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Invited Review

The role of vitamin D supplementation on erectile function

D vitamininin erektil fonksiyon üzerine etkisi

Raidh A. Talib[1,2], Kareim Khalafalla[1], Önder Cangüven[1,2]

ABSTRACT

In the last few years growing evidence highlighted vitamin D (VD) deficiency is one of the several dynamics that associates with increased atherosclerotic cardiovascular (ASCV) diseases. ASCV diseases and erectile dysfunction (ED) share common risk factors such as diabetes mellitus, hypertension, smoking, hyperlipidemia, and a sedentary lifestyle. The aim of this review was to summarize current progress in VD research by focusing effect of low VD level on different body systems and erectile function. Here we examine research linking VD deficiency and ED and discuss how VD influences ED and its classic risk factors-factors that also associate to increased ED risk. We also summarize research indicating that VD associates with reduced risk of several nonvascular contributing factors for ED. Available literature demonstrates relatively high rates of low VD serum levels in ED patients. Based on the preclinical and clinical data available in the literature, to date, we infer that VD play a critical role in maintaining erectile function in humans. Nevertheless, this should also be tested through randomized controlled studies on the effect of VD supplementation with larger population.

Keywords: Erectile dysfunction; health status; humans; nutritional requirements; primary prevention/standards; vitamin D deficiency.

ÖZ

Son birkaç yıl içinde giderek artan kanıtlar D vitamini (DV) eksikliğinin artmış aterosklerotik kardiyovasküler (ASKV) hastalıklarla ilişkili birkaç dinamik sürecin biri olduğunu vurgulamıştır. ASKV hastalıkları ve erektil disfonksiyon (ED) diabetes mellitus, hipertansiyon, sigara içimi, hiperlipidemi ve hareketsiz yaşam tarzı gibi sık görülen risk faktörlerini paylaşmaktadır. Bu derlemenin amacı düşük DV düzeyinin vücudun farklı sistemleri ve erektil fonksiyon üzerine etkisine odaklanmış, DV araştırmasındaki güncel ilerlemeyi özetlemektir. Bu makalede DV eksikliğini ED ile ilişkilendiren araştırmayı incelemekte ve DV'nin ED'yi ve aynı zamanda artmış ED riskiyle bağlantılı klasik risk faktörlerini nasıl etkilediğini inceledik. Ayrıca DV'nin ED'ye katkı sağlayan vasküler-olmayan faktörün riskini azalttığını belirten araştırmaları özetlemeyi hedefledik. Mevcut literatür ED hastalarında göreceli yüksek oranda düşük serum DV düzeylerinin varlığını göstermektedir. Literatürdeki şimdiye kadar mevcut klinik öncesi ve klinik verilere dayanarak, DV'nin insanlarda erektil fonksiyonun sürdürülmesinde kritik bir rol oynadığı sonucuna varmaktayız. Bununla birlikte, DV katkısının ED üzerine olan etkisi daha geniş popülasyonda gerçekleşen randomize kontrollü çalışmalarda sınanması gerekir.

Anahtar sözcükler: Erektil disfonksiyon; sağlık durumu; insanlar; besinsel gereksinmeler; birincil korunma/standartlar; D vitamini eksikliği.

[1]Hamad Medical Corporation, Department of Urology, Doha, Qatar

[2]Weill Cornell Medical College, Department of Urology, NY, USA

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Correspondence: Raidh A. Talib
E-mail: riad_talib@yahoo.com

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Introduction

Nearly a century ago in 1922, McCollum et al.[1] reported that the factor that cures rickets was a new vitamin, which they called vitamin D (VD). In the same year, Dr. Heaton was defining VD "as one of the substances necessary to the life of the cell and that it differs from most other such substances in undergoing dilution by diffusion into the surrounding medium".[2] Recent research suggests that nearly every cell of our body has receptors for VD, indicating a much more diverse role for this vitamin than we previously recognized. VD is now recognized not only for its importance in bone health, but also for other organs including the penis.

