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Vitamin D effects on androgen levels in men

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Abstract. Background. Accumulating evidence from animal and human studies suggests that vitamin D is involved in many functions of the reproductive system. Considering the potential link between vitamin D and human fertility, authors performed this review summarizing current literature on vitamin D and possible mechanisms explaining the link of vitamin D with androgen metabolism in men. The purpose of this review was to provide an overview on the effects of vitamin D on androgen metabolism in men. **Methods.** Author performed a systematic literature search in PubMed for relevant English language publications published from January 2011 until September 2021. **Results.** The vitamin D receptor and vitamin D-metabolizing enzymes are found in reproductive tissues. In men, vitamin D status has been associated with androgen levels and hypogonadism. Further, there is some evidence for a favorable effect of vitamin D supplementation on testosterone concentrations, although others failed to show a significant effect on testosterone levels. Vitamin D might play an important role in androgen metabolism. Existing evidence from available trials evaluating the effect of vitamin D supplementation on androgen levels in men is insufficient to recommend measurement of 25(OH)D levels or vitamin D supplementation in hypogonadal men. We cannot exclude vitamin D effects on androgen levels in men with low TT levels or in men with severe vitamin D deficiency. This question remains to be answered in future investigations. **Conclusions.** Vitamin D deficiency is associated with adverse fertility outcomes including hypogonadism, but the evidence is insufficient to establish causality. High-quality trials are needed to further evaluate the effects of vitamin D supplementation on androgen levels in men.

Keywords: vitamin D; testosterone; hypogonadism; review

Considering the high prevalence of an insufficient vitamin D status in many populations as well as the potential link between low vitamin D status and adverse health outcomes [1], vitamin D deficiency is classified as an important public health problem [2]. Vitamin D has been well known for its role in maintaining calcium homeostasis and promoting bone mineralization [3]. Beyond the established relationship between vitamin D deficiency and musculoskeletal diseases, evidence is accumulating that vitamin D deficiency is also a risk marker for insulin resistance [4], cardiovascular disease [5], infectious and autoimmune diseases [6], cancer [7], increased mortality [8] as well as decreased fertility [9].

Infertility is a complex disorder with significant medical, psychosocial and economic aspects, which affects about 15 % of couples [10]. Besides the important causes of female infertility, population-based studies found that in 30–40 % of infertile couples, the underlying cause is the male factor [11]. One major aspect regarding male fertility is the complex interaction between pituitary gland and testis. Of note,

testosterone is not only an important regulator of spermatogenesis, but decreasing testosterone levels might also contribute to many adverse aspects of male aging [12].

It is therefore worth mentioning that similar to the above stated association of low vitamin D status with adverse health outcomes, several lines of evidence suggest that low testosterone levels are associated with adverse events including higher cardiovascular and all-cause mortality [13, 14]. In this context, it should be noted that androgen and vitamin D metabolism seem to be associated [15].

Considering the potential link between vitamin D and human fertility, we performed this review summarizing current literature on vitamin D and possible mechanisms explaining the link of vitamin D with androgen metabolism in men.

We performed a systematic literature search in PubMed for relevant publications published from January 2011 until September 2021. We used the following search terms: “vitamin D” and “testosterone”, “vita-

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min D” and “hypogonadism”. In addition, we also used the search terms “25-hydroxyvitamin D (25(OH)D)”, “1,25-dihydroxyvitamin D” and “calcitriol” instead of vitamin D. We also used listed references from selected articles to expand the search.

In addition to its important regulatory effect on spermatogenesis, testosterone is an anabolic hormone with a wide range of beneficial effects on men’s health, including important physiological effects on brain, muscle, bone and fat mass [16]. There is accumulating evidence suggesting that androgen deficiency may contribute to the onset and progression of cardiovascular disease and play an important role in the development of the metabolic syndrome in men [17]. Men with combined vitamin D and androgen deficiencies are at high risk for all-cause and cardiovascular mortality, suggesting that a parallel deficiency of both hormones is a marker of poor overall health [18]. Thus, a causal relationship between vitamin D and testosterone and in particular a potential increase of testosterone levels after vitamin D treatment is of high clinical interest.

