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Vitamin D Deficiency Is Associated with Erectile Dysfunction in Men with Type 2 Diabetes

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Abstract: *Background and aims*: Evidence suggests strong a relationship of vitamin D deficiency (VDD) with erectile dysfunction (ED) in men. The prevalence and long-term complications of diabetes are being recognize more increasingly that has the possible association again with VDD. Thus, the study aimed to find out the association between VDD and ED among Bangladeshi adult men with type 2 diabetes. *Materials & Methods*: This nested case-control study recruited 2860 adult patients with type 2 diabetes mellitus (T2DM) who had ED (aging between 30 - 69 years). The patients who found to have normal vitamin D level, were taken as control and those had VDD, were categorized as the case. The study was conducted in eight diabetes care centers of Bangladesh. Socio-demographic and personal information of the respondents were collected by face-to-face interview and disease-specific data were recorded from the patient's diabetic record book. The bodyweight, height, waist circumference, hip circumference and blood pressure were also recorded. Fasting blood sample was collected to estimate serum levels of vitamin D, glucose, and free testosterone. *Results*: The diabetes patients with ED had more severe VDD [(25 OH)D <10 ng/mL] than the controls (61.28% and 62.16%, respectively). The more severe form of ED found in the lower levels of serum vitamin D. A linear relationship of VDD was found with ED [OR 2.83, CI 2.36, 3.97] in multivariate logistic regression analysis. *Conclusions*: Vitamin D deficiency is an independent risk factor of ED in men with type 2 diabetes mellitus and severity of ED is linearly associated with the degree of deficiency of vitamin D.

Keywords: Vitamin D, Erectile Dysfunction, Diabetes Mellitus

1. Introduction

Men with type 1 diabetes (T1DM) and type 2 diabetes (T2DM) are at increased risk of ED and of the adult men might have it [1, 2]. The Massachusetts male aging study [3], found men with diabetes to have a three-fold increased probability of having ED comparing with men without diabetes; the age-adjusted risk of ED was double in men with diabetes when compared to those without diabetes [4].

ED may occur 10–15 years earlier in men with diabetes [1, 2]. Moreover, ED is more severe [1, 3] and less responsive to oral drugs [5, 6] in diabetes, leading to reduced quality of life [7, 8].

The proposed mechanisms of ED in patients with diabetes are represented by vasculopathy, neuropathy, visceral adiposity, insulin resistance, and testosterone deficiency. On the other hand, macrovascular disease in diabetes corresponds to the atherosclerotic damage in the blood vessels, which limits blood flow to the penis. Many of the diabetes related cardiovascular risk factors contribute to the genesis of arterial insufficiency in penis [10, 11]: Above all pathophysiological changes ultimately lead to vasculogenic ED [9].

In diabetes, persistent hyperglycemia initiates anatomical and functional abnormalities that cause endothelial dysfunction leading to ED and other atherosclerosis disorders [12]. Thus, some argued that detection of ED due penile vascular atherosclerosis may be taken the sentinel event that require rigorous attempts to detect coronary artery disease (CAD) in patients with diabetes but do not have any symptom of ischemic heart disease [13]. Several hypotheses attempted to describe the process of endothelial dysfunction and development of ED in diabetes. In this situation decreased bioavailability of nitric oxide (NO) causes decreased relaxation of penile corpora cavernosa muscular relaxation associated with endothelial dysfunction. Advanced glycation end (AGE) products accumulation, increased reactive oxygen species (ROS) in the circulation contribute to reduce the bioavailability of NO. Impairment of both the endothelial and neural NOs and the altered vasoconstriction & relaxation pathway is likely to favor increased penile vasculature constriction [13, 14]. In a study Esposito et al [15] found a high level of endothelial microparticles in the circulation of men with ED than men without it.

