Vitamin D and Urogenital Functions in Postmenopausal Women

Subjects: Obstetrics & Gynaecology

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Recent years have witnessed the emergence of growing evidence concerning vitamin D's potential role in women's health, specifically in postmenopausal women. This evidence also includes its connection to various genitourinary disorders and symptoms. Numerous clinical studies have observed improvements in vulvovaginal symptoms linked to the genitourinary syndrome of menopause (GSM) with vitamin D supplementation. These studies have reported positive effects on various aspects such as vaginal pH, dryness, sexual functioning, reduced libido, and a decrease in urinary tract infections. Many mechanisms underlying these pharmacological effects have since been proposed. Vitamin D receptors (VDRs) have been identified as a major contributor to its effects. It is now well known that VDRs are expressed in the superficial layers of the urogenital organs. Additionally, vitamin D plays a crucial role in supporting immune function and modulating the body's defense mechanisms. However, the characterization of these effects requires more investigation. Reviewing existing evidence regarding vitamin D's impact on post-menopausal women's vaginal, sexual, and urological health is the purpose of this article. As research in this area continues, there is a potential for vitamin D to support women's urogenital and sexual health during the menopausal transition and postmenopausal periods.

Keywords: menopause ; sexual health ; vitamin D ; urogenital functions

1. Introduction

Menopause is characterized by many physiological and cellular changes in the external genitalia and urogenital tissues, including the vaginal epithelium, pelvic floor muscles, and urinary tract. These changes are clinically manifested by a broad spectrum of vaginal, urological, and sexual signs and symptoms that are mainly secondary to the hypoestrogenic state after menopause [1][2]. Changes in the vaginal flora, including a decrease in beneficial *lactobacillus* bacteria, lead to an increase in vaginal pH. These changes can cause vaginal dryness, itching, and irritation. The increase in the vaginal pH, in addition to changes in the innate defenses, promotes the overgrowth of harmful bacteria, potentially resulting in urinary tract and vaginal infections. Moreover, loss of the dermal collagen in the connective tissues of the vagina, bladder, and urethra leads to dyspareunia and other urinary symptoms such as dysuria, frequency, and urgency [1][3][4][5][6]. Collectively, these symptoms and signs are known as the GSM) [7]. GSM, although highly prevalent as reported by many international surveys [8][9][10][11][12][13], women frequently report symptoms due to sexual embarrassment and thus go untreated [14].

There is a growing focus on exploring the potential of vitamin D as a supplementary approach to hormonal therapies for managing symptoms associated with GSM. This perspective gains support from the observed links between vitamin D deficiency and various complications experienced by postmenopausal women, such as vaginal atrophy [15], sexual dysfunction [16][17], and urogenital infections [18]. Mediated by the VDR, the effects of vitamin D are exerted locally within reproductive tissues due to the expression of VDRs and vitamin D metabolizing enzymes. These tissues, including the urinary tract and vagina, exhibit responsiveness to and metabolic capabilities for vitamin D [19]. Notably, VDRs play a role in regulating the development, differentiation, and protection of the urinary tract and vaginal epithelium, with vitamin D promoting barrier integrity, upregulating genes encoding epithelial cell junction proteins, and stimulating vaginal epithelium proliferation [20][21][22].

2. Therapeutic Effects of Vitamin D on Urogenital Functions

2.1. Cellular Effects of Vitamin D on Urogenital Tissues

Menopause represents an important transition in vitamin D requirements due to the dependence of the VDRs on estrogen [23]. Urogenital organs expressing VDRs are sensitive to changes in vitamin D levels [19]. Vitamin D was shown to affect the activity of VDRs in the vaginal tissues. VDRs are involved in regulating the development, differentiation, and protection

of the epithelium of the urinary tract and the vagina [20][21]. Vitamin D was shown to increase the expression of the protein cornifin beta, a marker of squamous differentiation, and upregulates genes encoding epithelial cell junction proteins, promotes the barrier integrity of the vagina, and stimulates the proliferation of the vaginal epithelium [15][24]. Vitamin D also plays a role in the regulation of Ezrin protein [24]. Ezrin, in turn, controls actin-binding proteins that are responsible for interactions between the plasma membrane and cell-to-cell junctions. Ezrin is prominently expressed in the vaginal wall, contributing to the strength and flexibility of the tubular structure. Through activation of the VDR/p-RhoA/p-Ezrin pathway, vitamin D stimulates the proliferation of the vaginal epithelium, resulting in enhanced cell-to-cell junction [25][26]. This robust vaginal wall helps regulate the microbial environment within the vagina, including pH levels and flexibility [27]. In support of this, Lee et al. conducted experiments on a vaginal cell line and human vaginal tissue samples, demonstrating that vitamin D induces the expression of RhoA and Ezrin proteins in vaginal tissue. This induction leads to increased vaginal re-epithelization, comparable to the effects observed with estrogen use [15]. **Figure 1**. Depicts a simple illustration of vitamin D synthesis, metabolism, and effects on urogenital tissues.

