliferation markers cyclin D1 (Ccnd1) and proto oncogene Myc which have been reported to be over expressed in leiomyoma compared to normal myometrium. Hence a lower level of vitamin D will invariably lead to increased fibroid volume [23-25].

Conclusion

The study shows that plasma vitamin D levels are higher in women without fibroids and lower in those with uterine fibroids.. Early detection of vitamin D deficiency and its subsequent treatment in women especially of African origin may help reduce the risk of uterine fibroids and its associated morbidities. Encouragingly dietary intake / supplementation of vitamin D may forestall the development of uterine fibroids even in those with genetic predisposition.

Recommendations

This study looks promising, hence more interventional studies, involving administration of vitamin D to women at risk of developing fibroids will be required to further substantiate that vitamin D could be important in the prophylaxis of uterine fibroids.

Limitations of the Study

The study is a report from an institutional study on the relationship of fibroid and level of vitamin D in a tertiary hospital in Lagos. Similar studies may need to be carried out as a multi-center study for better generalization on the relationship between fibroids and vitamin D.

Conflict of Interest: None declared

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