Vitamin D is important hormone of bone metabolism that contributes to maintaining the skeletal strength. However, the ubiquitous distribution of vitamin D receptors suggests potential for widespread effects, that has led to new research exploring the effects of vitamin D on a variety of tissues [16]. The vitamin D receptors which help present on endothelium have recently been identified to take part in modulating its function [16, 17]. An association of low levels of serum vitamin D with increased coronary arterial calcification has been reported in observational studies [18]. Similarly, exposure to higher levels of vitamin D may increase the chances of arterial calcification [19]. Experimental studies found improvement in cardiac function with optimal serum vitamin D status, even with supplementation in insufficiency [20].

As both ED and VDD are significant problems among men with type 2 diabetes, the study aimed to determine whether VDD is independently associated with ED in diabetes and thereby generate evidence for developing an appropriate clinical approach, research, and interventions.

2. Materials and Methods

2.1. Study Design and Population

The nested case-control study was conducted in eight diabetes care centers, one from each of the eight administrative divisions of Bangladesh recruiting 2860 patients with T2DM who had the diagnosis of ED (aging between 30 to 69 years) from July 2018 to August 2019.

After receiving the serum vitamin D reports, the respondents were grouped into the case (those had serum vitamin D level <30 ng/mL) and control (those had serum vitamin D level >30 ng/mL). Thus, 2315 (80.94%) of the participants were cases and 545 (19.06%) were controls.

Before the commencement the research protocol obtained ethical clearance from the Institutional Review Board of Bangabandhu Sheikh Mujib Medical University (BSMMU) prior to the commencement.

2.2. Inclusion and Exclusion Criteria

The study included adult men with documented type 2 diabetes for at least 2 years. Men having any medical conditions that could affect vitamin D metabolism including metabolic bone diseases such as osteoporosis, liver disease, kidney diseases, hyperparathyroidism, tuberculosis, granulomatous disease, lymphomas or hyperthyroidism, malabsorption resulting from celiac disease, Crohn's disease, and bypass were excluded. Men who were taking calcium and or vitamin D supplements, were not included in the study [21].

2.3. Biochemical Measurements

A skilled laboratory technician collected morning fasting 10 ml venous blood from the respondent in a disposable syringe for the assay of serum 25(OH)D, HbA1C, and lipid profile. The blood samples were centrifuged at 2000 rpm for 15 minutes and serum was separated following that. The collected serum samples have been kept frozen at −80° C until further lab analysis. Serum vitamin D assay was done by using Chromsystems reagent kit on the Waters HPLC 2695 which allowed the main metabolites of vitamin D3 and D2 to be determined in a simultaneous chromatographic manner by using a fully validated, modified high-performance liquid chromatography (HPLC) method [22]. The intra- and inter-assay coefficients of variation (CVs) were 2.6% and 4.8%, respectively. Vitamin D status were categorized into three groups; Vitamin D insufficiency 25(OH)D <20 ng/mL; vitamin D deficiency - serum 25(OH)D <30 ng/mL and vitamin D sufficiency -serum 25(OH)D ≥ 30 ng/mL.

2.4. Data Collection

Socio-demographic, personal and family information were collected by face-to-face interview by well-trained research physicians and disease-specific data were recorded from the patients' record book. The status of physical activity was classified as sedentary (such as doing household activities most of the time or a little walking outside), moderate activity (i,e. regular jogging, brisk walking, or regular swimming) and vigorous activity which causes sweating or rapid breathing (like heavy lifting, aerobic exercises, or regular fast bicycling). The participants were asked about their intentional or unintentional exposure to sun during week days and weekend (times spent outdoor at a stretch for at least 30 minutes keeping more than 18% of the body exposed to sunlight) and the use of sunscreen. Measurement of height (centimeters) and body weight (kilograms) in light clothing were taken using a standard scale after the interview. The body mass index (BMI) was then calculated by dividing the weight (in kilograms) by height (in square meters). Overweight and obesity were defined according to the World Health Organization (WHO) definition for the South East Asian population. The subjects were considered overweight when BMI was 23.0–27.4 Kg/M^2, and the subjects were defined as obese when BMI was >27.5 Kg/M^2 [24]. After confirming rest for at least 5 minutes, the blood pressure of the T2DM man was measured. The WHO hypertension criteria were followed to categorize the patients; hypertension would be the diagnosis if blood pressure ≥140/90 mmHg [25].

