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Vitamin D status in women with uterine fibroid- A cross-sectional observational study

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Abstract
Introduction: Uterine fibroid also known as ''leiomyoma'', leiomyoma uteri or just simply as ''myoma'' are benign, monoclonal tumors of the smooth muscle cells of the myometrium and contain large aggregations of extracellular matrix composed of collagen, elastin, fibronectin, and proteoglycan. It is the most common benign tumor in women of reproductive age group.
Aims/Objective: To compare plasma vitamin D levels of women with and without uterine fibroids attending gynaecology clinic and patients admitted in gynaecological wards at SMGS HOSPITAL.
Results and conclusion: Fifty three percent (53%) Cases and 26% Controls were found to be Vitamin D deficient (<20 ng/mL), the difference being statistically highly significant (p=0.0001 highly significant). 25% Cases and 32% Controls reported Vitamin D insufficiency (20-29.9 ng/mL), the difference being statistically not significant (p=0.271). 42% Controls were found to have normal Vitamin D level (>30 ng/mL) compared to 22% in Cases, the difference being statistically highly significant (p<0.002).

Keywords: Leiomyoma, metabolism, tumor, myometrium, metabolism

Introduction

Uterine fibroid also known as ''leiomyoma'', leiomyoma uteri or just simply as 'myoma' are benign, monoclonal tumors of the smooth muscle cells of myometrium and contains large aggregations of extracellular matrix composed of collagen, elastin, fibronectin, and proteoglycan. It is the most common benign tumor in women of reproductive age group. Various risk factors have been associated with uterine leiomyomas which includes: advanced age, nulliparity, endogenous hormonal factors (early menarche, late menopause), hormonal replacement therapy, black race, smoking, overweight, red meats and beef, vitamin D deficiency and excessive physical exercise.

Vitamin D is a fat-soluble vitamin whose active metabolite [1,25(OH)D] plays a vital role in calcium homeostasis and thus is important for overall health of all individuals. In the recent years, there has been an increased understanding of the role of vitamin D in regulation of cell growth, calcium absorption, immunity and cell metabolism. Insufficient vitamin D status has received increased attention and has been shown to be associated with various extra-skeletalmedical conditions including cardiovascular disease, diabetes (Pittas AG *et al*., 2010), asthma (Allan *et al*., 2011), and pre-eclampsia (Shand AW *et al*., 2010). However, the most notable effect of insufficient vitamin D has been on musculoskeletal health (Venning G *et al*., 2005).

Recent studies have also shown VDR expression in the myometrium and the endometrium of human uterus throughout the menstrual cycle, and in addition to uterine fibroid tissues (Holicks MF, 2007). The diverse functions of vitamin D are mediated predominantly through a G1/S (gap1/synthesis) phase block of the cell cycle (Schnaper HW *et al.*, 2003). TGF - ß3 also upregulates the synthesis of many of the extracellular matrix (ECM) protein involved in fibrosis and hence plays an essential role in the extracellular matrix protein over production in human leiomyomas by stimulating the expression of collagen type 1, fibronectin, laminin and proteoglycans. The pathogenesis of uterine fibroids has been hypothesized to involve a positive feedback loop between extracellular matrix production and cell proliferation in which vitamin D might act to block the positive feedback (Baird DD *et al.*, 2013).

Methods and Methodology

Study Site

This study was conducted on indoor and outdoor Gynaecological patients with uterine fibroid and age matched controls of the Department of Obstetrics and Gynaecology, of Shri Maharaja Gulab Singh Hospital Jammu over a period of one year, from November 2021 to October 2022, after proper institutional ethical approval and informed written consents from the participants.

Study Design

This was cross sectional observational study designed to determine the status of vitamin D levels in women with uterine fibroid and their age matched controls.

Recruitment of Patients

Inclusion Criteria for Cases

- Women age 18 years and above with symptomatic uterine fibroid.
- Transvaginal or transabdominal ultrasonography diagnosed uterine fibroids of any size even in asymptomatic women.

Inclusion Criteria for Control

- Transvaginal or transabdominal ultrasound screening of fibroid free uterus in women of 18 years and above age matched as control.

Exclusion Criteria

- Non consenting women
- Women with ongoing pregnancy
- Patients currently on calcium/ vitamin supplements or hormonal treatments and within six months prior to start of study.
- Women with parathyroid dysfunction.
- Women on antipsychotics, anticonvulsants, corticosteroids, antitubercular therapy (rifampicin), and HAART.
- Women with chronic medical conditions like chronic kidney disease, heart failure, angina, arrhythmias on calcium channel blockers medications.

