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Original Research

Low Serum Level of Vitamin D is Associated with Uterine Leiomyoma in the Chinese Population

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Abstract

Background: The goal of this work was to compare the serum vitamin D level in women with uterine leiomyoma to that of controls, and to examine its association with the etiopathogenesis of this disease. **Methods**: This case-control study included 110 premenopausal women referred to a university hospital from January 2020 to December 2020. The study group consisted of 55 cases who underwent surgery for uterine fibroids, while the control group was comprised of 55 subjects without uterine fibroids. The number and volume of existing fibroids in each subject was assessed by transvaginal ultrasonography. Serum vitamin D status was determined by radioimmunoassay for 25-hydroxyvitamin D. **Results**: Average serum 25-hydroxyvitamin D levels in patients with uterine fibroids (20.52 $\pm$ 6.17 ng/mL) were significantly lower than in controls (24.18 $\pm$ 6.88 ng/mL; $p = 0.004$). Deficiency in 25-hydroxyvitamin D (*i.e.*, <20 ng/mL) was more frequent in women with uterine fibroids (28/55, 50.91%) compared to controls (13/55, 23.64%; $p = 0.001$). A trend for negative correlation was found between serum 25-hydroxyvitamin D levels and total uterine fibroid volume (r = –0.18) in the study group ($p = 0.20$). No significant associations were found between serum 25-hydroxyvitamin D level and the number of fibroids ($p = 0.38$) or their location ($p = 0.89$). **Conclusions**: The serum vitamin D concentration is lower in Chinese women with uterine leiomyomas compared to controls. Vitamin D deficiency could therefore be a risk factor for uterine leiomyoma in the Chinese population.

Keywords: serum 25-hydroxyvitamin D level; uterine leiomyomas; occurrence; Chinese population

1. Introduction

Uterine leiomyoma develops primarily from uterine smooth muscle cells and is the most frequent benign tumor in the female reproductive system. Although most women with uterine leiomyomas have no symptoms, some present with a range of symptoms that may include abnormal uterine bleeding, changes in menstruation, anemia, infertility, obstetric complications, and gastric disorders such as bloating and constipation [1,2]. Estimates of the prevalence of uterine leiomyomas range from as low as 5% to as high as 69% [3]. Their prevalence is around 70% by the age of 50 years, and up to 80% in African Americans [4,5]. Symptomatic uterine leiomyomas generate enormous medical and economic burdens and are the major reason for hysterectomy in the USA [6]. Moreover, the financial burden of uterine leiomyoma in the USA is estimated to be 34 billion dollars annually. This includes direct costs associated with medications and surgery, and indirect costs due to absence from work, related gynecological visits, and diagnostic tests [7]. Risk factors for uterine fibroids are thought to be estrogen, progestogen and ethnicity. However, the full etiology of leiomyoma is not yet known [3,8].

Vitamin D group members are fat-soluble steroid compounds consisting of two main groups of highly lipophilic substances: Calcitriol, also referred to as vitamin D3, and Ergocalciferol, which is also known as vitamin D2. Vitamin D undergoes metabolization in the liver and kidney where it is eventually converted to biologically active 1,25-dihydroxyvitamin D3 (1,25 (OH) 2D3). This binds to vitamin D receptor (VDR), which then activates vitamin D response elements in the promoter and regulatory regions of its target genes. The major physiological roles of vitamin D are regulation of calcium and phosphorus homeostasis in bone, intestine, parathyroid and kidney tissues [9]. Several recent studies reported that low serum levels of vitamin D correlated negatively with the presence of leiomyoma in various ethnic groups, indicating that vitamin D deficiency could be a risk factor for uterine leiomyomas [10,11]. Another study found that fibroid tumor size was significantly reduced by 1,25-dihydroxyvitamin D3, suggesting that paricalcitol could be effective and safe for treating uterine fibroids [12]. Most of the studies published to date on vitamin D and uterine leiomyomas have been from western countries, and there are still no firm conclusions regarding the correlation between serum vitamin D levels and this tumor type.

We previously reported that VDR expression was significantly lower in uterine leiomyoma tissue compared to healthy uterine smooth muscle tissue [13]. Based on this observation, we speculated that reduced VDR expression

may contribute to the pathogenesis of uterine leiomyoma. However, the serum level of vitamin D in Asian women with this disease is currently unknown. Therefore, in the current work we compared serum vitamin D levels between women with and without uterine fibroids in a Chinese population. We also explored whether a low vitamin D concentration is a risk factor for the etiopathogenesis of uterine leiomyoma.

2. Methods

2.1 Subjects and Study Procedure

Women participating in this case-control study were referred to our department from January 2020 to December 2020. The ethics committee from the first affiliated hospital, Nanchang University, granted approval (CDYFYYLK2021-9-022). Written informed consent was obtained from eligible participants before entering the study.

