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Vasculogenic Erectile Dysfunction and Vitamin D Level in the Blood

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Abstract

Objective: The impact of vitamin D (VD) insufficiency on erectile function is still not evaluated comprehensively, although, Vitamin D deficiency is recently introduced as one of the important risk factors related to cardiovascular disease (CVD), which share many common underlying mechanisms with Erectile dysfunction (ED). This study sought to evaluate the relation between vasculogenic (ED) and serum vitamin D.

Materials and methods: A comparative case-control study was conducted at Al-Hussein university hospital in Cairo, during the period of January 2016 and December 2016, 40 patients suffering from ED and 40 healthy age-matched controls were evaluated clinically and by sonography using the international index of erectile function (IIEF-5) questionnaire and penile duplex ultrasound. Serum 25-hydroxyvitamin D [25(OH)D] level was measured in both groups.

Results: Most of ED cases (72.5%) lie in the categories of either obvious deficiency or suboptimal levels of VD; conversely, none of the control group lies in such categories. Serum 25-hydroxyvitamin D [25(OH)D] was significantly decreased in ED patients compared to normal controls (26 ± 17 *vs.* 58 ± 16 ng/ml respectively, p value<0.01). This decrease in levels of 25-hydroxyvitamin D [25(OH)D] in patients with ED was not related to its underlying vascular cause, whether arteriogenic or venogenic (p value=0.43).

Conclusion: This research demonstrates a significant association between VD deficiency and vasculogenic erectile dysfunction regardless its type. This association may be attributed to the negative impact of VD deficiency on ED risk factor.

Keywords Vitamin D; Vitamin D deficiency; Erectile dysfunction; Vasculogenic erectile dysfunction; Vascular endothelial dysfunction; The international index of erectile function-5

Introduction

Since its discovery in 1922 as an innovative therapy for rickets, vitamin D is emerging as an important factor, for bone wellbeing, as well as for the wellbeing and the appropriate function of different organs, including the cardiovascular framework [1].

The clear majority of vitamin D in the human body is obtained by in vivo synthesis in the skin after sun exposure [2], However, numerous factors may influence the synthesis of VD including the nature of the environment, geographical location, diet, oral supplementation, clothing, and the common practice of sun avoidance because of worries about skin damage and malignancies [3].

This leads to an increase in Vitamin D deficiency (VDD) rates in the latest few decades [4]. It has been estimated that approximately 1 billion individuals suffered from (VDD) around the world [5].

In the last two decades numerous evidences has suggested that VDD might be related to increased risk of cardiovascular disorders [3]. Likewise, several reports have suggested that low vitamin D levels might be related to erectile dysfunction, which seems reasonable, considering that cardiovascular diseases and erectile dysfunction (ED) share common risk factors [6-8].

However, the impact of vitamin D inadequacy on sexual capacity is still not assessed extensively. In this study, we sought to determine whether vitamin D deficiency is related to vasculogenic ED or not.

Materials and Methods

This study included 80 persons of the age group 40-50 years old, half of them suffered from ED, while the other half was normal regarding sexual function. The study was conducted at Al-Hussein university hospital, Al-Azhar University in Cairo, during the period between January 2016 and December 2016. The study had been approved by the Ethical Research Committee of the faculty of Medicine, Al-Azhar University.

Considering the results of previous studies and considering probable loss to follow-up, the aimed study population was calculated as 80 participants, providing a power of 80%.

Patients who have non-vasculogenic ED, suffering from disorders that may affect vitamin D level in the blood, diabetes mellitus, smoking, hypertension, dyslipidemia, hepatic or renal failures, cardiovascular, neurogenic or psychogenic disorders, those who are under the effect of any drugs that affect erection or vitamin D level were excluded from the study.

ED was defined as an inadequate erectile response after adequate sexual stimulation. The international index of erectile function (IIEF-5) questionnaire was presented to both groups to detect the

presence/absence and severity of symptoms related to erectile dysfunction, as previously described [9].

Patients with IIEF-5 values between 0-7 points (which refers to sever ED) and IIEF-5 values between 8-14 points (which refers to moderate ED) were categorized as patient group, while patients with IIEF-5 value >21 points were categorized as control groups (which refers to absence of ED symptoms). Patients with borderline results (IIEF-5: 15-21, which refers to mild symptoms) were excluded from the study. Subsequently, patient group were further evaluated sonographically 9z using penile duplex ultrasound to confirm the inadequacy of erectile function, to confirm its vascular nature and to detect the underlying vascular cause (arteriogenic and/or venogenic).