Sample Size

A total of 100 cases and 100 controls were taken for this study.

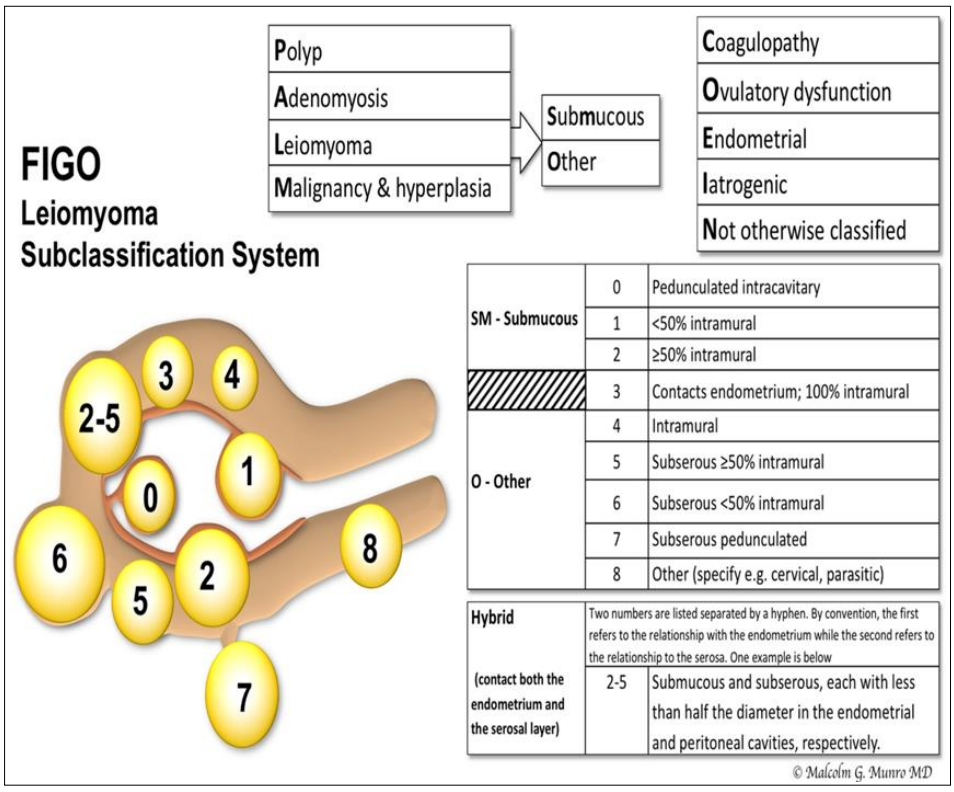

Fig 1: Figo classification system of uterine fibroid

Methodology

This was a cross sectional observational study in which consecutive women presenting at the hospital, both indoor and outdoor patients, asymptomatic or with symptoms and signs suggestive of uterine fibroids or without uterine fibroid above the age of 18 years was adequately counselled and their informed consent was obtained before being recruited into the study. A proforma was used to get socio-demographic data and information relating to uterine fibroids at presentation including

1. Age
2. Body mass index
3. Sun exposure
4. Family history of uterine fibroid in first degree relatives.
5. Obstetric history [parity, history of recurrent miscarriages, pain in pregnancy, malpresentation, previous preterm labour, IUGR, dysfunctional labour, previous caesarean section secondary to uterine fibroid, postpartum haemorrhage]
6. History of infertility
7. Associated comorbidities [prolong and heavy menstrual bleed, lower abdominal swelling, non-cyclic pelvic pain, dyspareunia,]
8. Urinary symptoms [frequency, urgency, incontinence, urinary difficulty]

Transvaginal and transabdominal ultrasound scan was done to assess fibroids status and blood sample was taken and send to the laboratory for plasma level of 1, 25 hydroxyvitamin D analysis.

Laboratory Test

- Serum 25 hydroxyvitamin D levels were determined by chemiluminescent microparticle immunoassay (CMIA) technique.

Results

Table 1: Group comparison for age distribution of patients

Age (years)	No. of Patients (%)		Z proportion	P value
	Case (with fibroids)	Control (without fibroid)		
19-28	9	12	.940	0.345
29-38	16	20	.370	0.713
39-48	65	52	.290	0.775
49-58	10	16	.000	1.000
Mean age ± SD	42.43±7.79	42.24±8.09		

Considering age distribution of patients undergoing study maximum number of patients were in the age group of 39-

48 years in Cases (65%) and in Controls (52%) respectively. 16 patients in cases (16%) and 20 patients in controls (20%) were in age group 29-38 years respectively. 10 patients in cases (10%) and 16 patients in controls (16%) were in age group 49-58 years respectively. 9 patients in cases (9%) and 12 patients in controls (12%) were in age group 29-38 years respectively. Mean age of Cases (42.43 years) and Controls (42.24 years) was comparable in the study.