Vitamin D receptor is expressed in most tissues and regulates cellular differentiation and

function of many cell types.[3-6] VD receptor is a member of the steroid receptor superfamily. Strikingly, over 3,000 genes are responsive to VD[7] and its biological effects are mediated through binding to the VD receptor and inducing either genomic or non-genomic down-stream effects (Figure 1).[4,5,8-10] Once bound with VD, the VD-receptor moiety translocates from the plasma membrane to the nucleus where it transcriptionally activates genes via the VD response element, thereby affecting transcription of other genes.[8]

When a man is sexually stimulated, neuronal nitric oxide (NO) synthase is triggered, inducing a smooth muscle dilatory effect of NO, which is then, amplified by the release of endothelial NO synthase (eNOS) and endothelial stimulated release of additional NO. Ultimately, the NO causes a locally mediated increase in levels of the second messenger cGMP which further enhance the smooth muscle induced vasodilation.[11] If this NOS-NO-cGMP chain reaction cannot occur, it is defined as erectile dysfunction (ED), which is the inability to attain and/or maintain a satisfactory erection for sexual intercourse. Male sexual arousal is a complex process that involves the brain, hormones, nerves, muscles, psychological factors, the environment and blood vessels.

Penile erection is predominantly a vascular event and according to the studies there is a strong association between ED and atherosclerotic cardiovascular (ASCV) diseases.[11] Moreover, ED can be viewed as an early marker of coronary endothelial dysfunction and atherosclerosis.[12,13] Risk factors such as diabetes mellitus, hypertension, smoking, hyperlipidemia, and a sedentary lifestyle are commonly seen in ED (Figure 2) and ASCV diseases.

Vitamin D has important functions all over the body beyond bone homeostasis. Recent evidence supports the presence of an association between VDD and ASCV diseases such as hypertension, peripheral vascular disease, metabolic syndrome, coronary artery disease, and heart failure (Table 1).[14] Although there are many links between ED, ASCV disease and VD, to date, there are no prospective studies evaluating VD supplementation in patients with ED.[9] The questions might be asked "What is the connection between "VD and ED?" and "Could VD supplementation offer further advantage in ED treatment?"

Effect of low vitamin D level on different body system and functions

Vitamin D deficiency and cardiovascular system

Penis is a highly vascularized organ and erections are primarily vascular events. In fact, both ED and ASCV diseases have frequently an identical functional and morphologic basis.[12] Because of its vascularity, ED is accepted as a marker of coronary endothelial dysfunction and atherosclerosis.[13]

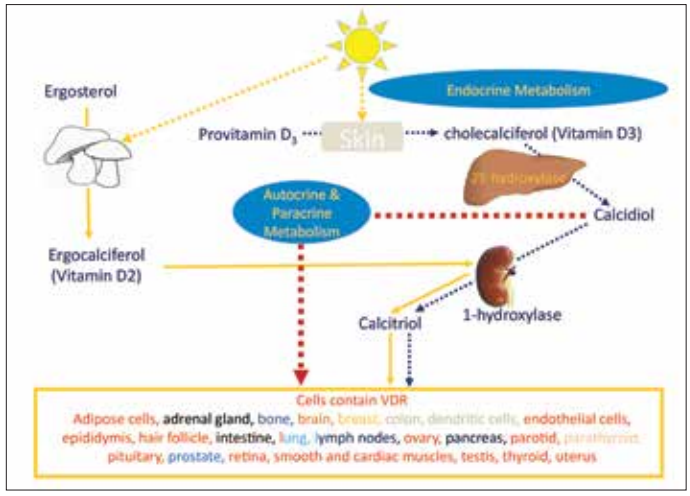

Figure 1. Synthesis, metabolism and target organs of vitamin D (Drawing by O.C.)

