Reviewing the Evidence on Vitamin D Supplementation in the Management of Testosterone Status and Its Effects on Male Reproductive System (Testis and Prostate): Mechanistically Dazzling but Clinically Disappointing

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ABSTRACT

Purpose: Vitamin D supplementation has been suggested to increase testosterone levels. The primary purpose of this literature review was to critically assess the physiologic effects of vitamin D supplementation on serum testosterone concentrations in men and the secondary purpose was to evaluate the feasibility of vitamin D status toward urologic health (testis and prostate).

Methods: A structured literature review was performed using the Cochrane, MEDLINE, and Web of Science databases. The literature search encompassed studies published between 2011 and 2019.

Findings: Observational studies suggest an association between higher testosterone and serum vitamin D concentrations. Conversely, most randomized clinical trials that investigated the effect of vitamin D administration on testosterone levels have failed to detect any significant effect. Physiologically, vitamin D is engaging in spermatogenesis, but it remains unclear whether vitamin D is a determinant of fertility. With prostate support, the management of vitamin D status has been associated with a decreased prevalence of benign prostatic hyperplasia and symptoms (ie, lower urinary tract symptoms). However, with prostate cancer, there is a paucity of evidence pertaining to vitamin D supplementation.

Implications: Mechanistically, vitamin D exhibits essential roles in the testis and prostate; otherwise, there is no apparent evidence to support the use of vitamin D supplementation to increase testosterone levels and to improve clinical outcomes related to the male reproductive system. (*Clin Ther*. xxxx;xxx:xxx) © 2020 Elsevier Inc.

Key words: male hypogonadism, 25(OH)D, testosterone, vitamin D.

INTRODUCTION

Vitamin D (VitD) deficiency, detected by low serum 25-hydroxyvitamin D (25[OH]D), is considered a worldwide pandemic.[1,2] Accordingly, observational data indicate that low 25(OH)D concentrations are associated with the prevalence of autoimmune diseases, cancers, sarcopenia, and dysregulation in gut microbiota.[3–8]

In addition to VitD deficiency, the prevalence of decreasing testosterone levels is also epidemiologically related to senescence[9] and daily endocrine disrupting chemical exposure regardless of age.[10–12] Fatigue, lack of energy, reduced strength, frailty, and decreased sexual performance are the main symptoms of low testosterone levels.[13] Indeed, testosterone management is essential for male health because lower levels are associated with an increased risk of all-cause and

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cardiovascular mortality.[14] Interestingly, the VitD receptor (VDR) is expressed not only in myocytes but also in the male sex system, including prostate and testis.[15,16]

Despite the putative benefits of VitD supplementation on health (eg, as a cardiometabolic support), $VitD_3$ supplementation, even in considerable doses, recently failed to prevent type 2 diabetes and cardiovascular disease in individuals at high risk for these diseases.[17,18] However, there is no discernable evidence regarding VitD supplementation for the management of male health, at least through an emphasis on the reproductive system. Therefore, our primary aim was to critically review the physiologic effects of VitD supplementation on serum testosterone concentrations, and our secondary aim was to assess the feasibility of VitD status to promote urologic health in the areas of semen and prostate.

METHODS

A literature review was performed using Cochrane, MEDLINE, and Web of Science databases with the goal of identifying relevant studies to describe and consolidate intervention data that analyzed the effects of VitD supplementation on serum testosterone in humans. A detailed English-language literature search was based on the following key words: *cholecalciferol* OR *ergocalciferol* OR *vitamin D* OR *vitamin* D_2 OR *vitamin* D_3 OR *25(OH)D* OR *25-hydroxycholecalciferol* OR *25-hydroxyvitamin D* AND *FSH* OR *follicle-stimulating hormone* OR *free testosterone* OR *LH* OR *luteinizing hormone* OR *sex hormone-binding globulin* OR *SHBG* OR *testosterone* OR *total testosterone*. The literature search encompassed studies published between 2011 and 2019. Fig. 1 shows the 2404 identified titles, yielding 192 potential abstracts, that were retrieved. Subsequently, 8 full-length publications of clinical trials that analyzed serum testosterone concentrations were included in the review. To expand the evidence on urologic health, an additional search was performed with the same databases with no delimitation of study type or publication date.

