

Review Article

Male sexual health and dysfunction

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Vitamin D and Male Erectile Function: An Updated Review

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Literature support that vitamin-D is important for different systems of the human body including, but not limited to endocrine and immune systems, vasculature and endothelial function of the body. Male erectile function depends on many factors and can be perceived as a health indicator of the body. Epidemiological data have shown that vitamin-D deficiency is also associated with erectile dysfunction. In this review, our aim is to interpret the mechanisms by which vitamin-D might regulate anatomy and physiology of penis. Evidence showed that vitamin-D is needed for an adequate erectile function. Briefly, vitamin-D is crucial for a better healthy body and sexual activity.

Keywords: Andrology; Endothelium; Erectile dysfunction; Hormones; Male; Vascular endothelium

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INTRODUCTION

Human sexual activity is the manner in which humans experience and express their sexuality. Male penile erection is a physiological phenomenon in which the penis becomes firm, engorged, and enlarged in response to sexual arousal during sexual activity [1]. Penile erection is the result of a complex interaction of psychological, neural, vascular, and endocrine factors in the presence of a normal penis anatomy [2]. Penile erection is initiated by nitric oxide (NO), a potent vasodilator, released from the nerve endings, further production of NO depends on increased blood flow which is also known as shear stress [3]. In most vascular beds, the NO is released by a stimulus that increases the shear stress over the endothelium. Endothelial

dysfunction is a key variable in the pathogenesis of atherosclerosis and its complications, including erectile dysfunction (ED).

ED is defined as the inability to attain or maintain erection sufficient for satisfactory sexual activity [2]. Over the past 20 years, there have been numerous reports on the epidemiology of ED all over the world [4-7]. In all studies, it was demonstrated that the prevalence of ED increases with age [4,7]. In other words, higher age is strongly associated with higher incidence of ED [7,8]. In men under the aged 40 to 49 years, the prevalence of ED was relatively low (~40%) and in men aged 70 to 79 years, the prevalence of ED was significantly higher (~90%) [6,7,9]. The etiology of ED has been studied comprehensively and found to be multifactorial. ED is frequently found in vascular syndromes, such

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as atherosclerotic cardiovascular (ASCV) diseases, hypertension, cerebrovascular disease, peripheral arterial disease and diabetes mellitus (DM) [8,10-12]. In fact, the penis is a highly vascularized organ and erections are primarily vascular events. Both ED and ASCV diseases have frequently identical functional and morphologic basis [3,12]. Because of its vascularity, ED is even accepted as a marker of coronary endothelial dysfunction and atherosclerosis [10,12].

In the last decades, several studies have correlated ED risk factors with vitamin-D (VD) deficiency (VDD) [5,13,14]. Observational and interventional studies published in literature have established a strong relationship between VD levels and ED. This important knowledge turned scientists to go in deep for the effect of VD on erectile function. Shortly, it is now well known that VD is a part of well-functioning penis starting from the early days of our lives.

VITAMIN-D

VD, which is actually a steroid hormone, has much more assorted role in human body for a vitamin than previously recognized just for calcium metabolism [15]. Since it was shown that VD-receptor (VDR) is expressed in all tissues of human body including penis, VD regulates cellular differentiation and function across many cell types [1,16-23]. VD effects are facilitated through binding to the VDR and stimulating not only genomic but also non-genomic effects [19,22]. Upon VD binding, VDR translocates from the plasma membrane to the nucleus where it transcriptionally activates genes *via* the VD response element, thereby affecting transcription of other genes [19]. Human Genome Project study results showed that a human DNA has between 20,000 and 25,000 genes [24], and more important to us, surprisingly, over 3,000 genes are responsive to VD [25].

Unfortunately, the estimated worldwide prevalence of VDD is really high and common among the elderly. VDD is about 50% at older ages and this result underlines the importance of VDD for public health [26,27]. If we consider that VD effect many tissues, VDD becomes more and more important for a healthy sexual life, in other words for erectile function.