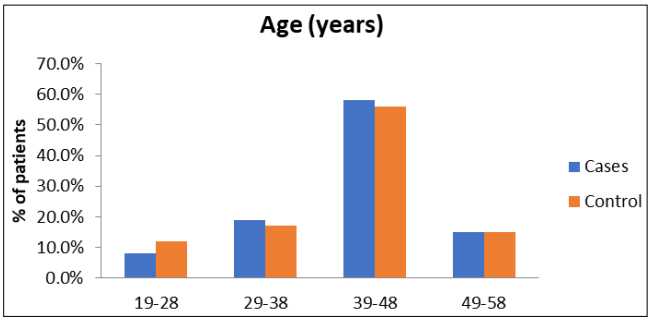

Fig 2

Table 2: Distribution according to parity

Parity	No. of Patients		P value
	Group A(Case)	Group B (Control)	
nulliparous	48	29	0.005 (highlysignificant)
1-2 births	36	50	0.043
>or equal 3 births	26	21	0.362

Considering the distribution of patients undergoing study according to parity 48 patients in cases (48%) and 29 patients in controls (29%) were nulliparous respectively. 36 patients in cases (36%) and 50 patients in controls (50%) had 1-2 births respectively. 26 patients in cases (26%) and 21 patients in controls (21%) 3 or more births respectively. The difference in pattern of distribution according to parity among patients undergoing study was found to be highly significant (p value =0.005).

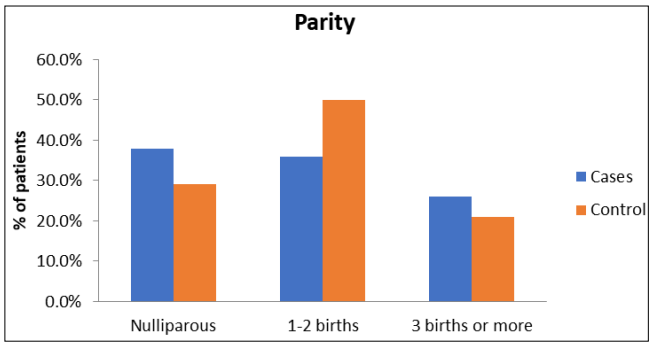

Fig 3

Table 3: Group comparison for BMI (kg/m^2)

BMI (kg/m^2)	Group A (Cases)		Group B (Controls)		P value
	No.	%	No.	%	
<18.5 (underweight)	11	11.00	09	09.00	0.602 0.602
18.5 – 24.9 (normal)	30	30.00	40	40.00	0.305 0.305
25.0 – 29.9 (overweight)	38	38.00	34	34.00	0.661 0
≥30 (obese)	21	21.00	17	171.00	0.257
Total	100	100.00	100	100.00	
Mean BMI ± SD (Range) kg/m^2	24.95±4.11		25.69 ±4.07		

Considering the comparison of groups according to BMI, 38 patients in cases (38%) and 34 patients in controls (34%) were overweight (BMI 25.0 – 29.9) respectively. 30 patients in cases (30%) and 40 patients in controls (40%) had normal BMI (18.5 – 24.9) respectively. 21 patients in cases (21%) and 17 patients in controls (17%) were obese (BMI ≥30) respectively. Mean BMI in cases was 24.95kg/m2 and in controls was 25.69kg/m2. The difference in pattern of distribution of BMI among patients undergoing study was found to be non significant.

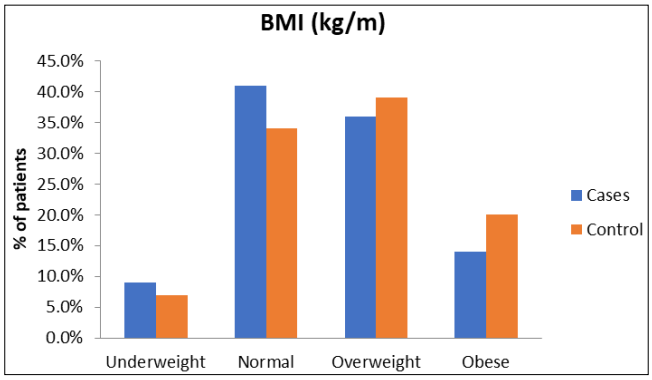

Fig 4

Table 4: Distribution according to Exposure to sunlight

Exposure to sunlight	No. of Patients	
	Group A Cases	Group B Control
1-2 hrs	42	33
2-3 hrs	24	38
3-4 hrs	23	21
4-5 hrs	11	08
p-value	0.030 (highly significant)	

