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ASSOCIATION OF VITAMIN D DEFICIENCY AND ERECTILE DYSFUNCTION IN YOUNG MALES – A SINGLE INSTITUTIONAL STUDY.

Urology

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ABSTRACT

Background - Erection is a vascular event and Erectile Dysfunction (ED) is thought to be an important indicator of silent cardiovascular disease (CVD). Patients who have ED have an increased prevalence of endothelial dysfunction and (Vitamin D) VD improves endothelial dysfunction Low VD levels may result in reduced NO synthesis. Though the association between VD and CVD and its manifestations like hypertension, Peripheral vascular disease (PVD), Coronary artery disease (CAD) and heart failure is well established, there are no studies on direct association between patients having VD deficiency and ED in the absence of CVD.

Materials and methods – Young males aged between 20- 40 years who presented to urology outpatient clinic at St Johns medical college and hospital, Bangalore , Karnataka , India with complains of erectile dysfunction , had vitamin D deficiency without any cardiovascular risk factors between January 2015 to January 2017 were considered for the study. They were randomized into two groups and treated with Tadalafil in both. Group A was given vitamin D supplementation while Group B was not .They were reassessed at 6 weeks with IIEF score.

Results – There was significant improvement in the IIEF scores in the cohort of patients treated with vitamin D and Tadalafil compared to the cohort that was treated with Tadalafil and placebo.

Conclusion – Low vitamin D levels are associated with ED. Hence, it is a potentially modifiable risk factor in men who present with ED and must be evaluated.

KEYWORDS

vitamin D, erectile dysfunction, endothelial dysfunction

INTRODUCTION

Erectile dysfunction, the inability to attain and/or maintain a satisfactory erection for sexual intercourse is one of the most commonly encountered problems in a urology outpatient clinic. Erectile dysfunction (ED) is a multifactorial disease, and its causes can be neurogenic, psychogenic, hormonal or vascular. Erection is a vascular event and ED is thought to be an important indicator of silent cardiovascular disease (CVD).Vitamin D (VD) deficiency is one of several dynamics that associates with increased CVD risk, but tilldate, it has not been proven as a possible contributor to ED.

Vitamin D receptor is expressed in most tissues and regulates cellular differentiation and function of many cell types[1-4]. VD receptor is a steroid receptor, once VD binds to its receptor the VD receptor moiety translocates to the nucleus, transcriptionally activates genes, affecting other gene functions [5].

Male sexual arousal is a complex process that involves the brain, hormones, nerves, muscles, psychological factors, the environment and blood vessels. On sexual stimulation, neuronal nitric oxide synthase (nNOS) and endothelial NO synthase (eNOS) is triggered, causing release of nitric oxide (NO), a smooth muscle dilator. Then NO causes an increase in levels of the second messenger cGMP which further enhance the smooth muscle induced vasodilation[6].Impairment in the NOS-NO-cGMP chain reaction causes erectile dysfunction (ED).VD has got receptors in all cells and tissues of the body. Patients who have ED have an increased prevalence of endothelial dysfunction and VD improves endothelial dysfunction[7].Low VD levels may result in reduced NO synthesis. Though the association between VD and CVD and its manifestations like hypertension[8], Peripheral vascular disease (PVD)[9], Coronary artery disease (CAD)[8], heart failure is well established , there are no studies on direct association between patients having VD deficiency and ED in the absence of CVD. We in our study have tried to evaluate this association between VD deficiency and ED in young males with no background of CVD.

MATERIALS AND METHODS

Young males aged between 20- 40 years who presented to urology outpatient clinic at St Johns medical college and hospital, Bangalore , Karnataka, India with complains of erectile dysfunction between January 2015 to January 2017 were considered for the study. Patients having diabetes mellitus, known cases of atherosclerotic cardiovascular disease, peripheral vascular disease, hypertension, hypogonadism, psychiatric disorders, smokers, patients on beta blockers, antidepressants, PDE5 inhibitors were excluded from the study.