1. Essentials of vitamin-D

Vitamins D2 (ergocalciferol) and D3 (cholecalciferol)

are two dominant forms of VD. Vitamin D2 is synthesized by invertebrates and plants after exposure to ultraviolet radiation [1]. Vitamin D3 is naturally present in a small range of foods (such as oily fish, egg and fortified dairy products) and is also made endogenously in the skin. Dietary VD typically comprises only 10% to 20% of circulating levels of VD [28]. If we look at the VD physiology, one can see that Vitamin D2 and D3 are biologically inactive and subjected to double hydroxylation, first mainly in the liver and then in the kidney, to produce the biologically active compound calcitriol [1,14,21,29,30]. Although $1,25(\text{OH})_2\text{D}$ is the most active form of VD and undertakes the major biological function, it has a shorter half-life (~0.3 and 25 days, respectively) and a 1,000-fold lower concentration than $25(\text{OH})\text{D}$ [31]. More importantly, serum $25(\text{OH})\text{D}$ is relatively stable and not directly influenced by diet (*e.g.*, calcium intake) and life style (*e.g.*, mobility) [31]. Hence, total-body VD stores are best reflected by $25(\text{OH})\text{D}$ [31]. Earlier, it was proved that availability of ultraviolet-B exposure, and its resultant VD production in skin, is highest in late spring through early fall and lowest from late fall through early spring [26]. In addition to seasonal variations, there are many other factors that can affect the prevalence of VDD. These can be summarized as region and latitude, diet and supplement use, clothing, obesity, smoking, concerns about sun damage, and the nature of built environment [32].

VITAMIN-D AND ERECTILE DYSFUNCTION

A general population study showed that low serum VD was associated with higher prevalence of peripheral arterial disease [33]. Likewise, a very recent cross-sectional analyses (3,390 men aged >20 years, free of ASCV disease) also reported that VDD was associated with an increased ED prevalence [14]. In support, deficient levels of VD <20 ng/mL were associated with increased ED risk, where a decreased prevalence of ED was associated with VD levels >35 ng/mL [14]. When researchers restricted their analysis to the 562 men (among 3,390 men) adjusted for sex hormone levels, the association of VD with ED became even stronger [14]. The biological link between VDD and ED exhibits several interlaced mechanisms that could suggest that the link of VD with ED appears to be independent of sex hormones [14].

1. Vitamin-D and architecture of the penis

There are many risk factors in the etiology of ED which might be directly arising from VDD. Since the latest literature showed the importance of VD on erectile function, Fernandes-Lima et al [34] investigated the effects of VD restricted diet on Wistar rats offspring penis morphology. Fernandes-Lima et al [34] demonstrated that VD restriction during perinatal and post-natal periods induced metabolic and structural changes and represented important risk factors for ED in the penis of the adult offspring. The latter findings suggest that VD is an important micronutrient in maintaining the cytoarchitecture of the penis [34]. In other words, human body requires VD for the proper anatomical development of the penis during embryonal life.

2. Vitamin-D and endothelial function

The pathophysiology of ED is multifactorial, but common point is a vascular disorder related to decreased endothelial function. Indeed, one of the most significant mechanism of VD on erectile function seems to work *via* endothelial integrity [30,35]. In molecular levels, VD stabilizes the quiescent endothelium, regulates certain stages of endothelial activation, and is involved in the repair of the damaged endothelium *in vitro* and *in vivo* models. A recent 12 cross-sectional studies, including 2,086 subjects of varying ethnic groups, showed an association between endothelial dysfunction and VDD [36]. Also, VD may directly protect endothelial cells against oxidative stress, and hence, VDD may contribute to ED through inflammation [30].