Definition of VitD Status: Serum Dosage and Supplementation Doses

According to the Global Consensus Recommendations of the Endocrine Society, serum 25(OH)D concentrations are classified as follows: insufficiency (30−50 nmol/L or 12−20 ng/mL), deficiency (<30 nmol/L or <12 ng/mL), sufficiency (>50 nmol/L or >20 ng/mL), and toxicity (>250 nmol/L or >100 ng/mL with hypercalciuria and suppressed parathyroid hormone).[19] The consensus for prevention of rickets and osteomalacia with VitD supplementation recommends 400 IU/d and at least 600 IU/d from birth to 12 months of age and beyond 12 months of age, respectively.[19] To the best of our knowledge, however, there are no specific recommendations for male hypogonadism.

Physicians and dietitians have appropriate roles for prescribing supplementation of VitD. However, dietitians should be limited to a tolerable upper limit. The upper limit of VitD was 2000 IU/d in the past,[20] but current guidelines expanded the upper limit to 10,000 IU/d for adult and elderly people, focusing on the pleiotropic effects of supplementation.[21]

VitD and Testosterone Levels

Genotypes of the VitD receptor gene are associated with serum sex hormone concentrations that have important clinical implications for testosterone.[22] The putative pathway between the active form of VitD, known as calcitriol or 1,25-dihydroxyvitamin D_3 ($1,25[OH]_2D_3$), and its receptors is shown in Fig. 2. Enzymatic actions are the presumed primary mechanisms that stimulate increases in testosterone and dihydrotestosterone in men.

In evidence-based practice, both clinical trials and observational studies deserve attention to characterize the association between VitD status and testosterone levels in men. The sections below provide and detail the hierarchy of evidence from randomized controlled trials and broaden the scope of evidence with observational studies.

Clinical Trials

Most intervention studies exerted no efficacy to increase total testosterone concentrations given the overall harmonized reference ranges (260−300 to 850−920 ng/dL; 2.6−3 to 8.5−9.2 ng/mL; or 9−10.4 to 29.5−1.9 nmol/L).[23] Collectively, the effects of VitD supplementation on testosterone concentrations in clinical trials are given in the Table I. Of all the studies, only a trial by Canguven et al[24] used ergocalciferol ($VitD_2$) supplementation. In this sense, the body of evidence assessing the more appropriate

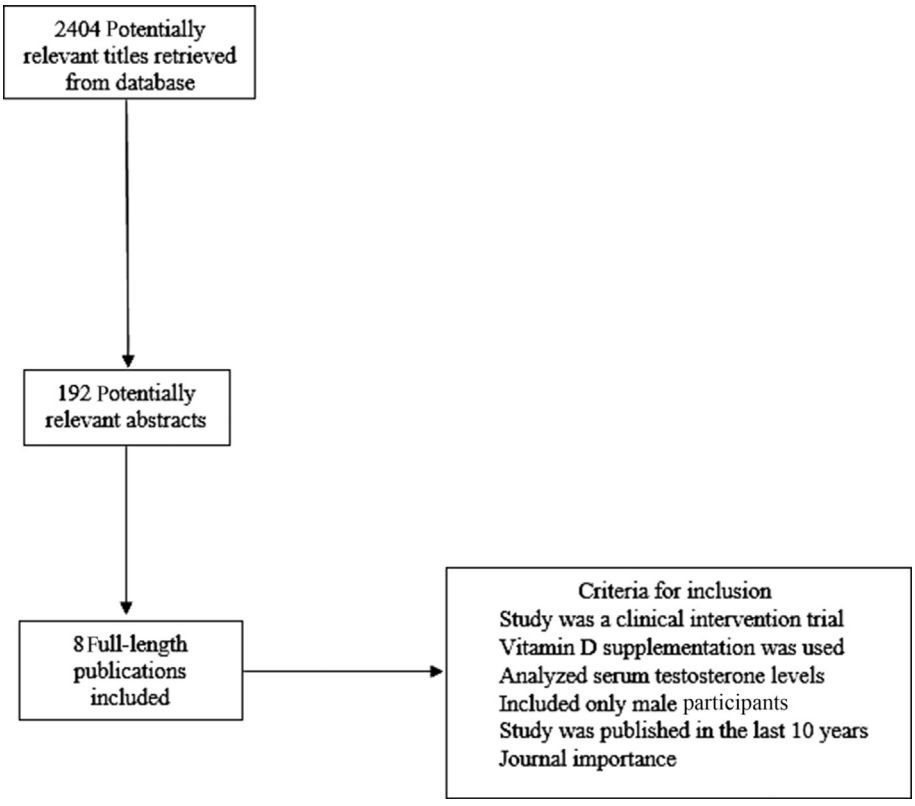

Figure 1. Flow diagram of the included studies on serum testosterone levels.