Considering distribution of patients undergoing study according to Sunlight exposure, 55 patients in cases (55%) and 45 patients in controls (45%) had a sun exposure of 2-3 hours respectively whereas 21 patients in cases (21%) and 32 patients in controls (32%) has a sun exposure of 3-4 hours respectively. 19 patients in cases (19%) and 15 patients in controls (15%) had a sun exposure of 1-2 hours respectively whereas 5 patients in cases (5%) and 18 patients in controls (18%) has a sun exposure of 4-5 hours respectively. The difference in pattern of distribution according to sun exposure among patients undergoing study was found to be highly significant (p value=0.030)

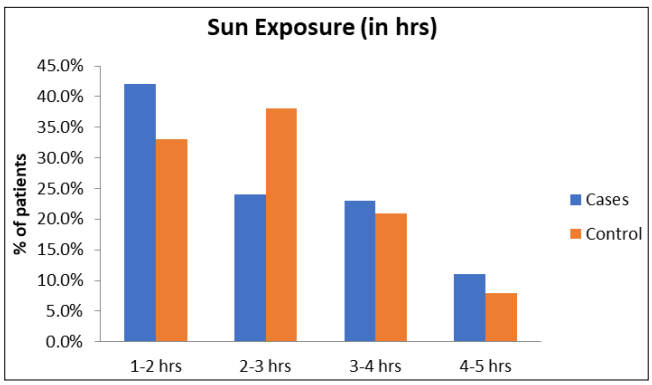

Fig 5

Table 5: Relation of sunlight exposure with vitamin D levels in Cases (with Uterine Leiomyoma)

Sunlight exposure	Vitamin D		Statistical inference (Unpaired t test)
	Mean	SD	
<3 hours (n=55)	8.74	4.57	t=1.38, p=0.17 (not significant)
≥3 hour (n=19)	10.22	5.39	

Considering the relation of sunlight exposure with vitamin D levels in Cases, mean vitamin D level in women with sunlight exposure <3 hours was 8.74 ng/mL, while those with sunlight exposure ≥3 hours was 10.22 ng/mL. The difference in mean vitamin D level was observed to be 1.48ng/ml. The difference in pattern of distribution according sunlight exposure with vitamin D levels among patients undergoing study was found to be statistically non significant (p value =0.17)

Table 6: Distribution according to family history of fibroid in first degree relatives

Family history	No. of Patients	
	Group A Case	Group BControl
present	52	42
absent	48	58
p-value	0.154(not significant)	

52 patients in cases (52%) and 42 patients in controls (42%) had a positive family history of fibrios in first degree relatives respectively family history of fibroid in first degree relatives, 52 patients in cases (52%) and 42 patients in controls (42%) had a positive family history of fibroid first degree relatives respectively whereas 48 patients in cases (48%) and 58 patients in controls (58%) had no family history of fibroid. The difference in pattern of distribution according to family history of fibroid in first degree relatives among patients undergoing study was found to be statistically not significant (p value=0.154).

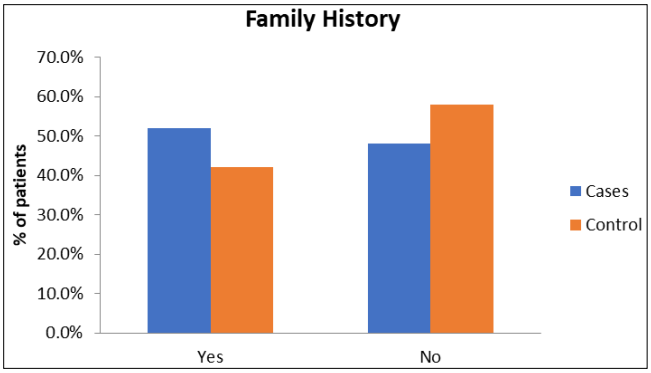

Fig 6

Table 7: Comparison of Cases and Controls according to Vitamin D levels

Vitamin D levels (ng/mL)	Cases		Controls		Statistical inference (Fisher's exact test)
	No.	%	No.	%	
<20(deficiency)	53	53.00	26	26.00	P value =0.0001 (highly significant)
20 – 29.9 (insufficiency)	25	25.00	32	33.00	0.271
≥30 (SUFFICIENT)	22	22.00	42	42.00	0.002(highly significant)
Total	100	100.00	100	100.00	–
Mean vitamin D ± SD (Range) ng/mL	9.81 ± 5.19 (2.4 – 24.4)		21.11 ± 8.30 (7.3 – 52)		–