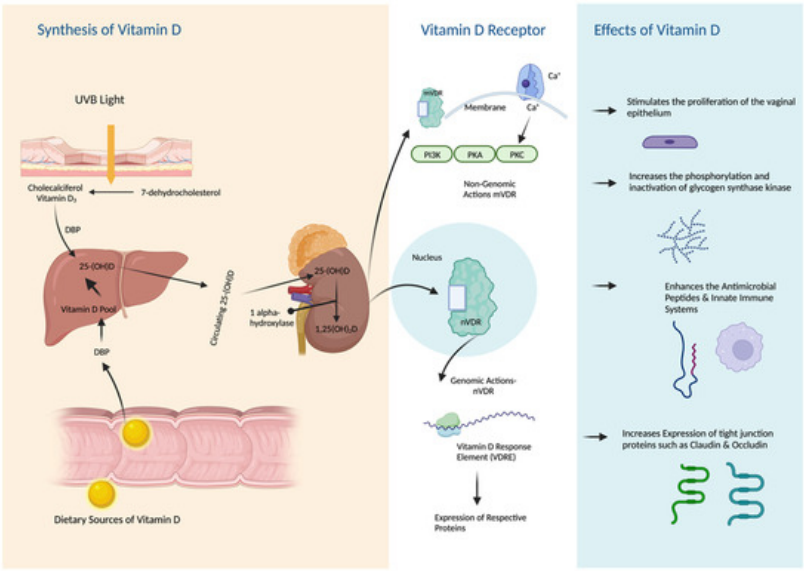

Figure 1. Synthesis, Metabolism, and Effects of Vitamin D on Urogenital Tissues.

2.2. The Effects of Vitamin D on Vaginal Epithelium and pH

The vaginal tissues consist of a nonkeratinized stratified squamous epithelium consisting of superficial, intermediate, and basal cell layers. One of its key functions is to store glycogen, which is converted to glucose. Lactobacillus, a beneficial bacteria, metabolizes this glucose into lactic acid and acetic acid, effectively maintaining a healthy vaginal pH within the range of 3.5–4.5. However, this entire pathway can be disrupted when estrogen levels are low [1][28]. Studies have demonstrated that vitamin D increases the phosphorylation and inactivation of glycogen synthase kinase that inhibits glycogen synthesis. This mechanism is particularly relevant in vaginal health. When vitamin D levels are sufficient, the vaginal glucose balance is positively influenced. This leads to an increase in glycogen deposition, as vitamin D promotes glycogen storage. [22][29][30]. **Figure 2** illustrates the role of vitamin D in maintaining balanced vaginal pH.

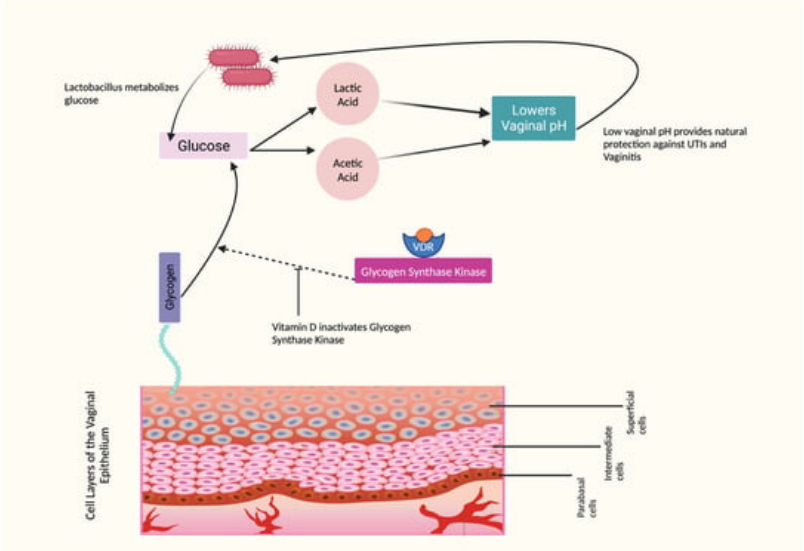

Figure 2. Effects of Vitamin D on Vaginal pH.