To avoid ethical issues of cost of assessment of vitamin D, only those patients who had got their VD levels assessed at our hospital by various other departments and had presented to us with erectile dysfunction were taken up for the study .A value of > 30 ng/dl was considered as normal .Levels between 20 to 30 ng/dl was considered as vitamin D insufficiency and levels less than 20 ng/dl was considered as VD deficiency. All patients with ED and vitamin D levels less than 30 ng/dl were considered for the study. A note was made of their physical activity status, cholesterol and BMI. Cholesterol levels of < 250 mg/dl was considered as normal, physical activity was noted as sedentary (no physical activity), low (light walking), moderate (brisk walking, stair climbing) and vigorous (jogging, swimming, dancing, jumping rope, sports). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters square .A clinical examination with recording of blood pressures (BP) and blood sugars was done, patients having a systolic BP > 140 or a diastolic BP > 90 mm of Hg or patients with HBA1C of >6.5% were excluded from the study. The extent of ED (erectile dysfunction) was assessed by IIEF-5 (international index of erectile function- table 1) scoring system .The IIEF-5 score is the sum of the ordinal responses to the 5 items the interpretation of which is as below -

22-25: No erectile dysfunction
17-21: Mild erectile dysfunction
12-16: Mild to moderate erectile dysfunction
8-11: Moderate erectile dysfunction
5-7: Severe erectile dysfunction

The IIEF 5 Scoring system was done by a trained paramedical staff who was well versed in multiple Indian languages to avoid a communication gap. The patients were randomized into two groups as odd and even as they were included in the study. A written informed consent was taken from all patients. Group A – all even patients were treated with vitamin D – oral sixty thousand units once a week for 6 weeks before food and tab Tadalafil 5 mg daily with another additional

dose of 20 mg, one hour before sexual activity. Group B – all odd patients were treated with Tab Tadalafil 5 mg daily and 20 mg one hour before sexual activity. However instead of vitamin D supplementation, placebo was given to them. Both the patient and the paramedic staff were blind to as what they were being given in the form of medication-placebo / vitamin D supplementation. Patients were reassessed after 6 weeks with a repeat IIEF 5 scoring system and it was compared with the previous IIEF 5 scoring system .The patients who had vitamin D deficiency and were given placebo, were given vitamin D treatment after 6 weeks.

RESULTS

Out of the 1750 patients who presented to us with ED over a period of 2 years ,305 patients were eligible for the study and met the inclusion criteria. Out of these 185 patients had their vitamin D levels done already .Out of these 162 patients had vitamin D deficiency. After meeting all the criteria, a total of 150 men were enrolled for the study . All men with even enrolment numbers were assigned to group A and those with odd ones to group B. The mean age of patients in Group A was 31.5 years and those in group B was 30.2 years which was comparable and statistically non significant. The mean Vitamin D levels in group A was 14.8 while that in group B was 14.7 with a range of 3 to 30 and 2 to 28 respectively (**table 2**). This was also statistically not significant. The cholesterol levels and BMI were recorded and it was noted that patients having a higher cholesterol level and BMI had a lower IIEF score. However both the groups were matched for cholesterol levels and BMI and the same was statistically not significant.

The IIEF scoring system was recorded in both the groups both before and after treatment. The mean IIEF score before treatment in group A was 12.3 and that after treatment was 20.4 with a 66.3% increase post treatment . The mean IIEF score in group B was 13.4 before treatment and 14.9 after treatment with an increase of 11.3 % (**figure 1 and 2**). The IIEF scores when compared between both the groups which was not significant before treatment became highly significant after treatment ($p<0.001$). When comparison of the IIEF score is done before and after treatment for group B, it is significant due to the fact that all the patients were treated with Tadalafil . However, when we look at group A, the difference in the IIEF score and the increase in IIEF score post treatment the p value is highly significant (P value <0.001). The intra and inter group comparisons of the IIEF in the two groups is as given in **table 3**. We also noted the physical activity and compared it with the IIEF score both before and after treatment. It was noted that the physical activity had a direct correlation to the degree of erectile dysfunction which correlated in the form of IIEF score. Greater the amount of physical activity correlated to better erectile function . The P value was significant in both the groups , before and after treatment . The relationship between physical activity and IIEF score is shown in **table 4and figure 3**

Statistical Analysis.

Results are presented as Mean±SD, Range values for continuous variables.

Intra group comparisons were made by Paired t test and unpaired t test was used for comparison of mean values between two groups.

One way ANOVA was used for simultaneous multiple group comparisons.

Spearman's Correlation and Coefficient was used for Physical activity and IIEF.