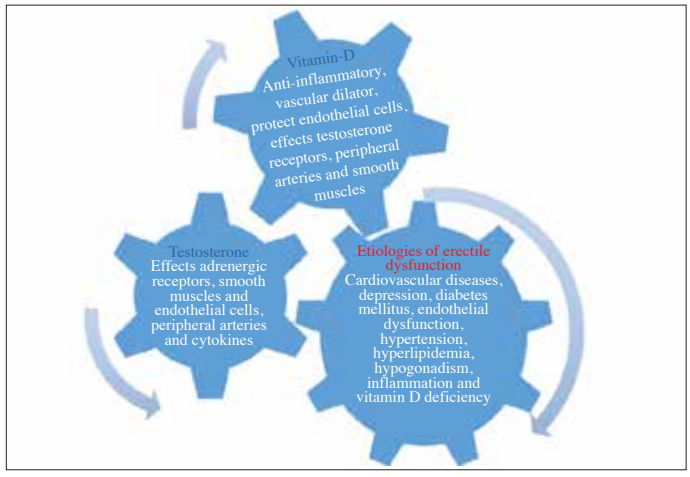

Figure 2. Etiology of erectile dysfunction and effects of testosterone and vitamin D

VDD is one of several conditions that is associated with increased CV disease.[9,14] Research in The United States has shown that low serum VD levels are associated with a higher prevalence of peripheral arterial disease in the general population.[30] Database information of more than 7,000 VD deficient patients showed an association between VDD, many CV disease states, including hypertension, coronary artery disease, and ASCV risk factors, such as hypertension, diabetes mellitus (DM), and hyperlipidemia.[14]

Many factors affect the prevalence of VDD including geographical location, diet, supplement use, clothing, obesity, smoking, concerns about sun damage and maybe most importantly the nature of the environment (Table 2). According to a cross-sectional analysis of 3,390 men aged >20 years, free of ASCV disease, VDD was associated with an increased prevalence of ED.[9] Nor-

Table 1. Higher prevalence of diseases which are associated with low serum Vitamin D levels

Abnormalities in calcium and phosphorus homeostasis[10,15]
Bronchial asthma[4,7]
Coronary artery disease[14,16]
Erectile dysfunction[9,17,18]
Heart failure[10,16]
Hypertension[9,14]
Hypogonadism[19-22]
Impaired vascular endothelial and smooth muscle function[9,16]
Increased immune or inflammatory response[23,24]
Infertility[25,26]
Metabolic syndrome[10,14,27]
Osteoporosis[19,28,29]
Peripheral vascular disease[15,30]
Respiratory diseases[3,4]

Table 2. Risk factors for vitamin D deficiency

Body mass index ≥30 kg/m^2
Clothing
Diet and supplement use
Fat malabsorption syndromes
Inadequate exposure to sunlight
Kidney and/or liver failure
Naturally dark skin tone
Nature of built environment
Patients on a wide variety of medications
Region and latitude
Smoking
Vitamin D malabsorption problems
Using sunscreen creams, lotions
Wearing sunscreen clothes

mal levels of VD [25(OH)D] range between 30-80 ng/mL; and mild to moderate, and severe deficiencies are typically observed when VD levels drop to21 to 29 ng/mL, and <20 ng/mL, respectively.[31] An increased risk for prevalent ED was seen for deficient levels of 25(OH)D below 20 ng/mL, while prevalence of ED decreases when VD levels are over 35 ng/mL.[9] The researchers of the latter study restricted their analysis to the 562 men (among 3,390 men) and found even stronger association between VD status and ED.[9]

Unfortunately, the available literature evaluating VD supplementation and its relationship to cardiovascular health are limited in number. However, in an observational retrospective study involving more than 10,000 patients, Vacek et al.[14] showed that use of VD supplement improved survival in VD deficient subjects, supporting the potential benefit of this intervention. In a randomized placebo-controlled preliminary study, Al-Dujaili et al.[32] suggested that daily VD supplementation may ameliorate risk factors for CV disease.

Although there are many triggering risk factors, vascular ED is a result of endothelial dysfunction and/or atherosclerosis; and low VD is correlated with endothelial dysfunction.[15] Arterial calcification indicates greater ED risk, and is inversely associated with serum VD levels.[9] Many ED patients are VD deficient, particularly patients with arteriogenic ED.[18] ED in both diabetic and non-diabetic men is characterized by marked endothelial dysfunction. 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.[33] Endothelium-dependent, flow-mediated smooth muscle relaxation is lost early in response to exposure to all of the major risk factors for atherosclerosis and markers of abnormal endothelial function.[34] Since improvement of endothelial function is the cornerstone of the treatment of ED, VD supplementation may be beneficial in the treatment of ED patients.