All Penile duplex examinations were made by the same experienced operator, blinded to patient clinical evaluation, with a high-resolution Color-Doppler ultrasound equipped with high frequency transducer (7.5-9.0 MHz), as previously described [10].

The patient is placed in supine position and the penis is positioned in its anatomical position along the anterior abdominal wall. Corpora cavernosa is localized as two well defined oval compartments with central cavernosal artery on both sides of bulbus spongiosa.

Pre-injection measurements, including inner diameter of cavernosal artery (normal value is 0.3-0.5 mm), baseline peak systolic velocity and end diastolic velocity were recorded. After intra cavernosal injection of 2 ml vasorine (papaverine), visual tumescence and erection were reported and post injection measurements (at 5, 10, 15, 20 minutes) were reported, including inner diameter of cavernosal artery (normal value is 0.6-1.0 mm), peak systolic velocity and end diastolic velocity.

Interpretation: Less than 60% increase in cavernosal diameter after papaverine injection and/or Peak systolic velocity <30 cm/sec during the examination were considered as indicators of arteriogenic impotence, while End diastolic velocity >5 cm/sec indicates venogenic impotence. Serum 25-hydroxyvitamin D [25(OH)D] levels were assessed in both groups.

Results

Serum 25-hydroxyvitamin D [25(OH)D] in patients with erectile dysfunction was significantly lower compared to control group (26 ± 17 vs. 58 ± 16 ng/ml respectively, p value <0.01) as seen in Table 1. About 72.5% of ED cases showed either obvious deficiency or suboptimal levels of serum vitamin D, while none of the control group lies in the above-mentioned categories (Spearman's Rank Correlation Coefficient=-0.21 not significant) as seen in Table 2.

Items	Group								p value
	Patient				Control				
	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum	
Vitamin D	26.25	17.31	11	91	57.97	15.8	32	96	<0.01
*Serum vitamin D in patients with erectile dysfunction was significantly lower compared to control group (26.25 ± 17.31 *vs.* 57.97 ± 15.8 respectively, p value <0.01).									

Table 1: Vitamin D level in patients vs. control group.

About 72.5% of ED cases showed either obvious deficiency or suboptimal levels of serum vitamin D, while none of the control group lies in the above-mentioned categories (Spearman's Rank Correlation Coefficient=-0.21 not significant) as seen in Table 2.

The vitamin D mean values did not show any significant difference between venogenic (No=19) and arteriogenic (No=21) cases (31 ± 22 vs. 22 ± 11 ng/ml respectively, p=0.43) as seen in Table 3.

		Control		Patient		Pearson Correlation	p value
		Count	%	Count	%		
Serum Vitamin D	Vitamin D Deficiency	0	0	23	57.5	-0.2052	Not Significant
	Suboptimal Deficiency	0	0	6	15		
	Optimal Vitamin D	17	42.5	8	20		
	Upper normal	15	37.5	2	5		
	Overdose not toxic	8	20	1	2.5		
*About 72.5% of ED cases showed either obvious deficiency or suboptimal levels of serum vitamin D, while none of the control group lies in the above-mentioned categories (Spearman's Rank Correlation. Coefficient = -0.2052, not significant).							

Table 2: Vitamin D levels in control and patient groups.

Items	Group								p value
	Venogenic (No=19)				Arteriogenic (No= 21)				
	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum	
Vitamin D	31.47	21.5	11	91	21.52	10.88	11	53	0.431
*The vitamin D mean values did not show any significant difference between Venogenic (N_o=19) and Arteriogenic (N_o= 21) cases (31.47 ± 21.5 vs. 21.52 ± 10.88 respectively, p=0.431).									

Table 3: Vitamin D levels in Venogenic vs. arteriogenic erectile dysfunction.

Discussion

Erectile dysfunction (ED) is defined as the steady failure to achieve and/or maintain a satisfactory erection for sexual intercourse [11]. ED is a multifactorial illness, and its causes could be neurogenic, psychogenic or hormonal factors, but it mainly involves a vascular issue resulted from impaired smooth-muscle relaxation, occlusion of the cavernosal arteries by atherosclerosis, or both [12].

Given the magnitude of the ED problem worldwide, conducting studies evaluating un-classical risk factors and its managements may be of high clinical and social importance. Vitamin D with about 3000 responsive genes is a multipurpose pro-hormone with several functions all over the body, beyond its well-known role in bone health and calcium homeostasis [3,13]. The functions of vitamin D are mediated by the VD nuclear receptors, which is expressed together with vitamin D metabolizing enzymes in various organs outside the skeletal system [14,15].

