Vasculogenic Erectile Dysfunction and Vitamin D level in Blood

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Abstract: Background: Endothelial dysfunction has been demonstrated to play an important role in pathogenesis of vasculogenic erectile dysfunction and other vasculogenic pathology as cardiovascular diseases. Vitamin D deficiency is deemed to promote endothelial dysfunctions**. Objective:** 1-Compare changes in vitamin D levels in serum of normal individuals and erectile dysfunction patients.2-Coorelate vitamin D levels in serum with severity and type of erectile dysfunction. **Patient and Methods:** The study included 80 men out of 162 men presented to the Andrology & STDs Department, Faculty of Medicine, Al-Azhar University after application of inclusion and exclusion criteria and after ethical approval and informed consent. They were allocated into: Healthy potent men (n=40) and Men with erectile dysfunction (ED) (n=40). Diagnosis and severity of ED was based on the IIEF-5 and Penile Duplex. It's aetiology was classified as arteriogenic, venogenic or mixed. Serum vitamin D level was measured by ELISA. **Results:** 40 patients were classified as 21 patients with arteriogenic erectile dysfunction and 19 patients with venogenic erectile dysfunction. Mean vitamin D level was 26.25 ng/mL; vitamin D deficiency (<20 ng/mL) was present in 57.5%, 15.0% had suboptimal vitamin D level (<30 ng/ml) and only 20.0 % had optimal vitamin D levels (30-50 ng/ml). 5% had upper normal vitamin D level (>70 ng/ml) and 2.5% had overdose non toxic vitamin D level (>150 ng/ml). p value <0.001. Vitamin D level in arteriogenic erectile dysfunction was lower than in venogenic erectile dysfunction patients. Penile Duplex revealed that arteriogenic erectile dysfunction was more frequent in those with vitamin D deficiency as compared to those with Venogenic erectile dysfunction. **Conclusion:** Vit. D serum levels with its VDR expression play a role of male sexual health being significantly decreased in men with erectile dysfunction. The research presented suggests that many common mechanisms underlie both cardiovascular disease and vasculogenic erectile dysfunction, and that vitamin D deficiency is closely associated with both disorders. We hypothesize that optimizing serum vitamin D levels through sunlight exposure or vitamin D supplementation helps delay the onset of erectile dysfunction. Coupled with positive changes in lifestyle, such optimization may restore normal sexual function to some men. **Recommendations: 1**-Including serum vitamin D assessment as a part of routine investigation for patient complaining with erectile dysfunction. **2**-Additional experimental and clinical studies to determine appropriate dose of vitamin D supplementation for patients with ED.
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1. Introduction

Vitamin D is a steroid hormone produced in human skin by sunlight stimulation, specifically the ultraviolet-B (UVB) portion of the sunlight spectrum; about 80% of vitamin D is thus obtained. **(Pilz S. *et al.*, 2011)**. Vitamin D deficiency (VDD) has increased profoundly in the last two decades. According to data from the National Health and Nutrition Examination Survey (NHANES), 45% of the US population had serum vitamin D levels of 30 ng/mL (considered adequate for health) in 1998–1994. Where as in 2001–2004, this figure was only 23%, a drop of 49%. **(Souberbielle JC. *et al.*, 2010).** Most cases of erectile dysfunction (ED) have a multifactorial origin and it is admitted the influence on its pathogenesis of systemic diseases, different kind of drugs, psychogenic factors, cardiovascular, endocrinological and neurological diseases. **(Valles Antuña C., et al., 2008).** It has been estimated that about half of ED is related to vascular causes. VDD also contributes to ED apart from its negative influence on classic cardiovascular diseases risk factors. **(Kloner RA., 2005).**

The presented work was a trial to:

1-Compare changes in vitamin D levels in serum of normal individuals and erectile dysfunction patients.

2-Coorelate vitamin D levels in serum with severity and type of erectile dysfunction.

2. Patient and Methods

The study included 80 men out of 162 men presented to the Andrology & STIs Department, Faculty of Medicine, Alazhar University after

application of inclusion and exclusion criteria and after ethical approval and informed consent. They were allocated into: Healthy potent men (n=40) and Men with erectile dysfunction (ED) (n=40).

Inclusion criteria: Aninadequate erectile response after adequate sexual stimulation/arousal in the age group (30-50 years old). This inadequate response is confirmed by the international index of eretile dysfunction and penile duplex.

Exclusion criteria: Diabetes mellitus, smoking, hypertension, dyslipidemia, cardiovascular disorders, hepatic or renal failures. No psychological diseases or any disease that may affect viatmin D level in blood. Not under the effect of any drug that affects erection or vitmain D level.