$VitD_3$ supplementation failed to produce clinically meaningful effects.

Observational Studies

Despite unsubstantiated support of VitD supplementation as a testosterone-boosting agent, there are strong linear associations between lower serum levels of 25(OH)D and reduced serum testosterone, the latter of which may be low enough to meet current hypogonadism diagnosis criteria.[24,25] The deficiency of 25(OH)D is strongly associated with low serum testosterone levels in elderly men.[34] A cohort study by Tak et al[35] of 652 Korean men (mean age, 57 years) reported that 49% of the men were 25(OH)D deficient and only 15% attained sufficient levels.[35] In addition, men in the highest quartile of serum 25(OH)D (26.51 ng/mL) exhibited higher total testosterone levels when compared with men in the lowest quartile (<15.28 ng/mL).

Analysis of data from the Longitudinal Aging Study Amsterdam of 643 Dutch men (aged ≥65 years) found similar positive associations among 25(OH)D levels, total testosterone levels, and bioavailable testosterone.[36] On adjustment for covariates, men with serum 25(OH)D levels >75 nmol/L exhibited higher total testosterone levels than men with serum 25(OH)D levels <25, 25 to 50, and 50−75 nmol/L. Interestingly, only the men with serum 25(OH)D levels >75 nmol/L had higher bioavailable testosterone compared with those with serum 25(OH)D levels <25 nmol/L. The association did not hold for any other serum 25(OH)D level comparison, and there was no association between lower serum 25(OH)D levels and hypogonadism or gonadotrophins.

In a cross-sectional study of 2299 elderly men, those with severe 25(OH)D deficiency and those with 25(OH)D sufficiency had 470 ng/dL and