P value of 0.05 or less was considered as statistically significant. SPSS (version 17) software was used for statistical analysis.

DISCUSSION

Erectile dysfunction (ED) is a highly-prevalent disorder among adult men and up to 80% of men aged 75 years and older are affected [10]. Erectile dysfunction can be psychogenic, organic or a combination of both. Erection is primarily a vascular event. Hence the most common cause of organic ED is vascular. Sexual stimulation causes the release of neurotransmitters from the corpus cavernosa and nitric oxide (NO), from the endothelial cells of the penis. NO is a relaxing factor; causes vasodilation that is essential to erection. The neurotransmitters, together with NO, cause the corpus cavernosa to relax and allows blood to flow into the penis, causing the penis to expand and sustain an erection[11]. Any condition causing endothelial dysfunction (END) will also interfere with vasodilation, which will prevent erection. END is an early marker for the development of atherosclerosis[12]. In fact, END is the key factor in the pathophysiology of ED, and men with penile END also have END in other blood vessels as well .

Low levels of vitamin D, defined as serum 25-hydroxyvitamin D [25(OH)D] below 30 ng/ml, affects an estimated 1 billion individuals worldwide[13]. Suboptimal vitamin D status is thought to influence atherosclerotic cardiovascular disease (ASCVD) risk predominantly through established vascular risk factors, namely hypertension, diabetes, inflammation, and endothelial dysfunction. According to Farag et al[14] , it has been postulated that low VD may contribute to ED through several mechanisms such as endothelial dysfunction, inflammation, impaired glucose homeostasis, and atherosclerosis, similar to the mechanisms linking low vitamin D with ASCVD, but the link between 25(OH)D levels and ED is still uncertain. There are no studies conducted till date that define vitamin D deficiency in a population of young patients without any background of CVD who present to us with erectile dysfunction and observe the improvement in the same population post treatment with vitamin D. In our study, we have tried to delineate this relationship between vitamin D deficiency and erectile dysfunction in young men who have no cardiovascular risk factors .

Out of the 150 patients, who were taken up for the study, we randomized them to group A and Group B and treated them with vitamin D and Tadalafil as explained in materials and methods .The Erectile dysfunction status was noted by the IIEF 5 questionnaire. The same questionnaire was repeated after treatment. It was noted that though there was an improvement in both the groups, the patients who had been treated with vitamin D reported a drastic improvement in erectile function post treatment. NO plays an important role in erectile function. 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 [6]. Molinari et al. demonstrated that VD is able to stimulate NO production in human umbilical vein endothelial cells through eNOS activation[6] . This relation is significant and relevant. It can point towards a substantial relationship between NO production, VD and ED. Activated VD stimulates the production of NO in endothelial cells and NO synthases which catalyze the production of NO from L-arginine [15] , is a key to vascular dilation and thereby critical for the prevention of ED [6].

ED is associated with inflammatory activity and inflammation plays a role in both ED and Cardiovascular diseases[6]. Sildenafil , a phosphodiesterase inhibitor (PDE) used as first- line treatment in ED, induces a significant acute decrease in levels of pro-inflammatory markers/mediators. VD inhibits the expression of inflammatory cytokines in monocytes, including IL-1, IL-6, TNF-α, IL-8, and IL-12, decreases endothelial stress, causes relaxation of penile musculature and hence may contribute to prevention of ED[16].

Our study clearly demonstrates a relationship between vitamin D and ED as most of our patients who were treated with vitamin D showed improvement in symptoms in terms of IIEF 5 score and had no significant cardiovascular risk factors. The recommendation for VD supplementation we followed was sixty thousand units once a week for 6 weeks and then reassessment for IIEF scores. The Endocrine Society defines VDD and insufficiency as a 25(OH)D <30 ng/mL [17]. The Endocrine Society recommends daily intake of adult VD supplements up to 4,000 IU/day [17] ; 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.

To conclude , there is growing evidence that the low vitamin D levels are associated with ED. Hence , it is a potentially modifiable risk factor in men who present with ED. Measurement of VD in patients with ED is warranted as it represents a low cost and effective way to treat the same without any major side effects. It can also act as adjuvant therapy to PDE5 inhibitors for management of ED.

TABLE 1 : International Index Of Erectile Function – 5 (IIEF -5)

1. How do you rate your confidence that you could keep an erection?

1	2	3	4	5
Very low	Low	Moderate	High	Very high

2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?