Testosterone is produced in the Leydig cells following pituitary pulsatile luteinizing hormone (LH) secretion, but its production is also modulated by paracrine and autocrine signals supplied by growth factors and cytokines secreted within the testis [19]. The vitamin D receptor (VDR) is almost ubiquitously expressed in human cells, which underlines the clinical significance of the vitamin D endocrine system [20]. VDR and vitamin D-metabolizing enzymes are concomitantly expressed in the entire reproductive male tract, including Leydig cells [21]. This VDR expression suggests local autocrine as well as paracrine action of vitamin D and indicates that vitamin D is involved in regulation of testis function. Obviously, vitamin D metabolites are locally synthesized and degraded and vitamin D metabolism seems to be regulated by local as well as systemic factors [22]. The negative effect of orchiectomy as well as testis dysfunction on circulating 25(OH)D levels, supports the hypothesis of vitamin D synthesis in the testis [23]. It has been shown in an experimental study that mouse Leydig cells basally secrete 25(OH)D, which is also stimulated by human chorionic gonadotropin (hCG) [24]. This notion is supported by the fact that hCG treatment in men with late-onset hypogonadism increased circulating 25(OH)D levels [24]. Despite this hypothesis of a local 25(OH)D production in the testis driven by Leydig cells, the exact regulation of testis vitamin D metabolism is largely unknown. Some evidence suggests that regulatory mechanisms resembling renal vitamin D metabolism exist. These mechanisms include parathyroid hormone (PTH) related molecules and fibroblast growth factor (FGF-23) pathways [22].

It has been shown that androgens increase 1- α -hydroxylase, a key enzyme in vitamin D metabolism that converts 25(OH)D to 1,25(OH)₂D [25]. The regulation of gene expression by vitamin D metabolites is modified according to androgen levels [26]. Vitamin D significantly increased testosterone production in a human primary testicular cell culture model [27]. After 1,25(OH)₂D supplementation, 63 genes were significantly upregulated in human testicular cells, such as *IGF-1*, *ALPL*, *DPP4* and other bone- and immune system-associated genes [27].

In male VDR-knockout mice, high LH and follicle-stimulating hormone (FSH) levels indicate the presence of hypergonadotropic hypogonadism [28].

Vitamin D may be critical for testicular function because vitamin D treatment upregulates certain testis-specific genes in mice including ATP-binding cassette transporter 1 [29]. ATP-binding cassette transporter 1-knockout mice have significantly reduced intratesticular testosterone levels as well as reduced sperm counts compared with wild-type animals [30].

Vitamin D effects on testosterone production might also be mediated via osteocalcin, which is produced by osteoblasts and involved in bone metabolism. It has been postulated that vitamin D-induced stimulation of osteocalcin expression might have an indirect relevant role in modulating testosterone production by the testis [22]. In humans a direct stimulatory genomic effect of vitamin D on steroidogenesis enzymes has been postulated [22].

The majority of studies found an independent association of vitamin D with circulating androgen levels or hypogonadism in men. K. Nimptsch et al. [31] reported an independent association of 25(OH)D with total testosterone (TT) and free testosterone (FT) levels in 1362 male participants of the Health Professionals Follow-up study. D.M. Lee et al. [32] observed no independent association of TT or FT with 25(OH)D in 3369 community-dwelling men aged 40–79 years from the European Male Aging study. There was, however, an independent association of 25(OH)D levels < 50 nmol/L with compensated as well as with secondary hypogonadism [32]. Similarly, R. Jorde et al. [33] found a significant positive association of vitamin D and TT levels (adjusted for age, BMI, season, presence of cardiovascular disease and DM and physical activity) in 893 men from the Tromsø Study. In that study, no significant association was found between 25(OH)D and FT, sex hormone binding globulin (SHBG), FSH or LH [33].

In 2854 Chinese men, 25(OH)D was positively associated with TT and estradiol after adjustments for age, residence area, economic status, smoking, BMI, HOMA-IR, diabetes mellitus (DM) and systolic pressure. Increasing quartiles of 25(OH)D were associated with significantly decreased odds ratios of hypogonadism [34].