2.3. The Effects of Vitamin D on Vaginal Symptoms

The effects of vitamin D supplementations were a subject of a few trials which examined the effects of oral vitamin D [21][31][32][33][34][35] and topical vitamin D vaginal suppositories and creams [30]. In a recent study, the effects of a vaginal cream containing 1000 IU of vitamin D and 100 IU of vitamin E per dose were examined. The participants applied the cream daily for two weeks and three times a week for an additional 10 weeks. After four weeks of treatment, an improvement was observed in vaginal dryness, itching, and burning [36]. It is worth noting that since this cream was a combination of both vitamin D and vitamin E, the observed effects could be synergistic, with both vitamins contributing to the improvements, in particular, that vitamin E has also shown potential in improving vulvovaginal symptoms associated with GSM in few other studies [37]. The work of Rad et al. found that vitamin D vaginal suppositories over eight weeks showed significant improvements in the superficial, intermediate, and parabasal cell types of the vaginal epithelium. Additionally, there was a significant decrease in vaginal pH [30]. Oral vitamin D supplementations significantly affected the differentiation of superficial, basal, and parabasal cells. However, no significant improvements were observed in vaginal pH [29][34][35]. Similar results were observed in other trials in terms of vaginal pH [31][32][33]. While there were positive findings, such as increased superficial cell count and improved 25(OH)D serum levels, the overall impact on vaginal pH, vaginal dryness, and vaginal atrophy remains inconclusive.

2.4. The Effects of Vitamin D on Vaginal Infections

Lactobacilli, yeasts, and bacterial vaginosis-associated bacteria are less commonly parts of the vaginal microflora in postmenopausal women who are not receiving estrogen replacement therapy. This could explain the decrease in the incidence of bacterial vaginosis and yeast vaginitis among these women [38][39]. Vulvovaginal candidiasis (VVC) more commonly occurs at lower pH, which is not present in postmenopausal women due to hypoestrogenism. Clinical observations have reported that postmenopausal women have VVC and candida albicans rarely isolated from vaginal tissues [40]. Interestingly, many studies suggested that estrogen or hormone replacement therapy plays a critical role in increasing the susceptibility of acquiring VVC in postmenopausal women [40][41][42][43]. The proposed mechanism is an interaction between estradiol and the estrogen-binding protein in yeast [44]. On the other hand, very few studies looked at the prevalence of bacterial vaginosis (BV) in postmenopausal women. According to Bodnar et al., there was a relatively high incidence of BV among women with a serum 25(OH)D concentration below 20 nmol/L, while the prevalence was much lower among women with a serum 25(OH)D concentration exceeding 80 nmol/L. The study also highlighted a dose-response relationship between the level of 25(OH)D and the occurrence of BV [45]. However, Kaur et al. found no association between serum vitamin D levels and BV [46]. Ginkel et al. concluded that women on estrogen replacement therapy are less likely to have vaginal colonization with anaerobic bacteria and that estrogen may potentiate the effects of lactobacilli on vaginal pH [47].

2.5. The Effects of Vitamin D on Sexual Functions

It was demonstrated by a few studies that there is an association between vitamin D deficiency and a decline in sexual functions, including sexual desire, orgasm, and satisfaction in women [17][48]. Small clinical trials demonstrated improved female sexual function with vitamin D supplementation. Although some of these studies were conducted on young premenopausal women, this improvement was supported by the fact that VDRs are present in the uterus and ovaries and may have a role in sexual function. Also, data has shown that symptom severity was correlated with vitamin D serum levels [16][48][49].

A three-arm randomized-blind clinical trial included postmenopausal sexually active women to test the effects of vitamin D vaginal suppositories on sexual function. Women were administered vitamin D suppositories (1000 IU) for eight weeks. The treatment group showed statistically significant changes in sexual function compared to the control group. However, looking at the scores in the intervention group over the follow-up period, this improvement was of minimal clinical significance. Surprisingly, after two months of treatment, sexual function dropped to below baseline levels [50]. A different study investigated how a combination of isoflavones, calcium, vitamin D, and inulin affects the sexual functioning of postmenopausal women. The findings revealed an improvement in sexual functions as measured by the Female Sexual Function Index after 12 months of treatment. However, it is difficult to determine whether the observed effect was solely due to the individual ingredients or if they worked together synergistically. Nonetheless, it is worth noting that serum vitamin D levels increased after 12 months. It is still difficult to specifically attribute its effects. Additionally, it is important to consider that the study had a limited sample size and lacked a direct comparison between the treatment group and the control group, affecting the findings' overall reliability [51]. A combined vaginal vitamin D and E cream improved libido, orgasm, and sexual frequency after only 4 weeks of application [36].