To evaluate sexual function, the validated Bengali version of International Index of Erectile Function (IIEF) was used. It comprised 6 items on erectile function domain. Based on a 5-point Likert scale, responses fall in 1 to 30 score; a lower score indicating relatively worser erectile functional status with a cut off of <26 for ED. The patter of erectile functional status is given as mild ED (EF score ranging from 17-25), moderate ED (EF score ranging from 11-16) and severe ED (EF score ranging from 6-10) and no ED (EF score ranging from 26-30) [26].

2.5. Statistical Analysis

All collected data were entered and analyzed by using statical package for social science (v 24). To assess the association between independent variables (i.e., vitamin D levels) the chi-square test was done. The blood pressure records, glycemic status (HbA1C), BMI, WHR, sun exposure, tobacco consumption, duration of diabetes etc. were divided into equal groups. A multivariate analysis was also done by developing models to determine the association of vitamin D status and ED in DM.

3. Results

Table 1 demonstrates the distribution of the base line characteristics of participating type diabetes patients with ED. In total, 2315 (80.94%) were cases with VDD and 545 (19.06%) were control with normal vitamin D level. The mean age of the cases was 52 (±9.8) and of control, 51 (±10.2) years. About 1167 (50.41%) of cases and 246 (45.14%) of control had secondary and higher secondary level education. Most of the participants [1204 (52.05%) of cases and 323 (59.28%) of control] came from rural areas. The highest number of participants [81.14% of cases and 79.81% of cases] earned 40,000 to 119,000 BDT [500 t0 1500 USD] monthly. Around 23.59% (546) of cases and 19.27% (105) of control were smoker; 28.12% (651) of cases 22.75% (124) of control were non-smoke tobacco consumer. About 73.17% (1694) of cases and 73.58% (401) of control were of a sedentary life style. Few patients [1.12% of cases and 0.55% of controls] had the history of sunscreen use.

Table 1. *Baseline characteristics of the respondents (n=2860).*

Variable	Frequency (%)		p value
	Case 2315 (80.94%)	**Control 545 (19.06%)**	
Age (years)			
< 40	192 (8.29)	41 (7.52)	
40 – 49	807 (34.86)	189 (34.68)	.002
50 – 59	1027 (44.36)	223 (40.91)	
60 - 69	289 (12.49)	92 (16.88)	
Mean	52±9.8	51±10.2	
Education			
Illiterate	102 (4.41)	23 (4.22)	
Primary	571 (24.67)	105 (19.27)	
Secondary & Higher Secondary	1167 (50.41)	246 (45.14)	.006
Graduate	419 (18.09)	159 (29.17)	
Postgraduate	56 (2.42)	12 (2.20)	
Residence			
Rural	1204 (52.05)	323 (59.28)	<.001
Urban	1111 (48.95)	222 (40.72)	
Monthly Family Income (In Thousands BDT)			
<40	177 (7.65)	34 (6.29)	
40-79	948 (40.95)	203 (37.24)	.043
80-119	935 (40.39)	232 (42.57)	
>120	255 (11.06)	92 (16.88)	
Smoking Tobacco			
Current smoker	546 (23.59)	105 (19.27)	
Quitted	161 (6.95)	31 (5.69)	.004
Nonsmoker	1608 (69.46)	409 (75.05)	
Non-smoke Tobacco consumption			
Consumer	651 (28.12)	124 (22.75)	.002
Non-consumer	1664 (71.88)	421 (77.25)	
Physical Activity level			
Sedentary/ Mild	1694 (73.17)	401 (73.58)	
Moderate	476 (20.56)	123 (22.57)	.000
Vigorous	145 (6.26)	21 (3.85)	
History Regular Sun Exposure			
Present	26 (1.12)	3 (0.55)	<.001