Since vitamin D deficiency is an important risk factor for cardiovascular disease, one would anticipate VD to contribute also to ED through similar mechanisms, however, available studies in this setting are very scarce and no enough evidence yet conclusively confirms this possible relation [16].

The aim of this study was to assess VD plasma levels in a group of patients with ED in comparison to age-matched control group and to investigate a possible relation between vitamin D level and severity of ED. This study included 80 participants, half of them suffered from ED, confirmed by using international index of erectile function (IIEF-5) questionnaire and by penile duplex examination, and the other half were normal age-matched (30-50 years) control group. The serum vitamin D level was assessed in both groups.

Since its development in conjunction with the clinical trial program for sildenafil in 1997-1999 [9,17], the international index of erectile function (IIEF-15) has been adopted by many investigators and regulatory authorities as a sensitive and reliable patient-based measurement used in confirmation and detection of severity of ED across a wide range of etiologies in clinical trials [18]. It has been linguistically validated worldwide and used as a primary endpoint in most of clinical trials related to ED, regardless of the study population [19].

An abbreviated version of the IIEF-15, the IIEF-5, also known as the Sexual Health Inventory for Men (SHIM), was developed and validated as a brief, easily administered screening instrument to discriminate between men with and without ED [20,21]. It should be stressed that, although sensitive and reliable in the diagnosis and grading of severity of ED, the IIEF scores did not discriminate the underling type of ED, which needs further penile Doppler blood flow evaluation [22].

We found that serum 25-hydroxyvitamin D [25(OH)D] in patients with erectile dysfunction was significantly lower than normal controls (26.25 ± 17.31 *vs.* 57.97 ± 15.8 respectively, p value <0.01). Furthermore, when dividing our study population, according to VD levels, most of ED cases (72.5%) lie in the categories of either obvious deficiency or suboptimal levels of VD. Conversely, none of the control group lies in such categories.

We observed that this decrease in levels of 25-hydroxyvitamin D [25(OH)D] in patients with ED was not related to its underlying vascular cause, whether arteriogenic or venogenic (p value=0.431). Barassi et al. reported that patients presented with severe erectile dysfunction were more frequent in the group of men with vitamin D levels <20 ng/ml as compared with those in the group with levels >20 ng/ml [23], The authors recommended that men with ED ought to be investigated for vitamin D levels.

Our result was also supported by another recent study done by Culha et al. and Tirabassi et al. which clarified that VDD were positively correlated with severity of sexual dysfunction assessed by the international index of erectile function (IIEF) questionnaire [24,25].

Also, Caretta et al. in another study, using IIEF-5 score and penile Doppler in assessment of severity and type of ED, reported that lower VD concentrations was associated with lower IIEF-5 score in contrast to patients with vitamin D levels more than 20 ng/ml [6]. Although, they found this association more noticeable in patients with arteriogenic ED in contrast to our results which clarified that the association between vitamin D deficiency and ED was not related exclusively to a specific underlying vascular cause. Our results seem sensible because VDD may contribute to ED through different vascular mechanisms, including arterial atherosclerosis and/or venous insufficiency due to endothelial dysfunction and not through single pathway.

Recently, Basat et al. found negative correlation between VD level and severity of ED [7]. However, Bellastella et al. denied this negative correlation as they found no correlation between the severity of erectile dysfunction and vitamin D levels in men with type 2 diabetes which may be explained by the fact that ED in diabetic patients has a multi-factorial issue which may be resulted from neurogenic, psychogenic, vascular, hormonal or metabolic factors [26].

Vitamin D deficiency could hinder erectile capacity theoretically at numerous levels. At the vascular endothelial level, activated vitamin D stimulates the creation of nitric oxide in endothelial cells, a key process in charge of the starting and maintenance of erection [27].

The normal vascular endothelium has its own anti-inflammatory properties. However, endothelial capacity is weakened in the presence of opposing inflammatory conditions and oxidative stress [12,28].

Vitamin D deficiency has been demonstrated to be associated with endothelial dysfunction, and vitamin D may directly secure endothelial cells against oxidative stress through its antioxidant capability [29].

Men with ED have increased levels of several pro-inflammatory cytokines, including CRP, tumor necrosis factor α (TNF-α) and endothelial cell adhesion molecules [30]. Current evidence suggests that adequate circulating levels of VD might be of vital importance for optimal anti-inflammatory response of immune cells, and VD supplementation has been associated with attenuation of the harmful inflammatory reaction responsible for vascular harm and endothelial apoptosis [30-33].

