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Vitamin D deficiency in women with uterine fibroids versus Vitamin D deficiency in the general population

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Abstract

Introduction: To estimate the prevalence of vitamin D deficiency in women with leiomyomas compared to that of the general population.

Materials/Methods: Cross-sectional study from a single high volume Surgeon's office Vitamin D levels in women with MRI or ultrasound documented uterine fibroids who came to one surgeon's office for follow up or initial visit June 2012 to September 2012. The data was analyzed in 2017. The women were compared to the vitamin D status of the U.S. population according to the National Health and Nutrition Examination Surveys.

Results: The prevalence of vitamin D deficiency in women with uterine fibroids was 85% compared to the prevalence of vitamin D deficiency in the general population of the United States which was 8%.

Conclusion: Women with uterine fibroids are more likely than the general population to be deficient in vitamin D indicating that vitamin D deficiency may serve as a risk factor for fibroid growth and development.

Introduction

Uterine fibroids, or leiomyomas are the most common benign tumors of the female reproductive tract, affecting up to 80% of American women [1]. with only 25% of women who are symptomatic. Symptoms do not always correlate with the size, number, or location of the fibroids [1,2].

For a long time, fibroid development and growth has been associated with hormones, namely estrogen and progesterone [3,4]. Unfortunately, treatments that interfere with estrogen have proven to be more effective in animal models than in humans [1].

In 2009, Blauer, Rovio, Ylikomi, and Heinonen, looked at vitamin D and its effect on myometrial and fibroid cell proliferation in vitro. They found that when treated with a physiologic concentration of vitamin D, both normal myometrial and fibroid cell growth was significantly suppressed [5]. Taking this vitamin D theory steps further, Halder, Sharan, and Al-Hendy found that treatment with 1.25-dihydroyvitamin D3 significantly decreased uterine fibroid tumor volumes [6].

While there is a plethora of research looking at the therapeutic mechanisms of vitamin D there have been no clinical studies evaluating the frequency of vitamin D deficiency in women with uterine fibroids compared to the general population. The overall goal of this cross-sectional analysis was to estimate the prevalence of vitamin D deficiency in women with uterine fibroids and to compare them to the general population.

Materials/Methods

This is a cross sectional analysis. Eligible patients presented to the office, as either follow-up or initial visits with MRI or ultrasound confirmed fibroids from June 2012 to September 2012, and analyzed in 2017. During the visit, patients were informed of the new evidence that vitamin D might play a role in uterine fibroid regulation and were given the option of having their 25 (OH) vitamin D levels checked. Charts (electronic) were then extracted and reviewed.

Demographic data was collected including age, race, past medical history, and prior medical or surgical treatments for uterine fibroids. Additionally, in-office sonogram results were collected noting overall uterine size and largest fibroid size. Inclusion criteria were all women with documented uterine fibroids. Women were excluded with renal disease and or parathyroid disease.

Optimal level of vitamin D has been suggested to be over 30 ng/mL as such a level is associated with suppression of PTH (parathyroid hormone), decreased fracture rates, and overall improved health outcomes [7]. While the definition of Vitamin D deficiency tends to vary, we decided to utilize the 2011 Endocrine Society definition of vitamin D deficiency (<20ng/mL), and vitamin D insufficiency (21-29ng/mL) [8]. To assess the prevalence of vitamin D deficiency in the United States, we utilized data from the National Health and Nutrition Examination Survey (NHANES) from 2001-2006 [9]. According to NHANES, vitamin D deficiency is defined as 25(OH)D value less than 30nmol/L (equivalent to 12ng/mL).

Statistical Package for the Social Sciences was used for comparisons. P values of less than 0.05 were considered statistically significant. This study was approved by the Mount Sinai Hospital Institutional Review Board.

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Results

During the study period, we identified 52 patients who met the inclusion criteria. Out of 52 patients, 86.5% of the patients had vitamin D levels below 30nmol/L (vitamin D deficient according to NHANES). According to the definitions established by the 2011 Endocrine Society, 50% were deficient and 36.5% were insufficient. The mean vitamin D level was 23.3ng/mL.

According to the National Health and Nutrition Examination Surveys that looked at vitamin D levels in the United States population from 2001 to 2006, 8% of the general population was vitamin D deficient (25(OH)D levels below 30nmol/L). A study done in 2008 found approximately 41% of men and 53% of women in the United States have vitamin D levels below 28ng/mL [7]. In our study population, 85% percentage of people had vitamin D levels below 28ng/mL. A recent study by Forrest and Stuhldreher, which defines vitamin D deficiency as less than or equal to 20ng/mL, found the overall prevalence rate of vitamin D deficiency in the American population to be 41.6%, [10]. Additionally, Zhao, Ford, Tsai, Li, and Croft studied vitamin D deficiency and inadequacy, which they defined as less than 12ng/mL and less than 20ng/mL respectively, among women in the United States and found the mean 25 (OH) D concentration to be 24.1ng/mL with a prevalence of vitamin D deficiency of 11.1% and inadequacy was 25.7%. They also found the mean vitamin D concentration to be lowest among non-Hispanic black women and the prevalence of both vitamin D inadequacy and deficiency to be highest among non-Hispanic black women [11].

When compared to the prevalence of vitamin D deficiency in the general population, women with uterine fibroids have an increased prevalence of vitamin D deficiency across the board. They also have a mean 25 (OH) vitamin D of 23.3ng/ml, supporting the notion that low levels of vitamin D might serve as a potential risk factor for fibroid development and growth.

Discussion

Results from our study indicate that approximately 85% of women with documented uterine fibroids had 25(OH)D levels below the lower cutoff for normal range (<30ng/ml) and that women with fibroids have an increased prevalence of vitamin D deficiency when compared to the general population.