They were subjected to: History taking, clinical examination, IIEF questionnaire, penile duplex, estimation of serum vitamin D by ELISA method.

3. Results:

Serum vitamin D demonstrated significant positive correlation with patients suffering erectile dysfunction according to their IIEF and penile duplex findings.

Table 1: Vitamin D level in control vs erectile dysfunction patients

	group										
	control					patient					P value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
vitamin D	*57.97*	*15.8*	*53*	*32*	*96*	*26.25*	*17.31*	*19*	*11*	*91*	*<0.001*

This table shows the relation between serum vitamin D level in normal people (control) vs patients with erectile dysfunction. Vitamin D level showed very significant correlation with erectile dysfunction.

Table 2: Venogenic vs arteriogenic erectile dysfunction

Patient no. and %	cause										
	venogenic					arteriogenic					
	19 (47.5%)					21 (52.5%)					
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	P value
vitamin D	*31.47*	*21.5*	*24*	*11*	*91*	*21.52*	*10.88*	*19*	*11*	*53*	*0.431*

This table shows the relation between venogenic and arteriogenic causes of erectile dysfunction and vitamin D level in blood. It was noticed that serum vitamin D level showed more decrease in cases of arteriogenic erectile dysfunction. Arteriogenic cases are slightly more than venogenic cases.

Table 3: Vitamin D level in control vs erectile dysfunction patients

		patient	
		control	patient
vitamin D	vitamin d deficiency	*0 (.0%)*	*57.5 (23%)*
	suboptimal vitamin d	*0 (.0%)*	*15.0 (6%)*
	optimal vitamin d level	*17 (42.5%)*	*20.0 (8%)*
	upper normal	*15 (37.5%)*	*5.0 (2%)*
	overdose not toxic	*8 (20.0%)*	*2.5 (1%)*

This table shows that about 72.5% of erectile dysfunction cases showed dercrease in serum vitamin D level either obvious deficiency or suboptimal levels.

4. Discussion

Erectile dysfunction (ED) is a multi-factorial disease, and it's causes could be neurogenic, psychogenic, hormonal and/or vascular. ED incidence is rising worldwide as the number of men with ED will

increase from 150 million in 1995 to an estimated 322 million in 2025 **(Miner et al., 2012)**. **(Jastrzębska et al., 2014)** observed ED risk associated with increased body mass index (BMI), lower urinary tract symptoms, diabetes, smoking and hypercholesterolemia. In addition, ED was demonstrated to be an important indicator of cardiovascular disease and a powerful early marker for asymptomatic disorders **(Sorenson and Grant, 2012)**.

OralPDE5-Is are nowadays considered as an important line of ED treatment (**Bruzziches *et al*., 2013**). However, in some men, such efficacy is lower whereas a poorer response is seen. Factors contributing to therapeutic failure of PDE5-Is are: inadequate intake instructions/ improper use, misdiagnosis, uncontrolled co-morbidities/concomitant high-risk drugs, severe ED, psychosocial issues/personal-related factors, partner-related factors and pharmacogenetic/ pharmacogenomic factors **(Aversa et al., 2015).** However, these addressed factors could not be the all underlying causes for such condition shedding a light on intense search for new responsible factors, if any. Vit. D is produced in dermis from 7-dehydrocholesterol through exposure to UV-B irradiation. A wide variety of extra-renal cells expressing vit. D nuclear receptor-VDR (adipocytes, cells of the immune system, colon, pancreas, skin and the vasculature) synthesize vit. D **(Krivošíková *et al.*, 2015)**. This local production of vit. D is responsible for extra-skeletal modulation of various physiological processes. Hence, hypovitaminosis D was demonstrated to extend its negative effects beyond calcium homeostatsis and skeletal health playing a patho-physiological role in different disorders **(Mutt et al., 2014)**. The current results demonstrated that men with ED had significant decrease in mean serum vitamin D level compared with healthy potent men. Available studies in this context are really rare. In their work, (**Barassi et al., 2014)** evaluated the status of serum vitamin D in patients with ED based on the IIEF-5 classified as arteriogenic, borderline and non-arteriogenic categories. Mean serum vitamin D level was 21.3 ng/ml whereas vitamin D deficiency (<20 ng/ml) was present in 45.9% and only 20.2% had optimal vitamin D levels. Patients with severeED had vitamin D level significantly lower than men with mild-ED. They concluded that a significant proportion of ED patients have vitamin D deficiency being more frequent in men with arteriogenic etiology.