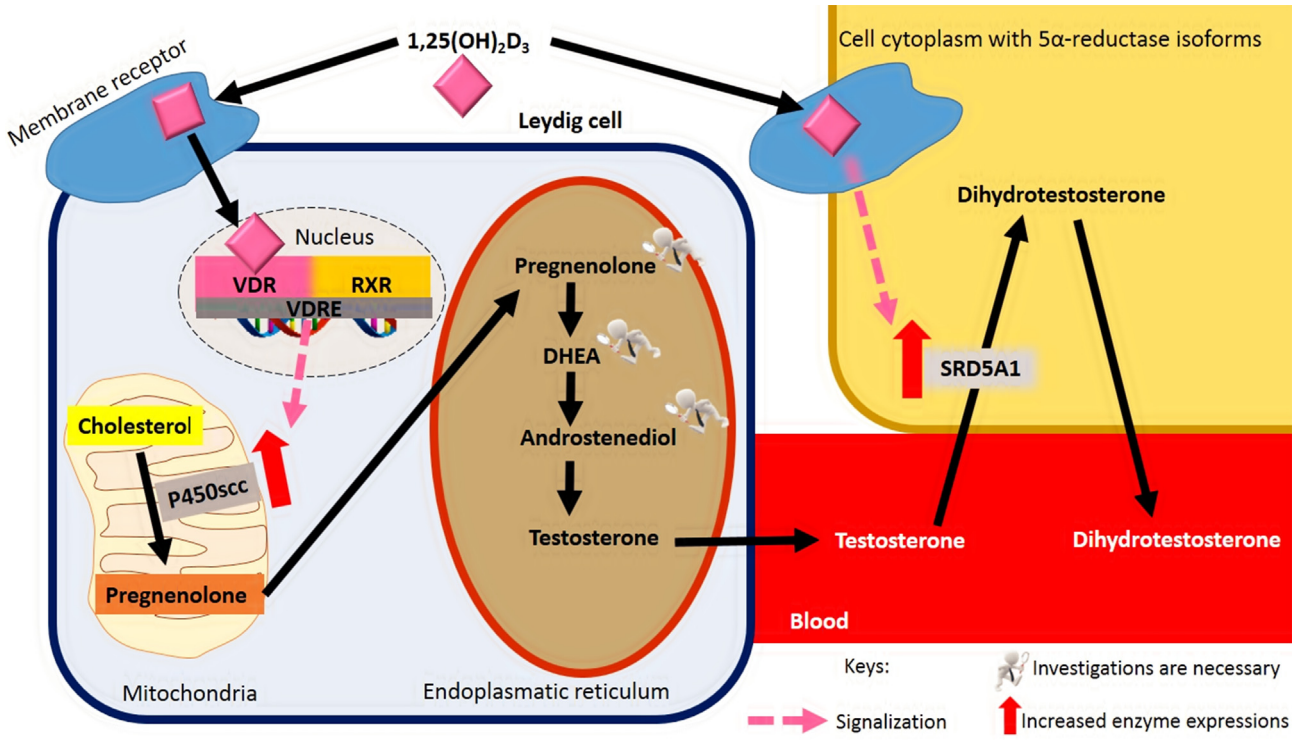

Figure 2. The active form of vitamin D (VitD) increases the expression of androgen metabolism enzymes (ie, P450scc and SRD5A1). 25-Hydroxyvitamin D_3 ($1,25[OH]_2D_3$) binds to its membrane receptor and consequently further binds to the nuclear receptor, forming the VitD receptor (VDR)—retinoid X receptor (RXR) heterodimer. There are VitD-dependent genes in the nucleus, and when the VDR-RXR heterodimer is activated, the vitamin D response element (VDRE) signals the expression of androgen enzymes in the mitochondria. P450scc acts primarily on the hormone cascade, which is responsible for converting cholesterol into pregnenolone. After pregnenolone is synthesized, several enzymatic actions lead to testosterone formation, whose processes occur in the endoplasmic reticulum. Increased expression of SRD5A1 by virtue of $1,25(OH)_2D_3$ signaling enhances the conversion of testosterone to dihydrotestosterone. The proposed pathway for the association between the active form of VitD and increased testosterone levels in humans occurs in the Leydig cells, whereas the association with increased levels of dihydrotestosterone occurs in cells that predominantly express isoforms of 5α-reductase, one of which is SRD5A1. Some precursors of the testosterone pathway should be investigated through randomized clinical trials for better clinical insight. DHEA, dehydroepiandrosterone.

531 ng/dL of total testosterone, respectively.[37] In another cross-sectional study, consisting of 1362 male participants, serum 25(OH)D was positively associated with total and free testosterone levels, indicating a linear association between 25(OH)D and total testosterone as well as 25(OH)D and free testosterone at lower levels of 25(OH)D of approximately >75–85 nmol/L, while reaching a plateau at higher levels (>100 nmol/l).[32]

A recent cross-sectional study found no statistically significant associations between 25(OH)D and testosterone concentrations among Polish male ice hockey players.[38] In context, the sample size was small (n = 50), and the mean concentrations of 25(OH)D and total testosterone were 30.3 ng/mL and 19.2 nmol/L, respectively, whereas both values fell within their respective reference ranges.[39,40] In contrast, among 404 Polish elderly men, a significant

Table I. Effect of VitD administration on testosterone concentrations.