1	2	3	4	5
Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always

3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?

1	2	3	4	5
Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always

4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?

1	2	3	4	5
Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult

5. When you attempted sexual intercourse, how often was it satisfactory for you?

1	2	3	4	5
Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always

Table 2: Descriptive information on different variables in two groups

Measurement		Gr A	Gr B	t value	P value
Age (Yrs)	Mean±SD	31.5±4.2	30.2±4.0	1.92	0.06, NS
	Range	24 - 40	24 - 40		
Vit D	Mean±SD	14.8±8.5	14.7±6.9	0.03	0.98, NS
	Range	3 - 30	2 - 28		

Table 3: Intra and Inter group comparisons of degree of IIEF in two groups

I I E F		BT	AT	AT - BT	% increase	Paired t	P value
Gr A	Mean±SD	12.3±4.0	20.4±3.1	8.1±1.4	66.3%	50.08	0.00**
	Range	6 - 20	14 - 25	5 - 11			
Gr B	Mean±SD	13.4±4.0	14.9±3.5	1.5±1.5	11.3%	8.91	0.00*
	Range	5 - 11	8 - 22	0 - 5			
Gr A v/s Gr B (Unpaired t)	t value	1.80	9.96	28.23	-		
	P value	0.07, NS	0.00**	0.00**			

Intra group(Horizontal): Paired t test
Inter group(Vertical): Unpaired t test
* P < 0.05, S
** P < 0.001, HS
P > 0.05, Not Sig.

Table 4: Relationship between Physical activity & IIEF

Physical activity	No.of cases	BT	AT
1. Sedentary	18	9.7±4.4	14.9±2.4
2.Low	62	11.4±4.5	16.6±3.6
3.Moderate	47	14.5±4.5	18.9±4.0
4.Vigorous	23	15.7±4.0	20.2±5.7
ANOVA	F	17.01	8.81
	P	< 0.001, HS	< 0.001, HS

One Way ANOVA

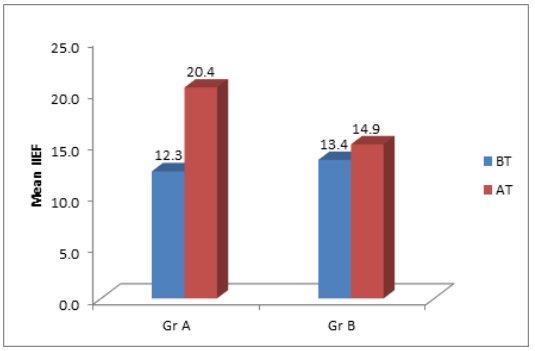

Fig 1.Mean IIEF levels in two groups at BT (Before treatment) and AT(after treatment)

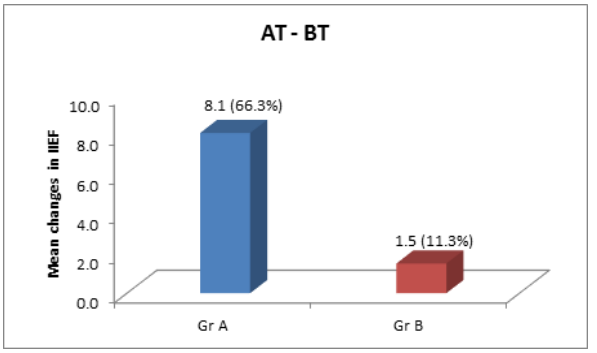

Fig.2: Mean increase(%) in degree of IIEF in two groups

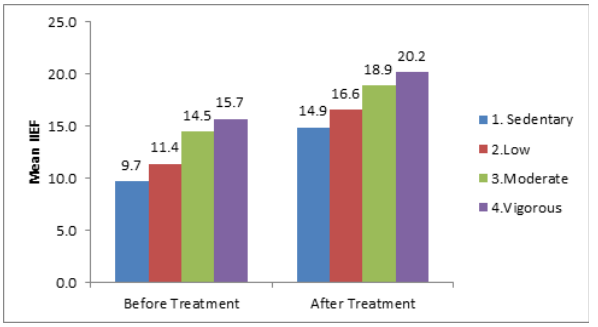

Fig.3: Mean degree of IIEF in relation to different levels of physical activity

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