There has been ample research investigating the mechanisms by which vitamin D acts as a regulator of various diseases. The aforementioned Eker rat study utilized western blot and immunohistochemical analysis to uncover the cellular changes that vitamin D causes in uterine fibroids. They found that vitamin D reduced the level of PCNA (proliferating cell nuclear antigen), along with cell cycle regulatory proteins like CDK1, 2, and 4. PCNA aids in DNA synthesis and replication while CKD1, 2 and 4 are proteins that aid in cell cycle progression [6]. Reducing expression of such proteins is one explanation for vitamin D's antiproliferative effects on uterine fibroids.

The study also demonstrated that the addition of vitamin D reduced the levels of anti-apoptotic proteins, BCL2 and BCL2L1, and slightly increased the pro-apoptotic BAD protein and caspase 3 in uterine fibroids [6]. It is not surprising that an overall increase in pro-apoptotic proteins after treatment with vitamin D might also explain the inhibitory effects of vitamin D on cell growth.

Research has demonstrated that uterine leiomyomas have a tendency to over express cyclin D1, whose activity is required for cell cycle progression from G1 to S phase, along with an overexpression of proto-oncogene MYC that promotes cell proliferation and has been linked to various cancers. The Eker rat study noted that expression of both cyclin D1 and proto oncogene MYC were significantly reduced in the vitamin D treated uterine leiomyomas compared to the control group [6]. It is clear from the Eker rat study that vitamin D's potentially therapeutic effect on shrinking uterine fibroids might stem from its antiproliferative and pro apoptotic mechanisms.

The hormonal effects of estrogen and progesterone on uterine leiomyomas have long been established and are evidenced clinically by their shrinkage after menopause. The Eker rat study demonstrated that vitamin D treated fibroids exhibited reduced expression of Estrogen Receptor 1 (ESR1), Progesterone Receptor A (PGR-A), and Progesterone Receptor B (PGR-B) [6]. It is therefore possible that through this mechanism, vitamin D results in shrinkage of uterine fibroids.

Research has supported the notion that uterine fibroids contain increased mRNA and protein expression of catechol-O-methyltransferase, an enzyme involved in the biological estrogen pathway [12]. A study in January of 2011 found that not only did vitamin D inhibit the growth of human uterine leiomyoma cells by 47+/- .03% at 1 μM and by 38+/- .02% at .01μM compared to controls but also that it was through the mechanism of decreasing catechol-O-methyltransferase. While this study demonstrated that similar to previous studies; addition of vitamin D reduced expression of kinases, BCL-2, BCL-w, CDK1 and PCAN, by noting a decrease in catechol-O-methyltransferase with addition of vitamin D, suggests that the estrogen pathway might be the mechanism by which vitamin D inhibits fibroid growth [13,14].

Studies have demonstrated that uterine fibroids are characterized as having a large extracellular matrix composed of both collagen and fibronectin. Research has revealed that this is due to over-expression of collagen type 1 and fibronectin in uterine fibroids. When treated with vitamin D, however, western blot analysis demonstrated a 2-fold decrease in fibronectin and a 4-fold decrease in collagen type 1 expression in uterine fibroids, suggesting yet another mechanism by which vitamin D might serve to inhibit uterine fibroid growth. [15]

A recent study exposed mesenchymal multipotential cells to active vitamin D and found that the addition of vitamin D not only decreased expression of pro fibrotic factors like tgfb1 and plasminogen activator inhibiter along with expression of collagen I, III but also increased expression of antifibrotic factors like BMP7 a tgfb1 antagonist, MMP8 a collagen breakdown inducer and follistatin, an inhibitor of the profribtoc factor myostatin, further exemplifying the antiproliferative effects of vitamin D [14].

Another in vitro study looking at vitamin D and its antiproliferative effects found that, similar to that which was found in the Eker rat study, the addition of vitamin D leads to a reduction of cells in the S phase (DNA synthesis phase). Their study supported the notion that it is vitamin D's effect on cyclin dependent kinase inhibitors; p21 and p27 that inhibits cell growth [5].

As tgf β has been defined as one of the key players in the growth factor pathway of uterine fibroids, Halder, Goodwin, and Al-Hendy's study examined the effects of vitamin D on tgf β specifically in uterine cells. In their study, human uterine leiomyoma cells were treated with tgf β3 with or without vitamin D. It was found that the pro fibrotic and proliferative effects of tgf β on leiomyomas; induction of fibronectin and collagen type 1 progression, induction of plasminogen

activator inhibitor 1 protein expression, phoshporylation and nuclear translocation of tgf β cell signaling mediators SMAD2 and SMAD 3 were all significantly reduced when treated with vitamin D [15].

Conclusion

The vast array of mechanisms by which vitamin D regulates cell growth combined with the evidence that women with uterine fibroids have a higher prevalence of hypovitaminosis D than the general population emphasizes the need to evaluate the use of vitamin D as a non-invasive and potentially therapeutic option for fibroids. Currently, hysterectomy remains the main option for treatment of uterine fibroids. More than 600,000 hysterectomies are performed each year in the US, with fibroids being the most common indication for the procedure [6]. While surgical treatment for uterine fibroids is the mainstay, the associated risks of morbidity, mortality, and infertility cannot be overlooked and the need for a safe effective nonsurgical therapeutic strategy is critical.

While hypovitaminosis D might serve as a risk factor for uterine fibroids, research needs to be done to assess the use of vitamin D as a non-invasive and successful therapy to prevent leiomyoma growth in women.

Declarations

Leigh Rosen MD, Suzanne Fenske MD, Heather Isola RPA-C, Charles Ascher-Walsh MD attest that they have met all authorship criteria.

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The authors declare they have no competing interests.

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