Source	Study Population	Study Design (Duration)	VitD Dose, IU	Serum 25(OH)D Pre → After [Difference], nmol/L	Total Testosterone Outcome in VitD Intervention	Secondary Endocrine Outcomes
Lerchbaum et al,[25] 2018	94 Men with low testosterone levels (12.7 nmol/L), mean age of 47 y	RCT (12 wk)	20,000 per week of $VitD_3$	56 → 89 [33]	↔	E2, LH, FSH, SBHG, free testosterone, and free androgen index did not change.
Saha et al,[26] 2018	180 Young healthy men	RCT (6 mo)	60,000 per week of $VitD_3$ for 8 wk followed by 60,000 fortnightly for 4 mo	22.5 → 85.9 [63.4]	↓2.1 for all groups	SBHG and free androgen index did not change.
Zittermann et al,[27] 2018	133 Patients with advanced heart failure, mean total testosterone level of 11.2 nmol/L, mean age of 55 y	RCT (36 mo)	4000 per day of $VitD_3$	36.5 → 63.9 [27.4]	↔	SHBG levels did not change And free testosterone and bioactive testosterone decreased significantly in vitamin D and placebo groups
Canguven et al,[24] 2017	102 VitD-deficient patients mean total testosterone level of 12.46 nmol/L, mean of 53 y	Prospective study (12 mo)	600,000 per month of ergocalciferol; once serum 25(OH)D level reached 75 nmol/L, VitD dose was switched to 600,000 every 2 mo	37.2 → 121.2 [84]	↑ 0.49	Increased erectile function scores and decreased E2 levels; LH concentrations did not change
Lerchbaum et al,[28] 2017	98 Healthy men, mean testosterone level of 19.1 nmol/L, mean age of 39 y	RCT (12 wk)	20,000 per week of $VitD_3$	52 → 107 [55]	↔	E2, LH, FSH, SBHG, free testosterone, and free androgen index did not change

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Table I. (*Continued*)

Source	Study Population	Study Design (Duration)	VitD Dose, IU	Serum 25(OH)D Pre → After [Difference], nmol/L	Total Testosterone Outcome in VitD Intervention	Secondary Endocrine Outcomes
Heijboer et al,[29] 2015	92 Patients, mean total testosterone level of 15 nmol/L, mean age of 63 y	RCT (6 wk)	2000 per day of $VitD_3$	46.5 → 73.5 [27]	↔	Not analyzed
	49 VitD-deficient patients, mean total testosterone level of 11 nmol/L, mean age of 82 y	RCT (16 wk)	600 per day of $VitD_3$	27 → 57 [30]	↔	
	43 VitD-deficient patients, mean total testosterone level of 13 nmol/L, mean age of 53 y	RCT (16 wk)	1200 per day of $VitD_3$	27.5 → 63.5 [36]	↔	
Jorde et al,[30] 2013	282 Heathy men, mean total testosterone level of 14.3 nmol/L, mean age of 51 y	RCT (6 −12 mo)	20,000−40,000 per week of $VitD_3$	48.2 → 70.6 [22.4]	↔	Free testosterone, LH, FSH, and SHBG did not change
Pilz et al,[31] 2011	54 Healthy, overweight men, mean total testosterone level of 10.7 nmol/L,	RCT (12 mo)	3332 per day of $VitD_3$	32.5 → 86.4 [53.9]	↑2.7	Increased bioactive testosterone (5.21 from 6.25 nmol/L) and free testosterone

Table I. (*Continued*)

Source	Study Population	Study Design (Duration)	VitD Dose, IU	Serum 25(OH)D Pre → After [Difference], nmol/L	Total Testosterone Outcome in VitD Intervention	Secondary Endocrine Outcomes
	mean age of 49 y					levels (from 0.222 to 0.267 nmol/L)

E2 = estradiol; FSH = follicle-stimulating hormone; LH = luteinizing hormone; 25(OH)D = 25-hydroxyvitamin D; RCT = randomized clinical trial; SBHG = VitD = vitamin D.

correlation among 25(OH)D levels, serum testosterone level, and the free androgen index was found with respect to different genotypes of VDR polymorphisms, including heterozygous AG (rs731236) and Ff (rs10735810) as well as homozygous GG (rs7975232) and BB (rs1544410).[41] Interestingly, a double cohort study examined the association between the VDR polymorphisms rs2228570 (Fok1) and rs731236 (Taql) and luteinizing hormone (LH) levels in the context of supraphysiologic testosterone doses.[42] At baseline, healthy men homozygous for Fok1 (C-allele carriers) had 30% higher LH levels at baseline than testosterone carriers before testosterone was administered, thus providing some evidence to support a biological mechanism among 25(OH)D levels, LH values, and testosterone levels in those with the Fok1 VDR polymorphism.

