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Vitamin D Status – A Clinical Review with Implications for the Pelvic Floor

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Abstract

Vitamin D is a micronutrient vital in calcium homeostasis and musculoskeletal health. Vitamin D insufficiency is a common variant of vitamin D deficiency which has clinical signs of rickets and osteomalacia. The clinical significance of vitamin D insufficiency is being explored in several medical conditions. However, the most robust work suggests a role in musculoskeletal disease. The pelvic floor is a unique part of the body whose function is dependent on interrelationships between muscle, nerve, connective tissue, and bone. Pelvic floor disorders result when these relationships are disrupted. This paper reviews current knowledge regarding insufficient vitamin D nutritional status, the importance of vitamin D in muscle function, and how insufficient or deficient vitamin D levels may play a role in the function of the female pelvic floor.

Keywords: pelvic floor disorders, urinary incontinence, vitamin D

INTRODUCTION

Vitamin D is one of the oldest hormones on earth and is vital to many different organisms. In humans, the role of vitamin D spans across many different organ systems. Vitamin D deficiency (serum level of 25-hydroxyvitamin D < 15 ng/ml) is known to cause osteoporosis, muscle weakness and pain, falls, and fractures, and has become a major public health problem. Vitamin D insufficiency (serum level of 25-hydroxyvitamin D < 30 ng/ml) is as a milder form of vitamin D deficiency with prevalence rates ranging from 38–73%.[1–6] It has few proven overt clinical characteristics, and its severity is determined by skin pigmentation, geographic location, and season. Poor vitamin D nutritional status affects people of all ages, but it is well known that older adults and chil-

dren have the greatest risk for severe consequences. The effects of vitamin D insufficiency are thought to be widespread affecting different organ systems. Many reports indicate that vitamin D has a role in the pathophysiology of some cancers, cardiovascular disease, and pregnancy morbidity. However, level I data confirm that there is a definitive impact of vitamin D concentration in musculoskeletal disease. Numerous skeletal muscle cell culture, animal, and human studies have confirmed that vitamin D affects muscle strength and function. Thus, it is biologically plausible that the vitamin D insufficiency/deficiency epidemic may have clinically significant consequences for the pelvic floor.

The female pelvic floor is a complex component of the body whose global function is reliant on delicate relationships between musculoskeletal connections to pelvic bones that support the abdominal cavity and pelvic viscera. Disorders of the pelvic floor include urinary incontinence (UI), fecal incontinence (FI), pelvic organ prolapse (POP), and other storage and emptying problems of the lower urinary and gastrointestinal tracts. Pelvic floor disorders are very common and increase in prevalence with age. Nygaard et al reported that 24% of US women ≥20 years of age had at least 1 pelvic floor disorder.[7] The prevalence of urinary incontinence varies by definition, but has been reported to range between 13–49%.[7,9–14] Among women aged 50–79 years included in the Women's Health Initiative study, reports indicate that 41% have pelvic organ prolapse.[9,15,16] The economic burden of pelvic floor disorders is projected to grow exponentially - by 2030 one fifth of US women will be over the age of 65 and one third of these women will have at least one pelvic floor disorder.[7,8]

In this clinical review, we surveyed literature that addressed the role of vitamin D in musculoskeletal health and obstetric morbidity to gain perspective on the potential role of insufficient vitamin D in the development and severity of pelvic floor disorders.

VITAMIN D AND OBSTETRIC AND OTHER MEDICAL CONDITIONS

Vitamin D is a lipid soluble micronutrient produced in the skin when provitamin D (7-dehydrocholesterol) in cell membranes is exposed to ultraviolet B rays and converted to cholecalciferol (D_3).[17] Circulating D_3 is then bound by vitamin D binding protein (DBP) and transported in serum to be stored in adipose tissue or delivered to the liver where it is converted to 25-hydroxyvitamin D_2 [25(OH)D]. This metabolite is then activated by conversion to calcitriol [1, 25-dihydroxyvitamin D (1, 25(OH) D_2] in the kidney. Synthesis of 25(OH) D and 1, 25(OH) D is coupled with calcium homeostasis. Serum levels of vitamin D are regulated by parathyroid hormone, phosphorus, and calcium levels. (Figure 1)

