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REVIEW ARTICLE

Vitamin D status: a review with implications for the pelvic floor

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Abstract Vitamin D is a micronutrient vital in calcium homeostasis and musculoskeletal function. Vitamin D insufficiency is a common variant of vitamin D deficiency that shows 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 and the function of which 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 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

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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 is thought to span across many different organ systems. Vitamin D deficiency (serum level of 25-hydroxyvitamin D< 20 ng/ml) has become a major public health issue and is known to cause osteoporosis, muscle weakness, and pain, and thus is associated with the sequelae of these conditions, including falls and fractures. 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% to 73% [1–4]. It has few proven overt clinical characteristics, and its severity is determined by many factors, such as skin pigmentation, geographic location, and body mass index [5, 6]. Poor vitamin D nutritional status affects people of all ages, but it is well known that older adults and children have the greatest risk for severe consequences [3, 7, 8].

The effects of vitamin D insufficiency are thought to be widespread [9]. Many reports indicate that vitamin D has a role in the pathophysiology of some cancers [10], cardiovascular disease [11–13], diabetes [14, 15], and pregnancy morbidity [16–18]. Strong level I studies exist supporting a relationship between serum vitamin D concentration and muscle function [19–22]. In vitro and in vivo skeletal muscle cell cultures, animal models, and human studies have characterized physiologic mechanisms involving vitamin D that affect skeletal and smooth muscle function. Whereas the exact mechanism of how vitamin D affects muscle function is unknown, there is significant biologic plausibility implicating vitamin D insufficiency with clinically significant consequences for pelvic floor dysfunction.

The female pelvic floor is a complex component of the body and its global function is reliant on delicate relationships between musculoskeletal connections to pelvic bones that

support the abdominal cavity and pelvic viscera. Pelvic floor dysfunction includes signs and symptoms of urinary incontinence (UI), anal/fecal incontinence (FI), pelvic organ prolapse (POP), and other storage and emptying problems of the lower urinary and gastrointestinal tracts [23]. Pelvic floor dysfunction is common, and its prevalence increases with age. The prevalence of UI varies by definition but has been reported to range between 13% and 49% [24–29]. Nygaard et al. reported that 24% of US women ≥20 years of age had at least one pelvic floor disorder (PFD) [24]. In addition, among women aged 50–79 years included in the Women's Health Initiative study, 41% have POP [30]. The economic burden of PFDs 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 PFD [24, 31]. In this review, we address the role of vitamin D in musculoskeletal function to gain perspective on the potential role of vitamin D insufficiency in the development and severity of female PFDs.

Vitamin D physiology and the importance of supplementation

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) [32]. Circulating D_3 is then bound by vitamin D binding protein 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 referred to as the total 25(OH)D and is measured in most clinical studies. The 25-hydroxyvitamin D_2 is then activated by conversion to calcitriol [1,25-dihydroxyvitamin D (1, $25(OH)_2D_3$)] in the kidney. Synthesis of 25(OH)D and $1,25(OH)_2D_3$ is coupled with calcium homeostasis. Serum levels of vitamin D are regulated by parathyroid hormone, phosphorus, and calcium levels. (Fig. 1)

The primary source of vitamin D is sunlight exposure, as only 100–200 IU per day of vitamin D comes from natural and fortified food sources. Vitamin D supplementation intake recommendations are controversial based upon the targeted condition. 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 [33]. They concluded that specifically for optimization of bone health, the recommended dietary allowance (RDA) of calcium for ≥97.5% of the population ranged between 700 and 1,300 mg/day depending on age. For vitamin D, the RDA for ≥97.5% of the population is 600 IU/day for ages 1 to 70 years, and 800 IU/day for those older than 71 years [33]. Nevertheless, there is ample evidence that vitamin D doses above these recommendations are well tolerated [34, 35]. Due to the lack of conclusive 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. Prior to this statement, there were many reports of longitudinal cohort and randomized studies using arbitrary doses of vitamin D supplementation as a therapeutic option targeting nonskeletal conditions such as cardiovascular disease, diabetes, and hypertension. Whereas many of these longitudinal cohort studies indicate a relationship, many supplementation trials inconclusively support the notion that these conditions are affected by vitamin D. The lack of a systematic approach to investigating this relationship may have predestined the ensuing level I studies to have inconclusive results because the optimal serum level of vitamin D needed to achieve a desired outcome for any of the nonskeletal conditions is yet to be determined. In addition, the appropriate dose of vitamin D supplementation needed for nonskeletal conditions is unknown. Despite the IOM recommendations, many clinicians demonstrate their confidence in the cohort and randomized studies by continuing to prescribe vitamin D supplementation to their patients for nonskeletal conditions with the premise that it will benefit overall health.