The clinical usefulness of VitD screening might differ, depending on patient metabolic status and the diagnosis of male hypogonadism. Both 25(OH)D deficiency and male hypogonadism significantly increase the risk of metabolic syndrome.[33,43,44] In a study composed of 612 men, a correlation was detected between 25(OH)D levels and testosterone concentrations in individuals without metabolic syndrome. These men exhibited higher 25(OH)D and testosterone levels when compared with men with metabolic syndrome (14.43 vs 12.53 ng/mL for 25[OH]D and 532 vs 458 ng/dL for total testosterone).[45]

The cross-sectional Survey on Prevalence in East China for Metabolic Diseases and Risk Factors (SPECT-China) study of 2854 men, using a definition of hypogonadism as total testosterone level <11.3 nmol/L or free testosterone level <22.56 pmol/L, reported strong associations between increased quartiles of 25(OH)D and decreased odds of hypogonadism ($P < .01$).[46] On a comparison of the lowest quartile to the highest quartile of 25(OH)D in an adjusted model, the association persisted (odds ratio = 1.50; 95% CI, 1.14−1.97). Notably, a recent mendelian randomization analysis[47] that assessed new data from the SPECT-China study replicated and confirmed the associations found by Wang et al.[46] In the analysis of 4254 Chinese men, lower 25(OH)D levels were associated with lower total testosterone, suggesting a biological effect on gonadal function and the hypothalamic−pituitary−gonadal axis. To date, however, randomized controlled trials have failed to find a causal effect (Table I).

Semen Parameters

VitD is metabolized in the testis where VDR-regulated proteins and enzymes mediate VitD in human spermatozoa, increasing intracellular calcium concentrations and thus inducing sperm motility.[15] The versatility of VitD as a signaling molecule in the male reproductive organs provides systemic and local underpinnings for its interplay with both sperm and testosterone metabolism. Mechanistically, testosterone is primarily important for the initiation and

maintenance of spermatogenesis,[48] especially in meiosis.[49]

In a recent cross-sectional study, a significant decrease in 25(OH)D levels in patients with altered sperm parameters (total count, motility, and morphology) was detected.[50] Patients with normal sperm parameters (n = 186) had 81 nmol/L of 25(OH)D, whereas those with altered sperm parameters (n = 127) had 65 nmol/L of 25(OH)D. Moreover, serum testosterone levels were significantly and positively correlated with 25(OH)D. Infertile patients with altered sperm parameters had 3.32 ng/mL of total testosterone, whereas fertile patients with normal sperm parameters exhibited 8.04 ng/mL. In turn, Tirabassi et al,[51] through a retrospective analysis of 104 andrologic patients, with 25(OH)D levels of 20.8 (lowest quartile) versus 40.8 ng/mL (highest quartile), had a positive association between total sperm motility and 25(OH)D values but not between total and free testosterone levels.[51] Other studies found no associations between 25(OH)D concentrations and testosterone levels, further indicating inconsistent data with regard to semen parameters.[52,53] Results of a cross-sectional study of young healthy men (n = 307), in which 8−62 nmol/L and 94−227 nmol/L were considered as low and high 25(OH)D levels, respectively, offered no evidence to suggest that 25(OH)D is a risk factor for poor semen quality, testosterone, LH, follicle-stimulating hormone (FSH), and inhibin levels.[53] Likewise, the Copenhagen-Bone-Gonadal Study, which examined 1189 infertile men, reported that neither total testosterone nor free T concentrations were altered between the lowest and the highest quartiles of serum 25(OH)D (<25 vs >75 nmol/L), as well as LH, sex hormone−binding globulin, and inhibin values.[52] Among sperm parameters, only motility was elevated in the highest 25(OH)D quartile.

According to Hammoud et al,[54] both high and low levels of serum 25(OH)D can be negatively associated with semen parameters.[54] In their study, men with concentrations between 20 and 50 ng/mL exhibited maximal values of semen parameters. Conversely, those with 25(OH)D levels >50 ng/mL had lower percentages of normal sperm head, progressive motile sperm, sperm concentration, and total progressive motile sperm count, whereas men with 25(OH)D levels <20 ng/mL had lower total sperm count and total progressive motile sperm. Besides 25(OH)D, it is important to provide an accurate characterization of the interplay between the VitD status and sperm parameters. In this regard, Zhu et al[55] found that oligospermia, asthenospermia, oligoasthenospermia, and azoospermia were significantly lower with serum $1,25(OH)_2D_3$ but not $25(OH)D_3$ in infertile Chinese men (n = 186) compared with fertile men (n = 79).