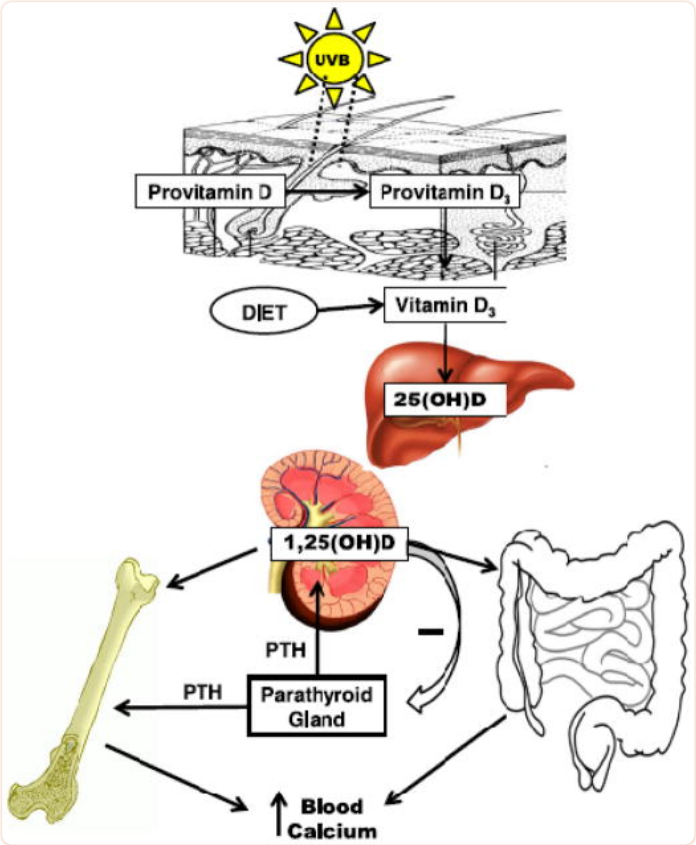

FIGURE 1

Vitamin D synthesis and metabolism. Vitamin D precursors are absorbed through the skin or provided through dietary supplementation. Vitamin D is hepatically metabolized and renally activated so that it may affect calcium homeostasis by targeting calcium deposition in bone and absorption in the bowel.

Observational studies have suggested that vitamin D insufficiency may be a factor in the pathophysiology of various cancers, cardiovascular disease, hypertension, diabetes, and obstetric morbidity. Data reported from the 2005–2006 NHANES survey showed that 69% of pregnant and 78% of non-pregnant US women had 25(OH)D <75nmol/L.[18] In pregnancy, the placenta is an extra renal source of calcitriol [1,25(OH)D_2]. The role of vitamin D in placental function has been characterized in translational studies in which vitamin D was shown to regulate inflammatory cytokine levels by modulating 1α hydroxylase and vitamin D receptor (VDR) activity.[19] When these two elements are removed from the trophoblastic cells of the placenta, interferon-gamma and interleukin expression is increased which represents increased inflammation. Thus, fetal trophoblastic vitamin D physiology is vital in placental inflammation.[19] Additionally, calcitriol inhibits TNF-α induced cytokine expression under the regulation of the VDR in trophoblasts.[20] Calcitriol also stimulates antioxidant gene expression in syncytiotrophoblast cells in a dose response, making it a potential target as a pharmacologic pro-oxidant.[21] The role of vitamin D in decreasing inflammation may be translated to a potential similar role in bladder wall pathophysiology associated with overactive bladder and cystitis.