Many ED patients are VD deficient, particularly patients with arteriogenic ED [5]. Epidemiological data in humans have shown that VDD is associated with hypertension, left ventricular hypertrophy, increased arterial stiffness, and endothelial dysfunction in normal subjects [30]. Men with ED have an increased prevalence of endothelial dysfunction, and VD may improve endothelial function [14]. A placebo-controlled randomized trial demonstrated that even a single large dose of VD improves endothelial function in patients with type 2 diabetes and VDD [37]. Since endothelial function improvement is the cornerstone of the treatment of ED, VD supplementation may be beneficial in the treatment of ED patients.

3. Vitamin-D and nitric oxide production

Another important mechanism of action of VD seems

to be *via* NO mediated vascular dilation. NO synthases (NOS) are a family of enzymes that catalyze the production of NO from L-arginine. NO-pathway is a well-known physiologic signal essential to penile erection. Shortly, sexual stimulation releases neurotransmitters from the corpus cavernosa as well as NO (a relaxing factor) from the endothelial cells of the penis [28]. Any kind of disorders that reduce NO synthesis or release in the erectile tissue are commonly associated with ED. Activated VD stimulates the production of NO in endothelial cells and NOS [38], and is a key to vascular dilation and thereby critical to preventing ED. Molinari et al [38] demonstrated that VD is able to stimulate NO production in human umbilical vein endothelial cells through endothelial NOS (eNOS) activation.

The finding of an involvement of VD in NO production by endothelial cells is quite relevant. Recently, Andrukhova et al [30] reported that VDR mutant mice are characterized by lower bioavailability of the vasodilator NO due to reduced expression of the key NO synthesizing enzyme *i.e.*, eNOS. Reduction in eNOS ends with endothelial dysfunction, increased arterial stiffness, increased aortic impedance, structural remodeling of the aorta, and impaired systolic and diastolic heart function at later ages, independent of changes in the renin-angiotensin system [30]. This may also clarify why endothelium derived; NO-evoked dilation is halved in arteries from VD deficient male rats [35]. Under the light of recent scientific researches, unsurprisingly, there exists a higher prevalence of ED among VD deficient patients compared to those with optimal levels [14].

4. Vitamin-D and atherosclerotic cardiovascular diseases

Penile erection predominantly depends on vascular event and according to several studies there is a strong association between ED and ASCV diseases [39]. Unfortunately, VDD is associated with atherogenic dyslipidemia, DM, and reduced serum testosterone (T) levels all of which are associated with endothelial dysfunction and are classic risk factors for the onset of ED [13,14,18].

Recently, Barassi et al [5] demonstrated a higher presence of VDD in arterial ED patients compared with non-arterial-ED patients and a lower serum VD levels in more severe ED patients. Melamed et al [33] has shown that low serum VD levels are associated with a higher prevalence of peripheral arterial disease in the general population. Additionally, an earlier

study done with more than 7,000 VD deficient patients showed an association between VDD and several cardiovascular disease (CVD) states such as hypertension, coronary artery disease as well as ASCV risk factors (DM, dyslipidemia *etc.*) [18]. However, a recent cross-sectional analysis of 3,390 men aged >20 years, found that VDD in individuals free of ASCV diseases was associated with an increased prevalence of ED [14].

The available literature evaluating VD supplementation and its relationship to ASCV diseases are limited in number. However, in an observational retrospective study involving more than 10,000 patients Vacek et al [18] showed that VD supplement use improved survival in deficient subjects, supporting the potential benefit of this intervention. Later, in a randomized placebo-controlled preliminary study, Al-Dujaili et al [40] suggested that daily VD supplementation may ameliorate CVD risk factors.

5. Vitamin-D and endocrine system

T modulates nearly every component involved in erectile function and its deficiency associated with ED [41]. In an ageing male population, hypogonadism is common (30% prevalence in men >60 years), and is associated with ASCV risks (*e.g.*, atherogenic lipid profile, insulin resistance and obesity) [42]. The Longitudinal Aging Study Amsterdam, showed serum VD was positively associated with total and bioavailable T levels [43]. In another study, with large population group (2,854 men), investigators revealed that a lower VD level is associated with a higher prevalence of hypogonadism [44]. The latter result was supported by another study of 652 men over 40 years of age [45]. VD was significantly and positively associated with T levels before and after adjustment for age and ethnicity [46].