Prostate Support

Adequate 25(OH)D levels have produced promising results toward prostate volume and benign prostatic hyperplasia (BPH). Clinical attention is required, especially when prostate volume is > 30 mL,[56] whereas diagnosed BPH, a phenomenon due to the excessive growth of both stromal and epithelial cells of the prostate, is a more common form of lower urinary tract symptoms (LUTS).[57] In a cohort of 434 men with LUTS, lower 25(OH)D levels were associated with higher total overactive bladder symptom scores, especially during the winter. In patients with 25(OH)D deficiency, consenting to intramuscular $VitD_3$ therapy administered as 200,000 IU in a single dose, the total overactive bladder symptom scores significantly decreased after 2 months of VitD replacement while increasing 25(OH)D levels from 13.7 to 25.3 ng/mL.[58] In a prospective case−control study, patients with LUTS (n = 70) had lower 25(OH)D levels and a larger prostate compared with the control group (n = 80). The mean 25(OH)D values were 41 vs 70 nmol/L, whereas mean prostate sizes were 50 and 31 g, respectively for cases (patients with LUTS) and controls.[59] In a prospective, observational study, associations among 25(OH)D deficiency, BPH, and LUTS in men with type 2 diabetes mellitus were found. Individuals with prostate volume ≤30 mL (n = 27) had a mean 25(OH)D concentration of 44.8 nmol/L, whereas a mean of 29.2 nmol/L was detected for those with a prostate volume ≥30 mL (n = 40).[60]

Along with VitD supplementation, analogues of VitD have emerged as appealing agents to decrease prostate volume in patients with BPH.[57] In this regard, a double-blinded, randomized, placebo-controlled clinical trial of 119 patients with diagnosed BPH and prostate volume ≥40 mL found that prostate volume decreased 2.90 mL in the treatment group compared with a 4.32-mL increase in the placebo group after 12 weeks of treatment with 125 μg/d of BXL628, a VitD analogue.[61]

Prostate and Testis Cancer

Taken together, the management of VitD status is a feasible approach as a part of routine screening for male health, particularly being a biomarker with applicability to mitigate the increased prevalence of BPH. However, with prostate cancer, the evidence is inconsistent throughout the wide spectrum of VitD. For instance, in an observational study in which 571 men with elevated prostate-specific antigen levels or abnormal digital rectal examination findings were investigated, serum levels ≥30 mL were inversely associated, especially in men with BPH, but not for prostate cancer.[62]

In 2012, Gilbert et al[63] investigated 1447 patients with prostate cancer and 1449 healthy controls, finding a 2-fold increased risk of advanced versus localized prostate cancer and high-grade versus low-grade cancer in men who were 25(OH)D deficient. However, there was no evidence pertaining to an association between total 25(OH)D and overall prostate cancer incidence. Moreover, the meta-analysis of Gilbert et al,[64] which encompassed 25 studies, found that neither an increase in serum levels of 10 ng/mL of 25(OH)D and 10 pg/mL of $1,25(OH)_2D_3$ nor an increment increase of 1000 IU from VitD intake decreased prostate cancer risk. In addition, Layne et al[65] did not find an association between 25(OH)D levels and overall prostate cancer among 226 patients with prostate cancer and 452 controls in black men.[65] On the other hand, serum VitD-binding protein was significantly and inversely associated with prostate cancer risk. More recently, a nested case–control study within the Melbourne Collaborative Cohort Study examined the association between serum 25(OH)D and prostate cancer in 824 middle-aged Australian case patients and 1648 controls.[66] In alignment with previous studies, serum 25(OH)D levels were not inversely associated with prostate cancer (hazard ratio = 1.11; 95% CI, 0.82–1.48).