Retrospective and observational studies have identified associations between decreased vitamin D intake, as well as low 25(OH)D concentration and cardiovascular disease, hypertension, and diabetes. However, cohort and randomized supplementation trials generally do not support such a relationship. This could be due to differences in the thresholds used for the definition of vitamin D insufficiency/deficiency. Additionally, the amount of vitamin D needed endogenously to make a clinical difference in these conditions is not understood. Thus these studies may be using doses of vitamin D supplementation that are insufficient for specific conditions.[22,23]

The primary source of vitamin D is sunlight exposure, as only 100 – 200 IU per day of vitamin D comes from fortified food sources. Vitamin D supplementation intake recommendations are controversial based upon the targeted condition. Randomized controlled trials that reported cardiovascular event rates as a secondary outcome used vitamin D_3 supplementation ranging from 400 – 1000 IU/d to up to 100,000 IU/4 months.[24–29] Pittas et al reviewed level I/II studies of vitamin D supplementation and diabetes-related outcomes. Randomized studies varied in the type and amount of vitamin D supplementation used. The majority of studies used vitamin D_3 with doses ranging from 400 – 4000 IU/d to 40,000 IU/week and 1000 IU once. These studies also revealed no significant differences in glycemia between the supplementation group and placebo ± calcium.[22,25,30–36]

To address the debate over how much vitamin D supplementation to recommend, the Institute of Medicine (IOM) published the 2011 report on dietary reference intakes for calcium and vitamin D. They concluded that, for optimization of bone health specifically, the recommended dietary allowance (RDA) of calcium for ≥97.5% of the population ranged from 700–1300mg/d depending on age. For vitamin D, the RDA for ≥97.5% of the population was 600 IU/day for ages 1–70 yrs, and 800 IU/day for those older than 71 years.[37] Nevertheless, there is ample evidence that vitamin D doses above these recommendations are well tolerated.

Due to the lack of convincing level I evidence, the IOM concluded that recommendations for vitamin D supplementation to address any other condition-specific goal must await larger epidemiologic or randomized studies. Despite this lack of evidence from randomized supplementation trials, many still believe there is a correlation between vitamin D and non-skeletal disease based on observational studies. The Vitamin D and Omega-3 trial (VITAL) initiated in 2011 is the first large-scale randomized clinical trial. This study aims to evaluate vitamin D for primary prevention of cancer and cardiovascular disease by comparing outcomes in healthy older men and women who receive either 2,000 IU/d of vitamin D_3 or placebo for 5 years (n=20,000).[38]

VITAMIN D AND MUSCLE PATHOPHYSIOLOGY

Due to the strong interrelationship between vitamin D and calcium, and the importance of calcium in muscle function, much is known regarding vitamin D and muscle physiology and function. In vitro skeletal muscle cell culture studies have demonstrated that vitamin D may affect muscle strength by influencing cell proliferation and differentiation and muscle fiber size. Vitamin D also protects against muscle degradation by preventing fatty degeneration, insulin resistance, and arachidonic acid mobilization.[39] Hence, vitamin D may play a role in the efficiency of muscle function that is distinct from the role of calcium in muscle contractility.

Vitamin D receptors are thought to be located in every cell type of the body. Bischoff et al demonstrated that the vitamin D receptors are present in skeletal muscle cells of their orthopedic patients independent of serum levels of vitamin D.[41] Immunohistochemical staining of the vitamin D receptor on muscle biopsies of women showed that the number of vitamin D receptors decrease with age. [41] Despite numerous reports of the vitamin D receptor on skeletal muscle, there is one notable study that argues the contrary. Wang et al studied all available vitamin D receptor antibodies and found that most cross reacted with proteins other than the vitamin D receptor, thus increasing the false-positive results. [42] Crescioli et al had previously shown that calcitriol ($1,25(OH)D_2$) and other analogs of vitamin D (BXL-253, BXL-628) modulated cell proliferation and apoptosis in vitro and in vivo from prostatic stromal cell cultures. [43]–[46]

They also demonstrated that the urothelial cells of the bladder neck have identical expression of the vitamin D receptors as the prostate. Thus the human bladder neck may be a target for vitamin D ligands.[47] Several clinical studies have confirmed the important role of vitamin D in muscle efficiency. (Table 1)