Vitamin D and muscle function

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 skeletal muscle physiology and function. Bischoff et al. demonstrated that vitamin D receptors (VDR) are present in skeletal muscle cells of orthopedic patients [36, 37]. Immunohistochemical staining of the VDR on skeletal muscle biopsies of women illustrate that the number of VDRs decreased with age [37]. In vitro studies specifically identified the receptors for the vitamin D active metabolite, $1,25(OH)_2D_3$, on skeletal muscle myoblasts and myotubes in cell culture [38]. A host of cell-signaling pathways are induced by exposure of muscle cells to $1,25(OH)_2D_3$ in vitro [39].

Specifically, $1,25(OH)_2D_3$ regulates calcium homeostasis via inducing rapid mobilization of calcium from the sarcoplasmic reticulum followed by an influx of calcium from the extracellular environment. Down-stream signaling then activates calmodulin and other signaling molecules, which further varies calcium influx. The activation of these pathways may play a role in regulating the force of muscle contraction in a muscle fiber. Skeletal muscle-cell culture studies also suggest that $1,25\text{-}(OH)_2D_3$ plays a role in muscle-cell differentiation by down-regulating myogenic transcription factors via an undiscovered mechanism that may involve the VDR [40]. $1,25\text{-}(OH)_2D_3$ has also been instrumental in protecting skeletal muscle against insulin resistance and arachidonic acid mobilization, which may implicate its role in