Despite a high prostate cancer prevalence, testicular cancer is the most common cancer in adult men (ie, 20–30 years old),[67] which is also a disease of concern in older men.[68] Nappi et al[69] detected reduced 25(OH)D levels among 82 patients with germ cell testicular cancer, with 65%–85% presenting with levels <30 ng/mL, 25%–36% with levels <20 ng/mL, and 6%–18% with levels <10 ng/mL. In turn, the study by Schepisi et al[70] of unilateral testicular cancer noted that 11 patients of 58 patients (19%) had normal 25(OH)D values, whereas 47 (81%) had suboptimal levels.[70] Similarly, Foresta et al,[71] investigating 125 normotestosteronemic patients with testicular cancer and unilateral orchiectomy, found that 25(OH)D levels were significantly lower in case patients compared with 41 age-matched healthy controls (41.6 vs 74.9 nmol/L). Interestingly, within the same study, hypogonadotropic hypogonadal patients after 3 months of therapy with gonadotropins had increased 25(OH)D levels from 38.2 to 58.9 nmol/L, suggesting an interplay between male gonadal health and VitD status.

ViTD Supplementation Versus Nutraceutical Agents

We have previously reported that medicinal doses of zinc and some herbal medicines (eg, mucuna and ashwagandha) are appealing tools as a natural testosterone adjuvant in physiologic ranges.[72,73] In the present review, $VitD_3$ supplementation failed as a testosterone adjuvant when the whole body of evidence was taken into perspective. Taking into account the search of natural products on urologic health, we also found that certain herbal medicines as well as foodstuffs have some degree of effectiveness to manage noncancer prostate diseases.[73] However, VitD supplementation remains inconclusive to the extent of improving clinical assessment of prostate diseases. Given the paucity of evidence on VitD supplementation and prostate health, instead of its use, widespread, healthy lifestyle changes based on physical exercise and weight management are more rational approaches.[74,75]

Limitations and Clinical Aspects

Even with a systematic search strategy to find quality evidence, only 8 interventional studies were included in the present review to describe findings about the effects of VitD supplementation on

testosterone levels. Most studies examined young males and addressed a small number of middle-aged men with borderline adequate 25(OH)D levels. Thus far, the evidence based on this clinical background with $VitD_3$ supplementation points to a lack of efficacy of $VitD_3$ as a testosterone adjuvant, especially in eugonadal conditions. This global insight is important because lay consumers have a wide aspiration to increase testosterone levels using nutraceutical agents that are vulnerable to unsubstantiated advertising, which even extends to clinical practice.

To the best of our knowledge, no clinical trials have analyzed the interdependence between VitD supplementation in elderly mean with low concentrations of 25(OH)D and testosterone. Therefore, further research with the particular aim to assess this population with requisite measures is worthwhile to provide key knowledge for endocrinologists, urologists, andrologists, and dietitians. On top of that, systematic reviews with meta-analyses are a reasonable means of propagating pooled estimates and general findings, but the focus on the clinical characteristics of patients should be extended to who would most need VitD supplementation.

Moreover, there is increasing evidence of resistance to the achievement of adequate 25(OH)D concentrations using conventional VitD supplementation. For instance, because VitD is fat soluble, accumulation is predominant in adipose tissue.[76] In this sense, obese individuals are more susceptible to serum 25(OH)D deficiency when the accumulation of VitD in the adipose tissue inhibits release into systemic circulation, resulting in lower levels.[77] Furthermore, very high doses of vitamin D supplementation may be required to minimally increase serum 25(OH)D concentrations, in patients with autoimmune diseases.[78] Situations such as these should be considered in future studies given that patients with obesity and autoimmune diseases often have deficiency of 25(OH)D and testosterone levels.[79–81]

CONCLUSION

Mechanistically, VitD has several essential roles in various organs (eg, heart, muscle, bone, and gut), including organs of the male reproductive system, such as testis and prostate. Thus far, despite physiologic importance of VitD in modulating the testicular steroidogenesis, there is no sound evidence for the use of VitD supplementation as a testosterone adjuvant, as detailed in this structured literature review. The evidence on VitD supplementation remains inconsistent in urologic conditions, particularly as an adjuvant to improve sperm and prostate parameters. Practitioners should refrain from any enthusiasm regarding VitD supplementation and 25(OH)D screening for urologic heath. The evidence presented in this review represents another nail in the coffin for VitD as a magic bullet. Definitive long-term clinical trials are needed to confirm the effects of VitD supplementation on diseases critical to urologic health with an emphasis on hypogonadism, BPH, and prostate cancer.

AUTHOR CONTRIBUTIONS

HOS wrote the manuscript and carried out the conception and design of the article; FJT, KN, SH wrote the manuscript.

CONFLICT OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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