A.C. Heijboer et al. [35] observed a significant positive association of 25(OH)D and TT levels in 183 men. In addition, a significant positive association of TT and SHBG with 25(OH)D levels was reported in 382 Chinese and Malaysian men [36]. Y.J. Tak et al. [37] found an independent association of 25(OH)D levels with TT (adjusted for body fat, WC, BMI, fasting plasma glucose, DM and dyslipidemia) and FT levels (adjusted for age, total muscle mass, smooth muscle mass, total cholesterol, DM, dyslipidemia and alcohol use) in 652 Korean men aged 56.7 $\pm$ 7.9 years. Vitamin D deficiency (< 50 nmol/L) was associated with an increased risk of TT and FT deficiency (adjusting for age, season, BMI, body composition, chronic disease, smoking and alcohol use) [37].

Data from the Longitudinal Aging Study Amsterdam, an ongoing population-based cohort study of older Dutch individuals (n = 643), documented an independent association of 25(OH)D levels with TT and bioavailable TT (adjusted for age, BMI, alcohol consumption, smoking status,

season of blood collection, number of chronic diseases, serum creatinine and physical performance) [38]. Others reported a significant positive association of 25(OH)D and TT as well as SHBG in 1315 men (NHANES III) and 318 men (NHANES 2001–2004), respectively (adjusted for age, race/ethnicity, body fat percentage and smoking) [39].

Data from 1427 infertile men indicated lower SHBG and TT/estradiol ratios but higher FT and estradiol in men with 25(OH)D levels < 25 nmol/L compared to men with 25(OH)D levels > 75 nmol/L [40]. This authors observed no independent association of 25(OH)D levels with hypogonadism, estradiol, SHBG, LH or FSH, respectively. In 3016 older men, lower 25(OH)D levels were associated with lower SHBG and higher FT levels after adjusting for demographic and lifestyle variables, whereas no independent association with TT was observed [41].

A.O. Hammoud et al. [42] observed no independent association of 25(OH)D levels with TT or FT levels in 170 healthy men. Similarly, results from NHANES III suggested no significant association of 25(OH)D with TT, FT, SHBG or estradiol in 1412 middle-aged men [43]. Cross-sectional results from 225 middle-aged men suggest a U-shaped association of vitamin D status and risk of hypogonadism [44]. Previous studies showing no association of vitamin D and androgens in linear analyses might therefore be supported by previous inconsistent results with possible U-shaped or non-linear associations that have been suggested for vitamin D and cancer [45], cardiovascular disease and mortality [8]. Furthermore, inconsistent results reported in observational studies might be related to different study populations with respect to sample size, age, comorbidities, ethnicity as well as to various statistical methods used for data analyses.

In addition to the above mentioned observational studies, there are some intervention studies evaluating vitamin D effects on androgen levels in men.

A small study investigating men with Klinefelter syndrome found no significant effect of vitamin D supplementation (vitamin D treatment, vitamin D and testosterone treatment) on androgen levels in men with baseline 25(OH)D < 50 nmol/L [46]. C. Foresta et al. [47] investigated the effect of cholecalciferol (5000 IU per week) or calcidiol (4000 IU per week) in 66 patients with hypogonadism and 25(OH)D < 50 nmol/L and found no significant effect on TT levels.

In contrast, O. Canguven et al. [48] observed a significant increase in TT levels (12.46 ± 3.30 to 15.99 ± 1.84 nmol/L) in 102 middle-aged men with 25(OH)D < 75 nmol/L who received an initial vitamin D dose and followed a vitamin D treatment regime thereafter. The authors observed an increase of erectile dysfunction scores as well as a decrease in estradiol levels after treatment.

Evidence from randomized controlled trials (RCTs) on vitamin D and TT is sparse. S. Pilz et al. [49] investigated the effects of 1 year of vitamin D supplementation (3332 IU daily) on androgens in 54 men undergoing a weight reduction program. The authors observed a significant increase in TT levels, bioactive testosterone levels, and FT levels compared to baseline levels, whereas no significant change was found in the placebo group. The study included men with vitamin D deficiency (25(OH)D < 50 nmol/L) and rela-

tively low baseline TT levels (11.4 nmol/L). Of note, no statistical analysis on treatment effect (between group differences) was performed.