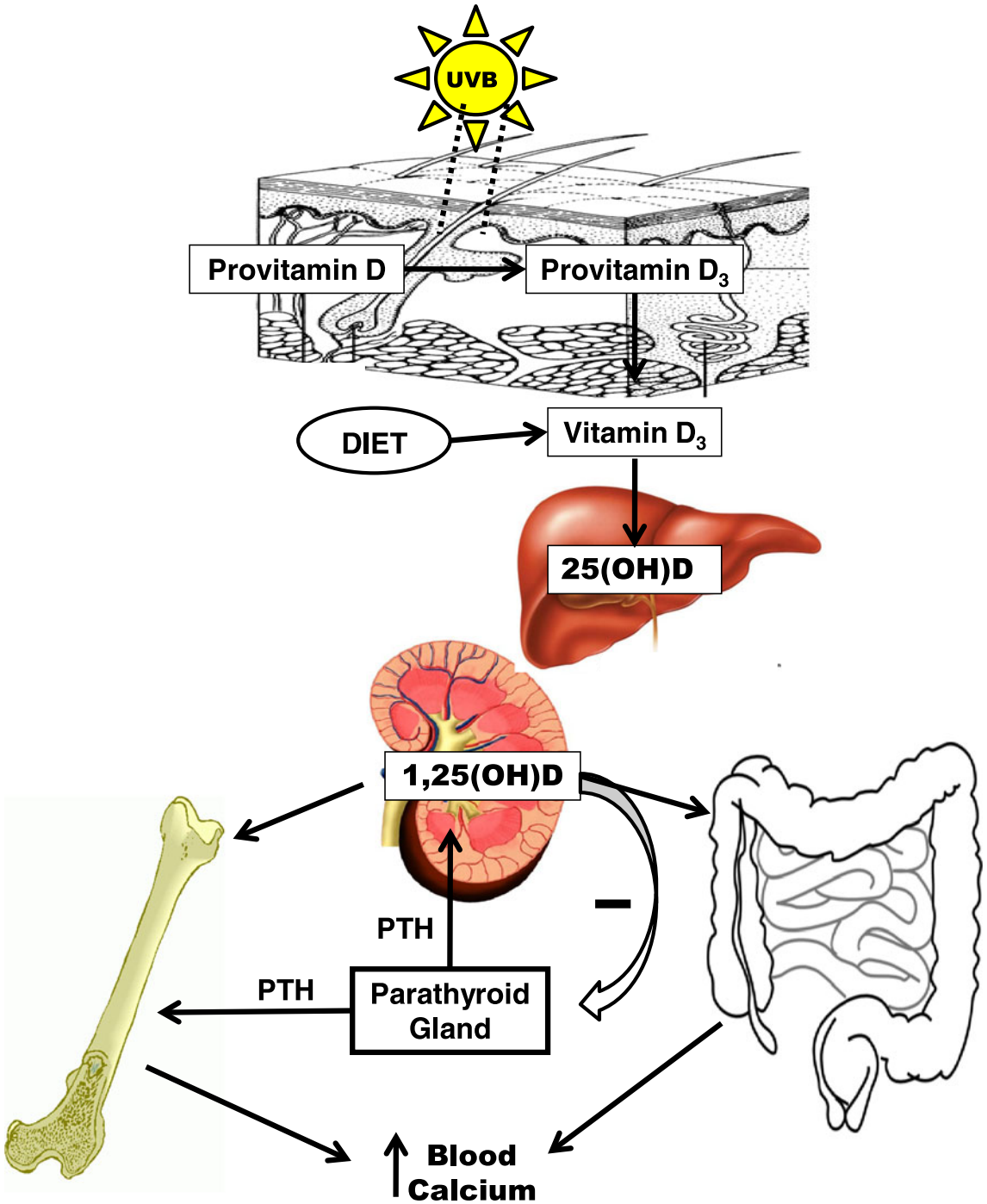

Fig. 1 Vitamin D synthesis and metabolism: Vitamin D precursors are absorbed through the skin or provided through dietary supplementation. Vitamin D is hepatically metabolized and renally activated so that it may affect calcium homeostasis by targeting calcium deposition in bone and absorption in the bowel

anti-inflammatory processes. Hence, vitamin D may be instrumental for skeletal muscle functional efficiency by regulating calcium homeostasis to affect muscle contractility and by protecting the muscle cellular environment against insulin resistance and inflammation.

Several clinical studies have investigated the role of vitamin D in muscle strength, efficiency, and function. Observational studies thus far have been limited to cross-sectional analyses that inconclusively support a significant relationship between vitamin D and muscle strength. Randomized studies performed subsequent to these studies also inconclusively demonstrate that vitamin D directly affects muscle strength (Table 1). However, an association between efficiency of skeletal muscle function has been supported.

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 musculoskeletal 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 ambulatory adults aged >70 years, all with serum 25(OH)D between 6 and 20 ng/ml	To examine the effects of a weekly dose of 8,400 IU Vitamin D_3 on postural stability, muscle strength, and safety	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 placebo. Weekly doses were well tolerated.
Dhesi et al.[22]	Randomized, double-blind, placebo-controlled trial. *N*=139 individuals >65 years with history of falls and 25 (OH)D≤12 mcg/L	To determine the effect of vitamin D supplementation on aspects of neuromuscular function as a risk factor for falls/fractures	Single intramuscular injection of 600,000 IU Ergocalciferol vs. placebo. Postural sway, choice reaction time (CRT), aggregate functional performance time (AFPT), and quadriceps strength were carried out at baseline and 6 months postintervention.	There was a significant difference in AFPT, CRT, in postural sway in intervention group (+6.6 s versus -2.0 s, p <0.05), (-0.06 s versus +0.41 s, p>0.01), and (+0.0025 versus -0.0138, p< 0.02), respectively. No difference in number of falls. Vitamin D improves neuromuscular function.