2.6. The Role of Vitamin D in UTIs: Effects on the Immune Function

The significance of vitamin D, specifically 1,25(OH)D_2 and its metabolites have become evident in immune function following the discovery of VDR expression in activated inflammatory cells [52][53]. Changes in the immune system and increased pro-inflammatory serum marker levels, cytokine responses in body cells, decreased CD4 T and B lymphocyte levels, and natural killer cell cytotoxic activity are all observed post-menopause [21]. Various protective factors, including antimicrobial peptides and the innate immune system, play a role in preventing UTIs. Vitamin D plays a supportive and enhancing role in these systems. Research indicates that vitamin D stimulates the production of cathelicidin in the urinary bladder [18][20][54].

2.7. The Role of Vitamin D in UTIs: Effects on Tight Junction Proteins

The role of vitamin D in tight junction proteins in the urinary tract remains relatively unexplored. Nonetheless, studies have shown that uropathogenic Escherichia coli infection disrupts the tight junction barrier by downregulating occludin and claudins in bladder epithelial cells [55]. Strengthening the urothelial barrier to prevent infections becomes an appealing approach. It is suggested that vitamin D deficiency decreases the expression of occludin and claudin-5 [56]. Moreover, the VDR was demonstrated to mediate the protective effect of vitamin D-induced expression of occludin, claudin-5, and zonula occludens [57].

2.8. The Effects of Vitamin D on Pelvic Floor Disorders

Difficulty in urination, hesitancy, delay in urination, dyspareunia, and vaginal prolapse are common in postmenopausal women and are attributed to pelvic floor dysfunction (PFD) [58]. A double-blinded controlled trial examining the effects of vaginal vitamin D on women with PFDs, including pelvic organ prolapse and urinary and fecal incontinence, found that women with PFDs had lower mean vitamin D levels than otherwise healthy postmenopausal women. However, the association was not statistically significant. Vitamin D deficiency was shown to increase the risk of overactive bladder (OAB) and urinary incontinence [59]. Thus, there is growing recognition of the role of vitamin D supplementation in reducing these risks. A study conducted on postmenopausal women with stress incontinence reported a positive effect with a combination of high-dose vitamin D and estriol. After six weeks of treatment with high-dose vaginal suppositories, a significant reduction in the risk of OAB onset was observed [60]. After six weeks of treatment with high-dose vaginal suppositories, a positive and significant effect was observed where higher intakes of vitamin D decreased the risk of OAB onset [61]. Similarly, a weekly dose of 50,000 IU vitamin D for eight weeks was shown to reduce the severity of UI and frequency of nocturia in postmenopausal women [62]. The VDR has also been identified in the detrusor wall; thus, its insufficient level may impact bladder function and pelvic floor muscle weakness. Vitamin D may play a role in the efficiency of muscle function that is distinct from the role of calcium in muscle contractility [48][49][58].

Future Research Directions

Understanding the benefits of vitamin D supplementation is crucial. Recent research shows promising evidence of its positive impact on urogenital health and sexual functioning in postmenopausal women. However, robust randomized controlled trials are lacking, with variations in participant characteristics, dosage, intervention length, and assessment methods. Objective indicators like the vaginal maturation index should be combined with subjective measures to strengthen evidence of vitamin D's effects, in measuring sexual functioning. Comprehensive investigations will inform evidence-based guidelines and personalized interventions for postmenopausal women. Filling knowledge gaps will provide clearer insights for clinicians and facilitate tailored strategies to enhance urogenital health and well-being. Figure 3 summarizes all potential therapeutic effects of vitamin D on urogenital health and sexual functions.

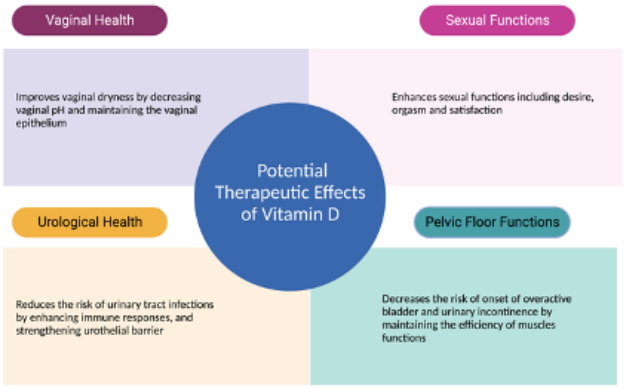

Figure 3. Therapeutic Effects of Vitamin D on Urogenital Functions.

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