VD is positively associated with T, exhibits a concordant seasonal changeability [47], elevates when T was supplemented in hypogonadism [48]. Surprisingly, the reverse situation is also true, suggesting that VD supplementation might increase T levels [49]. In a clinical randomized controlled trial, which is the first on this topic in literature, Pilz et al [49] investigated the effect of VD supplementation on androgens in men. The results were significant and the researchers observed that overweight men with VDD had a clinically meaningful increase in serum T levels after VD supplementation for 1 year [49]. Recently, it was

also demonstrated that VD supplementation improves T levels, metabolic syndrome and erectile function in middle-aged VD deficient men [8]. Canguven et al [8] supported earlier research where serum total-T effectively increased after VD treatment [49,50]. Likewise, Wehr et al [47] demonstrated that androgen levels were associated with VD levels in 2,299 older men; and also a cross-sectional analysis of men in a national survey found that increasing VD ends with higher total-T levels [51]. Certainly, it has been advocated that the most advantageous serum VD concentrations begin at 30 ng/mL, and the best are between 36 to 40 ng/mL [52].

6. Vitamin-D and androgen receptors

An extra mechanism of VD on erectile function seems to function *via* binding to T receptors. Computer (*in silico*) modeling shows that besides activating the VDR, 1,25-D displays high affinity for some of the body's other nuclear receptors. This suggests that when 1,25-D increases above its normal range, it binds the α/β thyroid, the glucocorticoid, and the T receptors, displacing their native ligands [53]. Marshall [54] showed the symmetry with which endogenous ligands exhibited very similar affinities across some members of the type 1 nuclear receptor family [54]. For example, 1,25-D docked into the VDR with a (nanomolar) Kd of 8.48, but also exhibited a Kd of 8.05 into the T receptor.

7. Vitamin-D and immune system

ED is associated with an incremental inflammatory activation and inflammation plays an important pathophysiological role in both ED and ASCV diseases [12,39,55]. It has been extensively debated that inflammation can exert a detrimental effect on the ASCV system *via* two pathways: chronic, low-grade inflammation and an acute systemic inflammatory response. The former has been implicated in atherosclerotic processes [56], while the latter accounts for adverse ASCV events following severe inflammatory stimulation. Sildenafil, one of the phosphodiesterase inhibitors used as first line treatment in ED, induces a significant acute decrease in levels of pro-inflammatory markers/mediators [55]. The anti-inflammatory action might play an important role in addition to relaxation of penile smooth muscles.

Ding et al [50] revealed that VD supplement may protect the cells through suppressing inflammation factors and alleviating cell apoptotic death, as well to

reproduction and T synthesis. Ding et al' study [50] indicated that VD played a protective role of testes and testicular damage induced by diabetes, and the possible mechanism might be regulating attenuating inflammation and inactivating caspase cascade. Emerging data suggests that VD has a potential role in regulating inflammation. In research, it was shown that VD inhibits the expression of inflammatory cytokines in monocytes, including interleukins-1, 6, 8, 12, and tumor necrosis factor- α [57,58]. In summary, VD may directly defend endothelial cells against oxidative stress; and VDD may contribute to ED through inflammation.

CONCLUSIONS

Based on the evidence from bench and bed, it was shown that VD is important for erectile function. Measurement of VD in ED patients is very crucial with supplementation as required. VD supplementation potentially represents a low-cost, low-risk method to treat and prevent ED. In summary, we need VD starting from the early embryonal days to the end of our lives for a better, healthy and sexually active life.

Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: OC. Data curation: OC. Formal analysis: OC, AHAM. Funding acquisition: OC. Investigation: OC. Methodology: OC. Project administration: OC. Resources: OC, AHAM. Software: OC. Supervision: OC. Validation: OC, AHAM. Visualization: OC. Writing – original draft: OC. Writing – review & editing: OC, AHAM.

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