Level II/III

Study	Design	Study population	Findings
Gilsanz et al. [41]	Cross-sectional. Percent muscle fat and muscle mass measured using computed tomography, serum 25(OH)D measured	*N*=90 women aged 16–22 years	Percent muscle fat was significantly lower in women with normal serum 25(OH)D levels compared with women with insufficient/ deficient levels (3.15±1.4 vs. 3.90±1.9, p=0.038)
Annweiler et al.[42]	Cross-sectional component of randomized trial. Maximal isometric voluntary contraction strength of lower limb and hand measure with computerized dynamometers, serum 25(OH)D and parathyroid hormone measured	*N*=440, ≥75 years. divided into 3 groups: <15 ng/ml, 15-30 ng/ml, >30 ng/ml	Mean value of muscle strength (quadriceps or hand) was not different among groups. Univariate analysis showed a significant association between serum 25(OH)D concentration and hand grip, not confirmed with multivariable analysis.
Ward et al.[43]	Cross-sectional. Muscle power, velocity, jump height were measured using jumping mechanography. Esslinger Fitness Index performed. Serum 25(OH)D, parathyroid hormone, and calcium measured	*N*=99 girls aged 12–14 years, community-based population from secondary school	25(OH)D levels had positive relationship with jump velocity (p=0.002), jump height (p=0.005), and jump power (p=0.003). Girls with lower 25(OH)D generated less muscle power, resulting in decreased jump height and velocity.
Bischoff-Ferrari et al.[44]	Population-based survey. Lower-extremity function measured by 8-foot walk test and timed sit-to-stand test. Serum 25(OH)D measured	*N*=4,100 NHANES ambulatory population aged 60–90 years	Subjects with highest quintiles of 25(OH)D had a mean decrease of 0.67 s sit–stand test [95% CI: −1.11, −0.23 s (or 3.9%); p for trend=0.017] and mean decrease of 0.27 s with 8-foot walk test [95% CI: −0.44, −0.09 s (or 5.6%); p for trend <0.001]. Serum 25(OH)D levels between 40 and 90 nmol/L were associated with better musculoskeletal function in lower extremities

The contractile mechanism of smooth muscle is essentially the same as that of skeletal muscle. However, there are important structural and functional differences. The muscle filaments of smooth muscle are thin and randomly organized, thus lacking striations and myotubules found in skeletal muscles. Visceral smooth muscle fibers, such as those composing the detrusor wall, are organized to act as a single unit to display rhythmicity. Similar to skeletal muscle, smooth muscle contraction is triggered by the release of calcium ions. Calmodulin is also critical in calcium binding and activating the muscle contraction mechanism. Analogous to skeletal muscle, the VDR has been identified in smooth muscle cells of the bladder and urethra. In vitro and in vivo studies of the prostatic stroma, which is composed of smooth muscle cells, have shown that calcitriol ($1,25(OH)_2D_3$) and vitamin D analogs (BXL-253, BXL-628) modulated cell proliferation and apoptosis [45–48]. The urothelial cells of the bladder neck also have VDRs. The identity of this receptor was confirmed with messenger RNA (mRNA) and Western blot analyses, matching it with the VDR found in the gastrointestinal tract. In addition, the VDR in the bladder was equally responsive to VDR analogs and thus may be a target for VDR ligands [49].

Despite numerous reports of the VDR in muscle cells, there is one notable study that argues the contrary. Wang and Deluca performed immunohistochemical studies on wild-type and knock-out mice and human cardiac and skeletal muscle tissue to test the reproducibility of VDR detection using monoclonal antibodies used in previous studies: 9A7 (Affinity BioReagents, Rockford, IL, USA) and D-6 (Santa Cruz Biotechnology, Santa Cruz, CA, USA) [50]. They used specimens known to have VDR expression as controls (rat duodenum/kidney). The 9A7 antibody was found to bind nonspecifically to the VDR and non-VDR proteins in control tissues and smooth and skeletal muscle. Whereas the D-6 antibody detected the VDR in control tissues, it did not detect the VDR in smooth or skeletal muscle tissue. This data challenges Bischoff and colleague's in vivo studies detecting the VDR in skeletal muscle tissue using the 9A-7 antibody [34].

The studies of Crescioli and colleagues were not refuted by Wang's results, as the mouse monoclonal antibody against the VDR was not tested by Wang and Deluca. In addition, they also confirmed VDR mRNA expression in smooth muscle cells and confirmed the identity of the VDR with Western blot. The discrepancy between Wang's results and those of Cresciolli may be explained by more sophisticated studies of the effect of $1,25(OH)_2D_3$ on cell signaling pathways in muscle cells. Buitrago and colleagues studied the nongenomic action of $1,25(OH)_2D_3$ and discovered that the first step in $1,25(OH)_2D_3$-induced pathways is translocation of the VDR to the plasma membrane or sarcolemma of the muscle cell [51]. Therefore, it is plausible that the VDR is not detected in some in vivo tissue studies because the cells are not exposed to the active vitamin D metabolite - $1,25(OH)_2D_3$, which may be responsible for VDR expression in skeletal and smooth muscle cells [51, 52]. It is also plausible that in a vitamin-D-deficient environment, skeletal and smooth muscle cells may not translocate the VDR. This may result in decreasing down-stream cell signaling responsible for muscle contractility, resulting in compromised muscle function.