Female participants were of reproductive age, had symptomatic uterine leiomyomas, and were scheduled to undergo laparoscopic hysterectomy or myomectomy surgery. All underwent a transvaginal ultrasound scan. The study group was defined as patients with more than one fibroid lesion of $\geq$2 cm^3 in volume. The control group was premenopausal women without uterine fibroids who were hospitalized in the same time period. The study and control groups were matched for age and BMI (Body Mass Index) parameters. The exclusion criteria were: women with a history of taking vitamin D or similar drugs within 3 months of hospitalization, history of malignant tumor, multiple sclerosis, autoimmune disease, hepatitis disease, current pregnancy or pregnancy within previous 6 months, currently lactating or lactating within previous 6 months, abortion within 6 months of starting the study, hormone therapy (including oral contraceptives) within 3 months, and history of myoma surgery [14,15].

The number and size of uterine leiomyomas was evaluated using transvaginal ultrasound. Lesion volume was calculated using the formula (a $\times$ b $\times$ c $\times$ 0.523), whereby a = length, b = width, and c = height [14]. Each leiomyoma was classified according to its location as submucosal, intramural, or subserosal. A pre-operative blood sample was obtained from each patient and the concentration of serum 25-hydroxyvitamin D determined by radioimmunoassay according to instructions from the Iodine [125I] 25-hydroxyvitamin D Radioimmunoassay Kit (NO. XF00983B, Shanghai Xinfan Biotechnology Co., Ltd., Shanghai, China). The serum samples and the standard references from the kit were treated with alkaline solution and neutralized with acid. The mixtures were then added to a defined amount of 125I-25 hydroxyvitamin D and binding protein, and stored at 37 °C for 30 minutes to allow competitive binding. Activated carbon was then added, followed by centrifugation, discarding of the supernatant, and measurement of the precipitated radioactivity. The combination rate for each reference tube was calculated to produce a standard curve. Finally, the concentration of 25-hydroxyitamin D in each sample was determined by referring to the standard curve. Based on results from blind replicates, intra- and inter-assay coefficient of variation was determined to be 8.0% and 8.8%, respectively. The vitamin D status of each patient was assigned to one of three groups: deficient ($\leq$20 ng/mL), insufficient (21–29 ng/mL), and sufficient ($\geq$30 ng/mL) [16]. The following information was obtained from hospital medical records: age, BMI, ethnic origin, clinical history, fibroid size and volume.

In a preliminary study, the average serum 25-hydroxyvitamin D level was 20.23 $\pm$ 5.42 ng/mL in the uterine leiomyoma group and 22.74 $\pm$ 3.19 ng/mL in controls. The required sample size was determined using a formula for the comparison of two groups [17]. The minimum sample size needed for the study was 50, but this was eventually increased to 55 to improve the statistical power.

2.2 Statistical Analysis

Statistical analysis was performed using SPSS 22.0 software (IBM Corp., Armonk, NY, USA). Differences in baseline characteristics and in the mean serum vitamin D level between women with uterine leiomyomas and those without (controls) were evaluated with the independent sample *t*-test or Fisher's test, respectively. The difference in 25-hydroxyvitamin D deficiency between the two groups was analyzed using the Cochran-Mantel-Haenszel test. Correlations between vitamin D level and total fibroid volume, fibroid number and fibroid location were evaluated using the Pearson correlation test and analysis of variance. Predictors of uterine fibroids were determined using a logistic regression model. $p < 0.05$ was considered to represent a statistically significant result.

3. Results

3.1 Baseline Characteristics of the Study Population

In total, 55 women with uterine leiomyomas and 55 without leiomyomas participated in the study. All subjects were from the Han race. The mean patient age in the leiomyoma group was 45.42 $\pm$ 4.95 years (range 33 to 51 years), while in the control group it was 43.84 $\pm$ 7.22 years (range 18 to 54 years). The difference in age between these groups did not reach significance (p = 0.18). Furthermore, no significant difference was apparent for either BMI (p = 0.45) or medical history (p = 1) (Table 1).

3.2 Serum 25-Hydroxyvitamin D and Uterine Leiomyoma

The serum 25-hydroxyvitamin D level of women with leiomyomas was 20.52 $\pm$ 6.17 ng/mL, while that of women in the control group was 24.18 $\pm$ 6.88 ng/mL (p = 0.004). Together with previous findings [10,11], this result suggests vitamin D deficiency may correlate with the presence of uterine leiomyoma. Deficiency was significantly more frequent in women with leiomyoma (28/55, 50.91%) than in

Table 1. Baseline characteristics of study population.