Table 1

Summary of pertinent clinical studies of vitamin D status and skeletal muscle

Clinical studies on vitamin D and skeletal muscle relationship				
Level I				
Study	Design	Aim	Interventions/measurements	Outcomes
Ward et al. [19]	Community-based, double- blind, randomized controlled trial in a secondary school *N*=69. Postmenarchal girls aged 12–14 years.	To determine the effect of vitamin D supplementation in the form of 150,000 IU/3 months for 1 year on the adolescent musculoskel et al system	Four doses of 150,000 IU vitamin D_2/1 year. Muscle function of lower limb and hand measured by jumping mechanography and grip strength, respectively.	The efficiency of movement improved 5% in girls with the lowest baseline 25(OH)D in the intervention group (p= 0.02). There were marginal increases in jump power and height, resulting in improved jump efficiency.
Zhu et al. [20]	Population-based, double-blind, randomized, controlled trial. *N*=302 community-dwelling ambulatory women aged 70–90, all with serum 25(OH)D<24 ng/ml	To evaluate the effect of vitamin D treatment on muscle strength/mobility in older vitamin D insufficient women	Vitamin D_2 1,000 IU/d vs. placebo, both groups received calcium citrate 1 g/day. Lower-limb muscle strength and mobility tested using the Timed Up-and-Go Test.	Vitamin D supplementation improved muscle function in women with weak and slow baseline muscle function in the lowest tertile.
Lips et al. [21]	Double-blind randomized controlled trial. *N*=226 community-dwelling	To examine the effects of a weekly dose of 8,400 IU Vitamin D_3 on postural stability, muscle strength,	Vitamin D_3 8,400 IU/week (*N*= 114) or placebo (*N*= 112). Postural stability and muscle strength measured by mediolateral body sway.	Treatment raised serum 25(OH) D concentrations but had no effect on mediolateral sway when compared to

The pelvic floor is a term that refers broadly to the complex structures of the bottom of the abdominal cavity. It is composed of peritoneum, viscera, endopelvic fascia, levator ani muscles, the perineal membrane, and external genital muscles.[57] The pelvic floor collaboratively functions to support the visceral contents of the abdominal cavity through sophisticated relationships between ligamentous connective tissue and skeletal muscles. Skeletal or smooth muscles are involved in the function and support of all pelvic viscera. While the etiology of pelvic organ prolapse and other pelvic floor disorders is multi-factorial, it is postulated that muscle weakness, neurologic compromise, and fascial detachment significantly contribute to the loss of support of pelvic floor viscera resulting in prolapse and incontinence.

The female lower urinary tract consists of the bladder and urethra. Together, they function to store and empty urine. The female continence mechanism is determined by proper function and communication between the central and peripheral nervous systems, urothelium, detrusor muscle layers of the bladder wall, smooth and skeletal musculature of the urethra, and pelvic floor musculature. Urinary incontinence is the most prevalent pelvic floor disorder. The two predominant types are stress urinary incontinence (SUI) and urgency urinary incontinence (UUI). Stress urinary incontinence occurs when increases in intraabdominal pressure is transmitted to the bladder coupled with urethral sphincter insufficiency and occurs with activities such as coughing, laughing, sneezing, and running. It can also occur with slight changes in body position, bending, and lifting. Urgency urinary incontinence (UUI) occurs when sudden bladder contractions result in a strong sense of urinary urgency often associated with an involuntary bladder contraction that is unable to be controlled, resulting in urinary leakage.

The etiology of stress urinary incontinence may in part be explained by the “Hammock hypothesis” which illustrates that the urethra and bladder rest on the anterior vaginal wall which has fascial connections to the levator ani muscles through the arcus tendineus fasciae pelvis. When these supportive connections are weakened, the urethra loses the hammock-like support that facilitates compression and closure of the urethra with increases in intraabdominal pressure.[58] This in turn results in involuntary loss of urine. Childbirth and other types of injury to the pelvic floor can cause muscle and or nerve damage, making the continence system more dependent on the support of the levator ani muscles and external urethral sphincter muscles. Both are striated skeletal muscle whose cell nuclei likely contain the vitamin D receptor. A weakened external urethral sphincter muscle would be less able to prevent urine loss by constricting the urethra voluntarily during times of increased abdominal pressure or with involuntary detrusor contraction. Pelvic floor muscle weakness occurs in many women who lack awareness and coordination of these muscles and is worsened with nerve damage and aging. Thus, pelvic floor muscle training is the basis of behavioral treatment for SUI and UUI.