In contrast, A.C. Heijboer et al. [35] failed to find an effect of vitamin D supplementation on serum TT concentrations in 3 independent intervention studies including male patients with heart failure, male nursing home residents and male non-Western immigrants in the Netherlands. Those studies were designed to investigate vitamin D effects on the renin-angiotensin-aldosterone system, effects of different vitamin D doses and vitamin D effects on insulin sensitivity. Similarly, R. Jorde et al. [33] failed to show a significant vitamin D effect on androgen concentrations (TT and FT) in pooled data from 3 vitamin D RCTs performed in Tromsø with weight reduction, insulin sensitivity and depression scores as endpoints. In that study, serum 25(OH)D and androgens were measured in 282 men at baseline and after 6–12 months of vitamin D supplementation (20.000–40.000 IU weekly vs placebo).

E. Lerchbaum et al. [50] presented results of the first RCT (Graz Vitamin D&TT-RCT) designed for the evaluation of vitamin D effects on serum androgens in men. Authors randomly assigned 100 men with TT levels ≥ 10.4 nmol/L and 25(OH)D levels < 75 nmol/L to receive 20.000 IU/week of vitamin D₃ or placebo for 12 weeks. They found no significant effect on androgen levels in these healthy men with relatively high TT levels at baseline.

Conclusions

Vitamin D might play an important role in androgen metabolism. Existing evidence from available trials evaluating the effect of vitamin D supplementation on androgen levels in men is insufficient to recommend measurement of 25(OH)D levels or vitamin D supplementation in hypogonadal men. We cannot exclude vitamin D effects on androgen levels in men with low testosterone levels or in men with severe vitamin D deficiency. This question remains to be answered in future investigations.

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Вплив вітаміну D на рівень андрогенів у чоловіків

Резюме. Актуальність. Отримані в попередніх дослідженнях на тваринах і людях дані показують, що вітамін D бере участь у багатьох функціях репродуктивної системи. Розглядаючи потенційний зв'язок між вітаміном D і рівнями андрогенів у чоловіків, автори огляду узагальнили поточну літературу про вітамін D та можливі механізми, що пояснюють зв'язок вітаміну D із метаболізмом андрогенів у чоловіків. **Метою** цього огляду було оцінити вплив вітаміну D на метаболізм андрогенів у чоловіків. **Методи.** Проведений систематичний пошук літератури в PubMed, щоб знайти відповідні публікації англійською мовою, опубліковані із січня 2011 року по вересень 2021 року. **Результати.** Рецептори вітаміну D і ферменти, що метаболізують вітамін D, знаходяться і в репродуктивних тканинах. У чоловіків рівень вітаміну D пов'язаний із концентрацією андрогенів у сироватці крові і наявністю гіпогонадізму. Крім того, наявні деякі докази сприятливого впливу додаткового призначення вітаміну D на концентрацію тестостерону. При цьому в окремих дослідженнях не встановлено істотного впливу адекватно-

го забезпечення вітаміном D на рівень тестостерону. Вітамін D відіграє важливу роль у метаболізмі андрогенів. Більшість опублікованих результатів досліджень підтверджують позитивний вплив додаткового призначення холекальциферолу на рівень андрогенів у чоловіків. Однак цих даних все ще недостатньо, щоб рекомендувати визначення рівня 25(OH)D або включати в комплекс лікування вітамін D у чоловіків із гіпогонадізмом. Автори констатують позитивний вплив вітаміну D на рівень андрогенів у чоловіків із низьким рівнем тестостерону або у чоловіків із тяжким дефіцитом вітаміну D. Остаточну відповідь на розглянуті аспекти проблеми ще потрібно отримати в подальших дослідженнях. **Висновки.** Дефіцит вітаміну D асоціюється з несприятливими наслідками репродуктивної функції, включаючи гіпогонадізм. При цьому все ще недостатньо доказів для встановлення причинно-наслідкового зв'язку. Для подальшої оцінки впливу додаткового призначення вітаміну D на рівень андрогенів у чоловіків необхідні подальші дослідження. **Ключові слова:** вітамін D; тестостерон; гіпогонадізм; огляд