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Table 2 shows the clinical and biochemical parameters of the participants. Almost all the participants were overweight or obese [mean BMI- 26.58±6.7 and 24.83±5.3, p=.002; WHR 0.95±0.08 and 0.91±0.05, p=<.001 for cases and control respectively]. Around half of the patients were hypertensive [51.07% cases and 50.35% controls, p=.004]. Lipid disorders were also present [62.11% cases and 59.87% controls, p=.008]

Table 2. *Clinical Variables of the participants (n=2860).*

Variable	Frequency (%)		P value
	Case 2315 (80.94%)	**Control 545 (19.06%)**	
Mean BMI (Kg/M^2)	26.58±6.7	24.83±5.3	.002
Mean waist-hip ratio (WHR)	0.95±0.08	0.91±0.05	<.001
Mean HbA1C (%)	9.28±2.6	8.65±2.5	<0.001
Hypertensives	1182 (51.07)	274 (50.35)	.004
Dyslipidemic	1437 (62.11)	326 (59.85)	.008

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Tables 3 shows the serum vitamin D status of patients with type 2 diabetes. Among the controls, vitamin sufficiency, insufficiency and deficiency are 22.20%, 61.28% and 16.51% respectably. About 18.39%, 62.16 and 18.6% of the type 2 diabetes patients with ED had vitamin D deficiency, insufficiency and sufficiency respectably [p <.001].

Table 3. *Distribution of the participants according to serum vitamin D levels (n=2860).*

Variable	Frequency (%)		P value
	Case 2315 (80.94%)	Control 545 (19.06%)	
Serum Vitamin D			
Deficiency (<20 ng/mL)	425 (18.39)	90 (16.51)	
Insufficient (20-30ng/mL)	1439 (62.16)	334 (61.28)	<.001
Sufficient (>30 ng/mL)	431 (18.6)	121 (22.20)	

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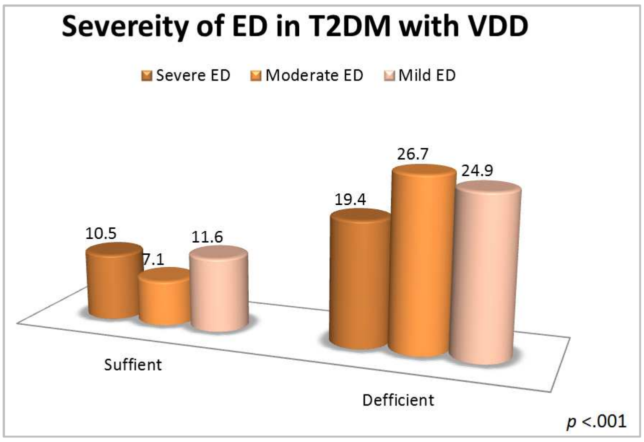

Figure 1. *Shows the stages of ED of the participants. The vitamin D deficient T2DM subjects were at the highest proportion of moderate ED (26.7% and 7.1%). These are similar for severe and mild ED [24.9; 11.6 and 19.4; 10.5] with a p value of <.001.*

Figure 1 depicts the stages of ED of the participants. The T2DM patients with VDD comprised the largest proportion of moderate ED (26.7% and 7.1%). The distribution is almost similar for severe and mild ED [24.9; 11.6 and 19.4; 10.5] with a p value of <.001.

Table 4 shows multiple logistic regressions which was applied to determine the factor relating to ED in T2DM adjusting for all possible confounders and cofactors. Age has been from the model due to co-linearity with age of onset and duration of diabetes. VDD [OR 2.83, CI 2.36, 3.97], BMI [OR 1.12, CI. 08, 1.42], WHR [OR 2.47, CI 1.88, 2.91], smoking tobacco [OR 1.94 CI 1.65, 2.36], smokeless tobacco consumption [OR 1.31, CI. 98, 1.57) and duration of DM increased [OR 1.51, CI 1.28, 1.87] probability of ED, whereas educational attainment (OR 0.91, CI 0.71, 0.98) and sun exposure (OR 0.85 CI0.68, 1.32) showed to have protective impact on ED.