Many studies have demonstrated a correlation between skeletal muscle weakness and low vitamin D concentrations. Deficient and insufficient 25(OH)D concentrations may also contribute to pelvic floor muscle weakness and predispose women to incontinence. However, few observational studies exist that have investigated the relationship between pelvic floor disorders and 25(OH)D nutritional status.

Urgency urinary incontinence is a urinary storage symptom that can result from a neurologic abnormality, bladder outlet obstruction, bladder wall inflammation, or may be idiopathic. In vivo studies have demonstrated that the vitamin D receptor is found in the bladder neck which consists of the urothelium and the inner longitudinal, middle circular, and outer longitudinal smooth muscle layers of the bladder wall.[47] For that reason, it is likely that vitamin D receptors may be distributed throughout the bladder wall. Since the active metabolite [1,25(OH)D_2] acts through the vitamin D receptor, vitamin D deficiency or insufficiency may result in abnormalities in calcium homeostasis with ensuing abnormal detrusor contractility. Weakened detrusor muscles may also become hyper-contractile or irritable similar to what is seen in hypocalcemic skeletal muscle function. Additionally, insufficient serum 25(OH)D may also affect the urothelium by allowing for more inflammatory cytokine activity with resultant bladder wall inflammation.

Dallosso et al hypothesized that there was a relationship between nutrient composition of the diet and the development of overactive bladder in women. As a component of the Leicestershire MRC Incontinence Study on the prevalence and incidence of incontinence and other lower urinary tract symptoms, a prospective cohort study was conducted with community dwelling women. These women were mailed baseline questionnaires to assess urinary symptoms and vitamin D intake. Symptoms of overactive bladder (OAB) were assessed with a questionnaire developed for this study modeled after the International Continence Society's standards for the diagnosis of OAB. Vitamin D intake was assessed using a food frequency questionnaire. This was the first study to demonstrate an association between vitamin D nutritional status and pelvic floor disorders.[59] (Table 2)

Table 2

Studies of vitamin D nutritional status and pelvic floor symptoms

Reference	Classification	Sample	No. description	Demographic features	Incidence of vitamin D insufficiency/deficiency	Me ng/
Dalloss et al. [57]	Prospective cohort	Leicestershire MRC Incontinence Study	*N*=6,371 community-dwelling women age ≥40 years completed UI symptom and food frequency questionnaires at baseline at 1 year later	Baseline OAB: 15.9% (incidence increased with age: from 12% (<50 years) – 26% (>80 years)	Not applicable	Not
Badalian et al. [58]	Cross-sectional	2005–2006 NHANES cohort	*N*= 1,881 women with data on PFD symptoms and serum 25(OH)D measurements	Mean age: 47.9 (46.4–49.6) years. 35% with BMI > 30	82%. [insufficient 25(OH)D <30 ng/ml]	21. 22.

UI urinary incontinence, *BAI* body mass index, *NHANES* National Health and Nutrition Examination Survey, *OAB* overactive bladder, *PFD* pelvic floor disorder, *OR* odds ratio, *CI* confidence interval

Badalian and colleagues examined the relationship between pelvic floor disorders and 25(OH)D concentration in 1,881 US women. In this study, UI was defined by the Incontinence Severity Index which is a 2 question derivative from the Incontinence Impact Questionnaire (IIQ). A score of greater than three defined the presence of urinary incontinence.[7] Fecal incontinence was defined as having at least one episode of leakage of stool monthly. Serum 25(OH)D was measured using the Diasorin's radioimmunoassay method. Vitamin D deficiency and insufficiency were defined as 25(OH)D concentrations <10ng/ml and <30ng/ml, respectively. The prevalence of UI and greater than one pelvic floor disorder was significantly higher in women with vitamin D insufficiency. A similar trend was seen for fecal incontinence, but the difference was not statistically significant.[60] (Table 2)