Vitamin D and endocrine system

Testosterone (T), modulates nearly every component involved in erectile function and its deficiency is associated with ED.[35] 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).[36] The Longitudinal Aging Study Amsterdam demonstrated that serum VD was positively associated with total and bioavailable T levels.[37] In another study, with large population group, investigators revealed that a lower VD level is associated with a higher prevalence of hypogonadism in Chinese men (2,854 men with a mean age of 53.0±13.5 years).[22] The latter result was supported by a study in 652 Korean men over 40 years of age.[21] VD was significantly and positively associated with T levels before and after adjustment for age and ethnicity.[19]

Vitamin D (actually is a potent steroid hormone) which is positively correlated with T, exhibits a concordant seasonal fluctuation[38], and elevates when T is supplemented in androgen deficient men.[28] Amazingly, the reverse situation is also true, suggesting that VD supplementation might increase T levels.[39] Although such a possible association between serum VD and T has been reported, still conflicting findings still exist.[40]

In addition to clinical studies, patients with hypogonadism often have low VD levels due to the hydroxylating enzyme CYP2R1 impairment in the testis.[41] On the one hand, evidence for a positive effect of VD supplementation on semen quality and T exists[42]; and a systematic review found that in men, VD was positively associated with semen quality and androgen status. [25] When viewed collectively, research suggests a relationship between hypogonadism and low VD.[20,43,44]

Regrettably, there are few studies investigating T levels after VD supplementation. In an animal study on diabetic rats, it was demonstrated that treatment with VD for 12 weeks increased the serum level of T in treatment groups.[26] In a clinical randomized controlled trial, which is the first on this topic in literature, Pilz et al.[39] 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.[39] Recently, it was also demonstrated that VD supplementation improves testosterone levels, metabolic syndrome and erectile function in middle-aged VD deficient men.[45]

There might be many factors effecting T levels after VD supplementation. One of the probable mechanisms seems to operate via binding to androgen receptors. Computer (*in silico*) modeling shows that in addition to activating the VDR, 1,25-VD displays high affinity for some of the body's other nuclear receptors.[27] It has been suggested that when 1, 25-VD levels rise above its normal range, it binds the α/β thyroid receptors, the glucocorticoid receptor, and the androgen receptor, displacing their native ligands.[27] Marshall[29] revealed the molecular modeling of the actions of angiotensin receptor blockers upon the nuclear receptors, and showed the symmetry with which endogenous ligands exhibited very similar affinities across some members of the type 1 nuclear receptor family. 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 androgen receptor.[29] The VDR is a member of the thyroid hormone and retinoic acid receptor subfamily of nuclear hormone receptors that heterodimerizes with retinoid X receptor isoforms to regulate the expression of genes encoding factors which, in a variety of cell types, control functions such as proliferation, differentiation, metabolism, ion transport, and apoptosis, etc.[46]

Vitamin D and immune system

Erectile dysfunction is associated with an incremental inflammatory activation and inflammation plays an important pathophysiological role in both ED and CV diseases. It has been extensively debated that inflammation can exert a detrimental effect on the CV system via two pathways ie.: chronic, low-grade inflammation and an acute systemic inflammatory response. The former has been implicated in atherosclerotic processes[47], while the latter accounts for adverse CV 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. [48] The anti-inflammatory drugs might play an important role in addition to relaxation of penile smooth muscles.

A recent study revealed that VD supplement may protect the cells through suppressing inflammation factors and alleviating apoptosis, as well as upregulating the expression of genes related to reproduction and T synthesis.[26] The latter study indicated that VD played a protective role for testes and against testicular damage induced by diabetes, and the possible mechanism might be effective through regulating attenuation of inflammation and inactivating caspase cascade.[26] 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 IL-1, IL-6, TNF-α, IL-8, and IL-12.[23,24] VD may directly protect endothelial cells against oxidative stress; and VDD may contribute adversely to ED through inflammation.