Vitamin D and the pelvic floor

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, perineal membrane, and external genital muscles [53]. 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. Whereas the etiology of POP and other PFDs is multifactorial, 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 continence mechanism is reliant on 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 (UI) is the most prevalent PFD. 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 urethral coaptation necessary to the continence mechanism [54]. Pelvic floor injury (such as childbirth) may disrupt the pubourethral ligaments in that anterior vaginal wall. Thus, the female continence system is more reliant on the strength and efficient function of the levator ani and extrinsic urethral sphincter muscles. Weak or dysfunctional muscles may suboptimally facilitate coaptation of the urethra voluntarily during times of increased abdominal pressure or with involuntary detrusor contraction, resulting in UI. Based on the aforementioned studies, these pelvic floor skeletal muscles may express the VDR. Accordingly, it is plausible that pelvic floor muscle function may be impacted by insufficient vitamin D serum levels by changing intracellular calcium homeostasis, possibly affecting muscle contractility.

Many studies have demonstrated a correlation between skeletal muscle weakness and low vitamin D concentrations. Pelvic floor muscle weakness occurs in many women who lack awareness and coordination of their pelvic floor muscles and is worsened with pelvic nerve damage and aging. Deficient and insufficient total 25(OH)D concentrations may also contribute to pelvic floor muscle weakness and predispose women to incontinence. Thus far, the majority of studies investigating the relationship between urinary incontinence and vitamin D nutritional status are observational and limited. Urgency urinary incontinence (UUI) 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 VDR 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 [49]. It is likely that the VDR is also found throughout the bladder wall. It is thought that the active metabolite [$1,25(OH)_2D_3$] acts through the VDR, therefore, vitamin D deficiency or insufficiency may result in abnormalities in bladder wall calcium homeostasis and thus ensuing aberrant detrusor contractility. A weakened detrusor muscle may become hypercontractile or irritable, similar to what is seen in hypocalcemic skeletal muscle activity elsewhere in the body, thus contributing to bladder overactivity and urinary urgency.

The urothelium is a transitional cell barrier covering the detrusor muscle. Recent advances implicate the urothelium in receiving mechanical, thermal, and chemical sensation and communicating this sensory information to underlying nerve and muscle systems of the detrusor [55]. Although the VDR has been identified in the urothelium, its exact role is understudied [49].

Many studies have confirmed the role of vitamin D in inflammation. In addition to regulating arachidonic acid mobilization in skeletal muscle, vitamin D has also been shown to regulate inflammatory cytokine levels by modulating 1α hydroxylase and VDR activity in human placenta [18]. When these two elements are removed from the trophoblastic cells of the placenta, interferon-gamma and interleukin expression is increased, which results in increased inflammation. Additionally, calcitriol inhibits tumor necrosis factor (TNF)-α-induced cytokine expression under the regulation of the VDR in trophoblasts [17]. Calcitriol also stimulates antioxidant gene expression in syncytiotrophoblast cells in a dose-response manner, making it a potential target as a pharmacologic pro-oxidant [56]. The role of vitamin D in decreasing inflammation may be translated to a potentially similar role in urothelium and detrusor-wall pathophysiology associated with overactive bladder (OAB) and cystitis. Specifically, insufficient serum 25(OH)D may 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 dietary nutrient composition and the development of OAB in women [57]. As a component of the Leicestershire Marlene Reid Center (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 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 validated food frequency questionnaire; 6,371 women were enrolled. The baseline prevalence of OAB was 15.9%; 429 incident cases of OAB were diagnosed over 1 year. Higher intake of vitamin D in the diet decreased the risk of OAB symptom onset ($p=0.008$) (Table 2). This study was limited by its longitudinal design, lack of measurement of serum vitamin D level, and the failure to account for confounding factors, such as BMI and caffeine intake in the development of OAB symptoms. Nevertheless, this was the first study to demonstrate an association between vitamin D nutritional status and a PFD [57].

Badalian and colleagues examined the relationship between PFDs and 25(OH)D concentration in 1,881 US women. In this cross-sectional study, UI was defined by the Incontinence Severity Index, a two-question measure assessing the presence of UI [58]. A score >3 defined the presence of UI [58]. FI 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 <10 ng/ml and <30 ng/ml, respectively. The prevalence of UI and >1 PFD was significantly higher in women with vitamin D insufficiency. A similar trend was seen for FI, but the difference was not statistically significant [58] (Table 2).