Parameter	Leiomyoma group (n = 55)	Control group (n = 55)	*p* value
Age (yrs)	45.42 ± 4.95	43.84 ± 7.22	0.18
BMI	23.24 ± 2.27	23.56 ± 2.18	0.45
Medical history			1
Diabetes	0 (0.00)	1 (1.82)	
Hypertension	4 (7.27)	4 (7.27)	
None	51 (92.73)	50 (90.91)	

Data are shown as mean ± SD, or as a number (percent of total). *p* values were determined using an independent sample *t*-test or Fisher's test, respectively.

those without (13/55, 23.64%; $p < 0.05$; Table 2).

3.3 Serum 25-Hydroxyvitamin D Level as a Predictor of Uterine Leiomyoma

To further examine whether vitamin D correlates with uterine leiomyoma, the factors of patient age, BMI, medical history and serum vitamin D level were entered into a multiple logistic regression model. Vitamin D was the only factor found to be significantly associated with uterine leiomyomas (Table 3). The model also showed that an increase of one unit in the vitamin D concentration reduced the risk of uterine fibroids by 10% (OR (odds ratio) = 0.90, 95% CI (confidence interval) = 0.84–0.98). The total volume of leiomyomas in women from the leiomyoma group ranged from 6.92 cm^3 to 753.07 cm^3, with 16 women having multiple leiomyomas and 39 having a single leiomyoma. The location of leiomyomas was submucosal in 5 women (9.1%), intramural in 48 women (87.3%), and subserosal in 2 women (3.6%). In the leiomyoma group, vitamin D levels showed a trend for negative correlation with total uterine fibroid volume (r = –0.18, $p = 0.20$). No significant correlations were observed between serum 25-hydroxyvitamin D levels and either the number ($p = 0.38$) or location ($p = 0.89$) of fibroids.

4. Discussion

Vitamin D can inhibit cell proliferation and angiogenesis, as well as inducing cell differentiation and apoptosis [18]. As reviewed recently [19], current data suggests that vitamin D supplementation may reduce cancer incidence. Low serum vitamin D levels have been reported in several gynecologic and obstetric abnormalities, such as infertility, polycystic ovary syndrome and premature delivery [20]. Low vitamin D levels may also be involved with the etiology of leiomyoma [21,22], since reports show that deficiency correlates with the development of uterine leiomyoma [11,23–25], whereas sufficiency correlate with less risk of developing fibroids [26]. A 2013 Italian case-control study [11] found that vitamin D levels were significantly lower in 128 cases with leiomyoma compared to 256 controls ($p = 0.010$). Moreover, the percentage of cases with a deficiency (<10 ng/mL) was higher in patients with leiomyoma than in controls ($p = 0.022$). The OR for development of leiomyomas in subjects with a deficiency was 2.4 (95% CI: 1.2–4.9; $p = 0.016$), and hence the conclusion reached in the Italian study was that low serum vitamin D correlated with the presence of uterine leiomyoma [11]. More recently, a cross-control study from north India [14] investigated 102 premenopausal women with uterine fibroids and 208 with normal morphology. This study also found a significantly lower vitamin D concentration in patients with fibroids compared to those without ($p < 0.05$). Moreover, deficiency (<10 ng/mL) was more common in patients with fibroids, whereas sufficiency (≥20 ng/mL) was more frequently observed in controls ($p < 0.05$). In contrast, the National Health and Nutrition Examination Survey (2001–2006) of 3590 women reported no significant correlation between serum vitamin D and the presence of uterine leiomyoma [27]. Discrepancies with previous results may be explained by the different methodology used. Currently there is no consensus for defining vitamin D deficiency [28,29]. In the present investigation, vitamin D status was separated into three groups: deficient (≤20 ng/mL), insufficient (21–29 ng/mL), and sufficient (≥30 ng/mL), as per Endocrine Society guidelines from 2011 [16]. The 25-hydroxyvitamin D concentration in patients with uterine fibroids was significantly lower (20.52 ± 6.17 ng/mL) than that of women in the control group (24.18 ± 6.88 ng/mL; $p = 0.004$), while the proportion with 25-hydroxyvitamin D deficiency was higher (50.91% *vs.* 23.64%, respectively; $p = 0.001$). These results concur with the findings of previous studies [11,14,17,25].

To date, there are no firm conclusions regarding possible correlations between serum vitamin D and the volume and location of uterine leiomyomas. Among women with three or more leiomyomas in the report by Paffoni *et al.* [11], 7 (37%) were 25-hydroxyvitamin D3 deficient and 21 (19%) were not ($p = 0.08$). Moreover, these workers found no associations between 25-hydroxyvitamin D3 deficiency and the dimension, location and number of leiomyomas. Several other studies also reported no correlations between serum vitamin D concentrations and location, size, volume and number of uterine leiomyomas [24,25,30]. One study found a trend for lower serum vitamin D levels in patients with >3 fibroids compared to those with <3 fibroids ($p = 0.26$) [25]. Other workers have reported a negative association between vitamin D concentrations and total leiomyoma volume, with larger volumes correlating with lower levels, and vice versa [10,14]. It is also worth noting that differences can occur in serum vitamin D levels between different races. For example, African-American women have more frequent vitamin D deficiency due to increased amounts of skin melanin (leading to lower vitamin D production) and less dairy consumption (because of lactose intolerance). A negative correlation has been reported between serum vitamin D level and the volume of fibroids in black patients (r

Table 2. Serum vitamin D status in the leiomyoma and control groups.