Vitamin D and erectile dysfunction

Earlier research across the general population in the USA showed that low serum VD levels were associated with higher prevalence of peripheral arterial disease.[30] Likewise, in a very recent cross-sectional analyses (3,390 men aged >20 years, free of ASCV disease) it has been also reported that VDD was associated with an increased ED prevalence.[9] 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.[9] When researchers restricted their analysis to 562 men (among 3390 men) with serum levels of sex hormones and adjusted for sex hormone levels, the association of VD with ED became even stronger.[9]

Vitamins D biological activities are mediated through VD receptor (VDR). VDR and enzymes that metabolize VD are present in the testes (Sertoli cells, germ cells, Leydig cells, spermatozoa) and epithelial cells that line the male reproductive tract.[49,50] 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.[9] Men with ED have an increased prevalence of endothelial dysfunction, and VD may

improve endothelial function.[9] One mechanism linking low VD levels with ED may be via reduced synthesis of NO. Recently Barassi et al 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.[18]

Both observational and interventional studies have established the presence of an association between VD levels and ED. This relation is more than a simple relation, because there are many risk factors (Figure 2) in the etiology of ED which might be directly caused by VDD.

Vitamin D and nitric oxide production

Penis is a vascular organ, and erections have a vascular basis. NO pathway is known to mediate penile erection. NO is a physiologic signal essential for penile erection, and disorders that reduce NO synthesis or release in the erectile tissue are commonly associated with ED. Sexual stimulation releases neurotransmitters from the corpus cavernosa as well as NO from the endothelial cells of the penis.[17]

Another important mechanism of action of VD seems to be via NO- mediated vascular dilation. NO synthases are a family of enzymes that catalyze the production of NO from L -arginine. Activated VD stimulates the production of substantial quantities of NOS and NO in macrophages produced in bone and in endothelial cells in response to tuberculosis. NO is vital to vascular dilation and thereby important for the inhibition of ED.[17] Because of the presence of VD and VDR in the endothelial cells and the pivotal role of NO and eNOS in the endothelial activity, it is conceivable that an interaction between VD and NO is capable of influencing vascular function.[51] Molinari et al.[51] demonstrated that VD is able to stimulate NO production in human umbilical vein endothelial cells through eNOS activation. The finding of an involvement of VD in NO production by endothelial cells is quite relevant. NO is an essential molecule and serves multiple functions including vasodilatation and many anti-atherogenic properties. Indeed, dysregulation of eNOS activity is thought to contribute to the pathogenesis of certain vascular diseases such as atherosclerosis and hypertension.

Activated VD stimulates the production of NO in endothelial cells and NO synthases which catalyze the production of NO from L-arginine[51], is a key to vascular dilation and thereby critical for the prevention of ED. Interestingly, the latter study showed that VD response occurs within seconds and, for this reason, it appears that VD has a non-genomic direct effect on endothelial cells. Recently, Andrukhova et al.[52] reported that VD receptor 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 advanced ages, independent of changes in the renin-angiotensin system.[52] The latter group demonstrated that VD is a direct transcriptional regulator of eNOS.[52] This may also clarify why endothelium derived, and NO-evoked dilation is reduced nearly 50% in arteries from VD deficient male rats.[16] 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.[9]

Recommendations on Vitamin D supplementation

The total serum VD concentration has been uniformly accepted as an indicator of VD status.[53,54] The Endocrine Society defines VDD and insufficiency as a 25(OH)D <30 ng/mL.[10] The Endocrine Society recommends daily intake of adult VD supplements up to 4,000 IU/day[10]; and that obese children and adults be given at least two to three times more VD for their age group to satisfy their body's VD requirement. Certainly, higher doses of VD may be needed for various age groups (0-1 year, 2,000 IU/d; 1-18 years, 4,000 IU/d, and >19 years, 10,000 IU/d) to correct VDD.[10]

In conclusion, a growing body of observational data demonstrates relatively high rates of low VD serum levels in ED patients. The low VD levels may be an independent, potentially modifiable ED risk factor and treatment target. According to several evidence-based studies, measurement of VD in ED patients is logical with supplementation initiated, as required. VD supplementation potentially represents a low-cost, low-risk method to treat and reduce rates of ED. Further research with randomized controlled studies on the effect of VD supplementation seems warranted.

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