As erection is a vascular event, and ED is often a vascular disease caused by endothelial damage and subsequent inhibition of vasodilation with increased oxidative stress (OS). It is suggested that many common mechanisms underlie both cardiovascular disorders and ED, and that vitamin D deficiency is closely associated with both disorders. Low vitamin D levels may contribute to the manifestation of different vascular risk factors via distinct biological pathways; modulating blood pressure by suppressing the renin–angiotensin–aldosterone system **(Li, 2013),** affecting insulin synthesis, release, β-cell function and insulin sensitivity **(Sadeghi et al., 2006)**, affecting body fat mass **(Ding et al., 2012),** modulating lipid profile indirectly through its effect on serum parathormone and/or on calcium balance **(Zittermann et al., 2009)**.

Therefore, many studies associated inadequate vitamin D status and cardiometabolic risk factors as obesity, insulin resistance, hyperglycemia, hypertension, dyslipoproteinaemia, and disbalanced immune function. **(Crowley, 2014)** pointed that low vitamin D levels were associated with higher levels of systemic inflammation, glycoxidative, lipoxidative, and OS markers. Also, the inflammatory response, production of ROS and adipokines, among others, are affected by vitamin D **(Mutt et al., 2014, De Vita et al. 2014)** added that in different populations; hypertensives, obese subjects, elderly, vitamin D levels were associated inversely with multiple inflammatory markers suggesting a potential anti-inflammatory role for this vitamin.

On the other hand, vitamin D induces its biological effects by binding to its receptor, vitamin D receptor (VDR), on target cells and organs present in almost all human cells and tissues **(Bouillon et al., 2008)**. VDR has the ability to exert extensive biological responses when activated by ligand-binding, via regulation of gene transcription and stimulation of intra-cellular signaling pathways. VDR dominant action is to regulate plasma calcium and phosphate homeostasis via stimulating intestinal calcium absorption, renal tubular reabsorption of calcium and resorption of bone **(Ryan *et al.*, 2015)**. Identification of VDR in cardiomyocytes and vascular smooth muscle cells pointed that vitamin D exerts profound effects on vascular system as anti-inflammation and anti-atherosclerosis beneficial effects are mediated by VDR **(Dimitrov *et al*., 2014)**.

Zhong *et al.* (2014) showed that vitamin D induced a dose- and time-dependent increase in VDR expression, an increase in VEGF and Cu Zn-SOD expression in endothelial cells. These findings suggested that circulating vitamin D levels may determine VDR expression and possibly its downstream biological functions in the vasculature. They believed that vitamin D-deficiency associated with increased OS could be linked to aberrant VDR expression/inactivation. This OS induced down-regulation of VDR expression could be prevented by pre-treatment of endothelial cells with vitamin D. They concluded that VDR is sensitive to OS and sufficient vitamin D could protect VDR from

OS insults evidencing that sufficient circulating vitamin D levels are beneficial for vascular endothelium against oxidative insult. Penile erection is a vascular event that requires and intact endothelium, thus the pathogensis of both endothelial dysfunction and ED are intimately linked through decreased expression and activation of eNOS **(Yan et al., 2014)**. Previous studies proved that vitamin D deficiency and replacement are very important determinant factors for normal endothelial cell function**. (Andrukhova *et al.*, 2014)** pointed that vitamin D had direct effect on endothelial cells for synthesis of NO suggesting that vitamin D is closely related to the mechanism of ED. In this situation, the precise action of vitamin D on endothelial function is based on its beneficial effects on endothelial cells, such as anti-inflammatory response by inhibition of cytokine and adhesion molecule production **(Kudo et al., 2012)**, anti-oxidative activity, the ability to promote endothelial NO production **(Molinari et al., 2011)**, increased VEGF **(Grundmann et al., 2012)** and Cu Zn-SOD expression. Thus, it is speculated that sufficient vitamin D levels and proper VDR expression are fundamental for endothelial health **(Zhong et al., 2014)**. During the National Health and Nutrition Examination Survey (NHANES) **(Farag YM et., al)** performed cross-sectional analyses of 3390 men aged ≥20 years free of ASCVD who participated in NHANES 2001-2004. Serum 25(OH)D was measured by the DiaSorin radioimmunoassay; deficiency was defined as levels <20 ng/ml (<50 nmol/L). Self-reported ED, assessed by a single validated question, was defined as men who reported being "never" or "sometimes able" to maintain an erection. We assessed the relationship between 25(OH)D deficiency and ED prevalence using adjusted Poisson regression methods. After accounting for NHANES sampling, the weighted prevalence of 25(OH)D deficiency and of ED were 30% and 15.2%, respectively. 25(OH)D levels were lower in men with vs. those without ED (mean 22.8 vs 24.3 ng/mL, respectively; p = 0.0005). After adjusting for lifestyle variables, comorbidities, and medication use, men with 25(OH)D deficiency had a higher prevalence of ED compared to those with levels ≥30 ng/ml (Prevalence Ratio 1.30, 95% CI 1.08-1.57).

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