Parameter	Leiomyoma (n = 55)	Controls (n = 55)	*p* value
Vitamin D mean ± SD (ng/mL)	20.52 ± 6.17	24.18 ± 6.88	0.004
Vitamin D status			0.001
Deficient	28 (50.91)	13 (23.64)	
Insufficient	25 (45.45)	34 (61.82)	
Sufficient	2 (3.64)	8 (14.55)	

Data are presented as the mean ± SD for vitamin D level, or as a number (percent of total) for vitamin D status. *p* values were calculated using an independent sample *t*-test or Cochran-Mantel-Haenszel test, respectively.

Table 3. Adjusted odds ratio for predictors of uterine leiomyomas identified using a multiple logistic regression model.

Parameter	Estimate	Adjusted OR	95% CI	*p* value
Age	0.06	1.06	(0.98, 1.15)	0.13
BMI	–0.10	0.90	(0.73, 1.11)	0.33
Medical history (Yes *vs.* No)	–0.25	0.78	(0.15, 4.16)	0.77
Vitamin D	–0.10	0.90	(0.84, 0.98)	0.01

OR, Odds ratio; CI, Confidence interval.

= –0.42, $p = 0.001$), but this was not observed in white patients (r = –0.86, $p = 0.58$) [10]. In the present work, a negative association was found between the 25-hydroxyvitamin D level and volume of uterine fibroids (r = –0.18, $p = 0.20$) in women with leiomyoma, but this was not statistically significant. Furthermore, no significant associations were found between serum 25-hydroxyvitamin D and the number ($p = 0.38$) or location of fibroids ($p = 0.89$). Additional investigations using larger cohorts are therefore required to clarify relationships between vitamin D and the load and location of uterine leiomyomas.

An early study on vitamin D treatment of uterine fibroids reported that Calcitriol showed dose-dependent inhibition of leiomyoma and myometrial cells [31]. This work stimulated further research into the possible inhibitory effect of vitamin D on leiomyomas [9]. Vitamin D can inhibit the proliferation of human uterine leiomyoma cells by decreasing the expression of cell proliferation nuclear antigen, Bcl-w, catechol-O-methyltransferase and cyclin-dependent kinase 1 [32]. It can also do this by inhibiting the Wnt/β-catenin and TGFβ pathways to reduce cell proliferation and the synthesis of extracellular matrix [33]. Animal work has shown that vitamin D can reduce the size of uterine fibroids in a murine model, and may therefore be a novel therapeutic approach to prevent the development of uterine fibroids [12,34,35]. These results support the idea that vitamin D could be used in non-surgical management of uterine leiomyoma. The results from several clinical studies suggest that vitamin D supplementation can reduce leiomyoma-related symptoms and stabilize the volume of uterine leiomyoma [15,36,37]. However, the data showing clinical benefit is still quite limited and preliminary in nature because of the small sample size of most studies so far.

There has been very little research on vitamin D and its possible association with uterine leiomyoma in the Chinese population. This study found that Chinese patients with uterine fibroids had significantly decreased serum 25-hydroxyvitamin D levels compared to those without. However, there were several limitations to this case-control study. First, it was an observational rather than prospective and randomized controlled study. Second, the study had a relatively sample size. Finally, the study was not completely representative of women with uterine leiomyomas because it was hospital-based. More large, prospective and population-based cohort studies are warranted to confirm the association between serum vitamin D levels and uterine leiomyomas.

5. Conclusions

In conclusion, the level of serum vitamin D was found to be lower in Chinese patients with uterine leiomyomas compared to those without, indicating that its deficiency may be a risk factor for this disease.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Author Contributions

Conception and design—FL; Administrative support—FL, XC; Provision of study materials or patients—ZS, XT, JY; Collection and assembly of data—XC, FY, ZS, XT; Data analysis and interpretation—FY, FL; Manuscript writing—XC, FY, ZS, XT, JY, FL; Final approval of manuscript—XC, FY, ZS, XT, JY, FL.

Ethics Approval and Consent to Participate

The study was approved by institutional review board of the first affiliated hospital of Nanchang University

(CDYFYYLK2021-9-022). Written informed consent was signed by eligible subjects before taking part in the study.

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Conflict of Interest

The authors declare no conflict of interest.

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