Prospective cohort or randomized studies investigating the relationship between vitamin D nutritional status and pelvic floor disorder symptoms are lacking. However, Jen-Tzer Gau reported two case studies of resolution of UI with vitamin D supplementation. The first case was a 78-year-old female with UUI symptoms who had vitamin D deficiency [25(OH)D = 10 ng/ml]. She used 50,000 IU of vitamin D_2 twice monthly for 1 year, and then 100,000 IU/month for another year prior to being seen. Her repeat 25(OH)D after this prolonged supplementation was 21 ng/ml. She was treated with 50,000 IU of vitamin D_2 weekly for 6 months with improvement of her 25(OH)D to 54 ng/ml. This patient reported that her UUI had resolved and she no longer wore protective pads. The second reported case was a 59-year-old female with SUI symptoms who had a 25(OH)D level of 13 ng/ml. She was given 50,000 IU of vitamin D_2 supplementation weekly for 12 weeks and her vitamin D level was increased to 43 ng/ml after 6 weeks. At her 3 month follow-up she reported resolution of her SUI symptoms.[61]

Alkhatib et al reported a small case series of 10 patients with fecal incontinence (8 males, 2 females). Patients with known causes of hypovitaminosis D (chronic kidney and liver disease, malabsorption) were excluded. All patients were found to have hypovitaminosis D - 60% 25(OH)D <20 ng/ml and 40% 25(OH)D <29 ng/ml. The mean 25(OH)D concentration was 17ng/ml.[62] As fecal continence requires normal function and strength of the levator ani muscles (puborectalis), the internal, and external anal sphincter muscles, weakened or disrupted muscles may significantly compromise the continence mechanism.

VITAMIN D AND PELVIC FLOOR MUSCLE TRAINING

Vitamin D insufficiency and deficiency may interfere with normal pelvic floor muscle and visceral function and contribute to pelvic floor disorders by affecting vitamin D receptor function in pelvic floor musculature and its calcium homeostasis. Vitamin D has been shown to increase skeletal muscle efficiency at sufficient levels. Pelvic floor muscle training (PFMT) targets the levator ani muscles, which are critical in the female continence system. It is the first line treatment for SUI, OAB, UUI, and FI symptoms. Pelvic floor muscle training is a fundamental component of behavioral therapy that has successfully decreased urinary incontinence episodes by 54 – 75% in randomized studies.[63] It is thought to work by increasing muscle strength, improving bladder and urethra support, and by teaching women how to voluntarily contract the external urethral sphincter muscle to occlude the urethra with increases in abdominal pressure and involuntary detrusor contractions.

Skeletal muscle efficiency may be important to urethral function and may be compromised in the presence of insufficient 25(OH)D concentrations. It is also plausible that normal vitamin D concentrations would have an effect on the efficiency of the levator ani, extrinsic urethral sphincter, or the external anal sphincter function. Thus, low vitamin D concentrations may have an impact on how successful women are with PFMT in a behavioral therapy approach for the management of urinary and fecal incontinence. Prospective studies are needed to confirm the role of vitamin D in pelvic floor muscle function, and the potential impact of vitamin D supplementation in conjunction with PFMT for the management of pelvic floor symptoms.

CONCLUSION

Vitamin D affects skeletal muscle strength and functional efficiency. Vitamin D insufficiency has been associated with notable muscle weakness. The levator ani and coccygeus muscles are skeletal muscles that are critical components of the pelvic floor and may be affected by vitamin D nutritional status. Weakened pelvic floor musculature is thought to contribute to pelvic floor symptoms such as urinary and fecal incontinence. Aging women are at increased risk of both pelvic floor disorders as well as vitamin D insufficiency. Small case reports and observational studies suggest that there is an association between insufficient vitamin D and pelvic floor disorder symptom severity. Prospective observational, cohort, and randomized studies are needed to begin to investigate this relationship. Vitamin D supplementation may prove to be a beneficial adjunctive treatment helping to optimize the response to PMFT and the quality of life of women with these disorders.

Footnotes

DISCLOSURE: None of the authors have a conflict of interest.

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