In a similar manner, serum vitamin D levels and arterial calcification have a solid inverse relationship [34]. Also, vitamin D has an antiproliferative impact on vascular smooth muscle cell, which represent a significant piece of the process of atherosclerosis and VDD was reported to be associated with higher penile intima media thickness, which indicates anti-atherosclerotic properties of VD that may positively influence the process of erection [6,35,36].

Likewise, VDD may also induce impairment of erection by disruption of the integrity of hypothalamic-pituitary-gonadal axis. VD receptors were reported to be found in the hypothalamus and in the pituitary gland [37,38]. Vitamin D receptors have also been found in the human testis and vitamin D is able to increase testosterone production from Leydig cells [15,39]. A seasonal positive relationship between testosterone levels and VD has been reported [40]. However, findings shown by Farag et al. who evaluated data of 3390 US men aged ≥ 20 years, suggested that the link of vitamin D with erectile dysfunction although existed, was independent of testosterone levels which may indicate that mechanisms other than endocrinal dysfunction may be responsible for the negative impact of VDD on sexual function [41].

The impact of VD and sexual function is likely to be a complex rather than a simple causal relation, because ED might indirectly influence by VDD through implication on several ED risk factors, in view of its correlation to obesity, diabetes mellitus and hypertension [31].

Vitamin D research showed a nearby relationship between vitamin D and DM, as blood glucose levels were reported to be lower during summer [42], low-serum VD levels correlate with impairment of insulin secretion [43], insulin resistance, glucose intolerance and overt type 2 diabetes mellitus [44,45], moreover, exposure to UVB light increases insulin secretion [46], and VD supplementation in patients with impaired fasting glucose was associated with an enhanced insulin sensitivity [47].

The relationship between obesity and VD insufficiency has been well demonstrated. It may be attributed to lower sunlight exposure or greater VD sequestration by fat tissue or both [48]. It has been reported that men with low vitamin D levels had 6.13 times the danger of developing hypertension [49,50]. Vitamin D may suppress hypertension by concealment of renin biosynthesis which may explain the observation that the incidence of hypertension, heart attacks and stroke is considerably higher in winter [51-53]. This may also explain that UV light from sunlamps was reported to successfully treat hypertension [54-56].

However, whether treating VDD state with vitamin D supplementation or sunlight can prevent ED or reverse its process is still debatable and there is no enough data to draw a firm conclusion regarding the beneficial effect of such supplementation in treatment or prevention of ED. Studies conducted by Canguven et al. and Pliz et al. by evaluating male patients with low serum vitamin D level, found that vitamin D supplementation improves serum testosterone and sexual function [57,58]. Conversely, two clinical trials found that vitamin D supplementation did not influence testosterone levels in men [59,60]. The authors inferred that the improvement of erectile function after vitamin D supplementation is not related to the increase in testosterone levels.

Lerchbaum et al. in a more recent study found that Vitamin D treatment had no effect on testosterone levels in middle-aged healthy men with normal baseline testosterone [61]. Also, other investigators, by assessing the impact of cholecalciferol supplementation in dialysis patients found no critical change in any of the studied sexual parameters [8]. Similarly, in a study by Blumberg et al. in 1980, dialysis patients with secondary hyperparathyroidism were appeared to have no change in the sexual parameters following of vitamin D replacement therapy for 2-4 months [62]. Though, the absence of beneficial effects of VD supplementation in this sub-group of dialysis patients may be related again, to the multifactorial nature of ED in those patients that may not attributed solely to VD deficiency.

Considering that ED represents an early predictor of cardiovascular disorders and that both illnesses sharing common risk factors, such revolutionary therapy if proven, would offer an additional benefit in prevention of cardiovascular insults related to VDD [31,63-66].

If the beneficial effect of VD supplementation was confirmed prospectively in specific groups of ED patients by future studies, it should be stressed that vitamin D levels should not be excessively high; this can paradoxically intensify vascular calcification [67].

Conclusion

Our work demonstrates that vitamin D is vital for the health of male sexual function, and some ED cases may simply be attributed to VDD. If our data were proven by further research on a larger scale of patients, vitamin D assessment through a simple and inexpensive laboratory test may be merged into the routine work-up for assessment of male sexual dysfunction in the near future.

Further studies are needed to clarify whether VD substitution may delay the onset or even restore normal sexual function to men experienced VDD-related ED or not.

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