Table 4. *Multiple logistic regression of erectile diabetes and vitamin D status adjusting for possible confounders.*

	OR (95% CI)	P
VDD	2.83 (2.36, 3.97)	0.001
BMI	1.12 (.08, 1.42)	0.006
WHR	2.47 (1.88, 2.91)	0.001
Sun Exposure	0.85 (0.68, 1.32)	0.03
Education	0.91 (0.71, 0.98)	0.060
Monthly Income	1.18 (0.99, 1.30)	0.001
Smoking Tobacco	1.94 (1.65, 2.36)	0.000
Smokeless Tobacco Consumption	1.31 (.98, 1.87)	0.005
Duration of DM	1.51 (1.28, 1.99)	0.000
Nagelkerke R Square	0.067	

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4. Discussion

This study revealed that the men with T2DM VDD (serum 25(OH)D <30 ng/mL) are found to have 2.83 times more likelihood to suffer from ED than the T2DM patients with adequate vitamin D status (serum 25(OH)D ≥ 30ng/mL). Several other studies showed correlation between low 25(OH)D plasma levels and ED [27, 28] and particularly in patients with poor glycemic control and longer diabetes duration [29]. Several studies showed an inverse association similar to what was found in the present study [29].

The study determined and staged erectile function of men with T2DM. The vitamin D deficient T2DM patients were mostly in the moderate ED (26.7%). The patients with severe and mild ED, the vitamin deficient T2DM patients had higher frequency [24.9; 11.6 and 19.4; 10.5] with a p value of <.001.

One study reported lower serum vitamin D in atherogenic ED. These patients had significantly low IIEF scores, lower peak systolic velocity in penile duplex study measurements as well [32], Another study reported relation of hypovitaminosis D with ED [21, 22] hypothesizing in a review that hypovitaminosis D might be the pivotal pathophysiological event in causing ED in DM [23] that warrants further vigorous researches. A good number studies demonstrated the relationship of VDD with ED and the probable mechanisms were depicted as well. To date, DM is one of the well-established risk factors of atherosclerotic cardiovascular diseases including ED [30], as men with DM may have 3 times more likelihood to be affected by ED [34]. This association may be imparted by VDD modified pancreatic beta cell dysfunction leading insulin secretory deficiency and incident T2DM [31, 33-36].

It is now established that men with ED have an increased risk of endothelial dysfunction [37], and adequate serum vitamin D may improve endothelial functional status [38]. The mechanism of ED in low vitamin D levels may be due to reduced synthesis of nitric oxide. Secretion of nitric oxide is needed for relaxation of the smooth muscles of the corpora cavernosa and subsequently penile erection, and vitamin D may be a regulator of endothelial nitric oxide synthase [29]. Vitamin D directly protects endothelial cells from oxidative stress as well [39].

The study found 74.16% of cases and 70.28% of controls had VDD (≤ 20 ng/mL) (p<.001), which appears to be consistent with previous studies within Saudi Arabia. Naeem et al. showed that the mean vitamin D levels were 32 ng/mL and 23 ng/mL among Saudi males and females, respectively [40]. Alsuwaida et al. described similarly findings found in the nationwide Saudi Arabian survey [41].

5. Conclusion

The patients with diabetes have high rate of VDD. There is inverse relationship between serum vitamin D status and ED among men with T2DM. Obesity, tobacco consumption, physical inactivity and duration of diabetes contribute in causing ED. Sun exposure and better education were found to be protective among them. So, it can be hyposensitized that patients with diabetes may consider maintaining vitamin D sufficiency by adequate sun exposure or supplementation with the hope to lessen the incidence of ED.

Conflicts of Interest

There are no conflicts of interest.

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