Considering the distribution of patients undergoing study according to vitamin D levels, 53 patients in cases (53%) and 26 patients in controls (26%) had vitamin D deficiency (< 20) respectively (p=0.0001 highly significant) whereas 25 patients in cases (25%) and 32 patients in controls (32%) had vitamin D insufficiency (20 – 29.9) respectively (p=0.271) and 22 patients in cases (22%) and 42 patients in controls (42%) had sufficient vitamin D levels (≥30)(p=0.002 highly significant).

Mean vitamin D level in Cases was 9.81ng/mL while in Controls it was 21.11 ng/mL, the difference being statistically highly significant (p<0.0001).

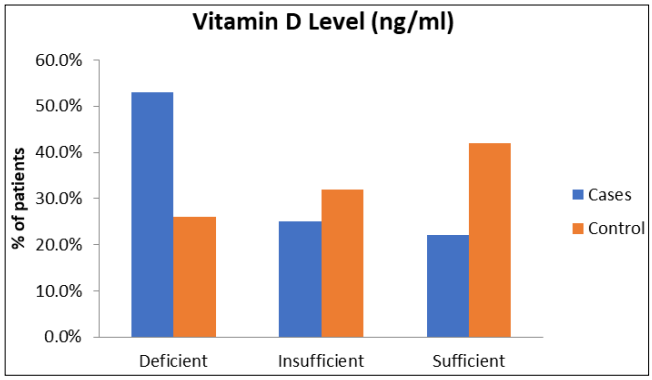

Fig 7

Conclusions

All the participants included in the study were subjected to detailed history, general and systemic examination. The following observation was made:

- Maximum women were in the age group of 39-48 years in Cases (65%) as well as in Controls (52%). Mean age of Cases (42.43 years) and Controls (42.24 years) was comparable in the study.
- There were more women with nulliparity in Cases (48%) compared to Controls (29%), the difference being statistically significant (p value=0.005)
- Number of women with normal BMI (18.5-24.9 kg/m2) in Cases was 30%, while in Controls it was 40%, while number of underweight women (<18.5 kg/m2) in Cases was 11% compared to only 9% in Controls. However, the difference between the two was statistically not significant.
- More women were from rural areas in both Cases (65%) and Controls (71%), the difference being statistically not significant (p=0.363).
- In cases vitamin D was higher in patients residing in urban areas (10.83 ± 5.26 ng/ml) as compared to rural areas (9.26 ± 5.12 ng/ml), while as in controls, it was higher in rural areas (22.16 ± 8.04 ng/ml) as compared to urban areas (18.54 ± 8.53 ng/ml). The differences in vitamin D status between cases and control with regard to residence was found significant. (p value <0.0001)
- Sunlight exposure was <3 hours in 74% women in Cases and 60% in Controls respectively, the difference being statistically not significant (p=0.030).
- In Cases, mean vitamin D level in women with sunlight exposure <3 hours was 8.74 ng/mL, while those with sunlight exposure >3 hours was 10.22 ng/mL. The difference in mean vitamin D level was observed to be 1.48ng/ml.

- Major history of obstetrics complications in women with uterine fibroids were postpartum hemorrhage (25%) followed by preterm labour (22%) and recurrent miscarriage (11%). P value for preterm births in both cases and controls is 0.019 (highly significant).
- Fifty three percent (53%) Cases and 26% Controls were found to be Vitamin D deficient (<20 ng/mL), the difference being statistically highly significant (p=0.0001 highly significant). 25% Cases and 32% Controls reported Vitamin D insufficiency (20-29.9 ng/mL), the difference being statistically not significant (p=0.271). 42% Controls were found to have normal Vitamin D level (>30 ng/mL) compared to 22% in Cases, the difference being statistically highly significant (p<0.002).
- Mean vitamin D level in Cases was 9.81ng/mL while in Controls it was 21.11 ng/mL, the difference being statistically highly significant (p<0.0001).
- History of myomectomy in past were reported in 36% Cases and 22% in Controls, the difference however was statistically significant (p=0.029).

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