Prospective cohort or randomized studies investigating the relationship between vitamin D nutritional status and PFD symptoms are lacking. However, one investigator reported two case studies of UI resolution with vitamin D supplementation. The first case was a 78-year-old woman with UUI symptoms who had vitamin D deficiency [25(OH)D=10 ng/ml]. She took 50,000 IU of vitamin D_2 twice monthly for 1 year, followed by 100,000 IU/month for another year prior to being seen. A repeat 25(OH)D after this prolonged supplementation was 21 ng/ml. She was subsequently treated with 50,000 IU of vitamin D_2 weekly for 6 months with improvement of her 25(OH)D level to 54 ng/ml. This patient reported that her UUI had resolved

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	Mean 25(OH)D ng/ml	Outcome
Dallosso 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 applicable	429 new cases of OAB diagnosed over 1 year. Higher intake of vitamin D in the diet decreased the risk of OAB symptom onset (p=0.008)
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]	21.6 (20.4–22.7)	Prevalence of 1 or more PFD in women aged ≥20 years (25(OH)D <30 ng/ml vs. >30 ng/ml): 25% vs. 17% respectively. Prevalence of 1 or more PFD in women aged ≥50 years (25(OH)D <30 ng/ml vs. >30 ng/ml): 36% vs. 28%. Prevalence of UI in women aged ≥20 years (25(OH)D <30 ng/ml vs. >30 ng/ml): 17% vs. 9%, respectively. Prevalence of UI in women aged ≥50 years (25(OH)D <30 ng/ml vs. >30 ng/ml): 26% vs. 14%. Vitamin D-UI association is stronger in older women: OR (95%CI) 0.55 (0.34–0.91), p=0.22

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

and she no longer wore protective pads. The second reported case was a 59-year-old woman with stress urinary incontinence (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 a repeat 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 [59]. These two cases may be confounded by other factors, including placebo effect, and do not present a level of evidence to recommend vitamin D as a treatment for UI. However, the results are intriguing and suggest that stronger studies are needed.

Alkhatib et al. reported a small case series of ten patients with FI (eight men, two women). 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 17 ng/ml [60]. As FI requires normal function and strength of the levator ani muscles (puborectalis), and the internal and external anal sphincter muscles, weakened or disrupted muscles may significantly compromise the continence mechanism. These findings also pose a level of physiologic plausibility for a relationship between vitamin D and PFDs.

Vitamin D and pelvic floor muscle training

It is plausible that vitamin D insufficiency and deficiency may interfere with levator ani and urethral sphincter function, as well as with detrusor wall neuromuscular activity. Insufficient vitamin D may contribute to PFDs by disrupting VDR expression and calcium homeostasis in pelvic floor skeletal and visceral musculature. In addition, vitamin D at sufficient levels has been shown to increase skeletal muscle efficiency. Pelvic floor muscle training (PFMT) targets the levator ani muscles and is the first-line treatment for SUI, OAB, UUI, and FI symptoms. As a fundamental component of behavioral therapy, PFMT has resulted in decreased UI episodes by 54–75% in randomized studies [61]. Pelvic floor muscle efficiency may be important to urethral function, and treatment success may be compromised in the presence of insufficient total 25(OH)D concentrations. The skeletal muscle weakness found with insufficient vitamin D concentrations may result in inefficient function of the levator ani, extrinsic urethral sphincter, or external anal sphincter muscles. Thus, low vitamin D concentrations may impact the success rate of women undergoing PFMT in a comprehensive behavioral therapy approach for the management of UI and FI. 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 skeletal muscles are critical components of the pelvic floor and may be affected by vitamin D nutritional status. Weakened pelvic floor musculature is thought to be associated with the development of UI and FI symptoms. Aging women are at increased risk for both PFDs as well as vitamin D insufficiency. To date, only small case reports and observational studies have shown an association between insufficient vitamin D and PFD symptom severity. Prospective observational, cohort, and randomized studies are needed to further investigate this relationship. Vitamin D supplementation may prove to be a beneficial adjunctive therapy in the setting of a multicomponent behavioral therapy approach to optimize response to PFMT and improve the quality of life of women with these conditions.

Conflicts of interest None.

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