

Role of vitamin d supplementation in erectile dysfunction patients with vitamin d deficiency

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Abstract

Erectile dysfunction (ED) is a common problem affecting 30-50% of male population above 40 years of age and PDE5 inhibitors are the only successful pharmacotherapy available. ED is considered as early marker for endothelial dysfunction which also results in systemic vascular disease. Vitamin D deficiency is strongly associated with atherosclerotic cardiovascular diseases. Patients with severe vitamin D deficiency have increased risk of ED particularly arteriogenic ED. A prospective randomised study was done in patients with severe Vit D deficiency comparing effects of Tadalafil 10mg, Vit D 60,000 units weekly and a combination of the two. The use of Tadalafil in combination with Vitamin D in Vit D deficient ED patients act better than Tadalafil or Vit. D alone. The combined therapy was well tolerated with no major side effects.

Keywords: Erectile dysfunction, Vitamin D deficiency, Tadalafil.

Introduction

Erectile dysfunction is inability to achieve and/or maintain penile erection for satisfactory sexual intercourse. When a man is sexually aroused, neural nitric oxide synthase (nNOS) is activated, that causes release of NO, which is further augmented by the release of endothelial nitric oxide synthase (eNOS).¹ Finally NO leads to increase cGMP levels which results in smooth muscle relaxation and vasodilatation that maintains penile erection.² Detumescence is a result of cessation NO release and breakdown of cGMP by phosphodiesterase. Phosphodiesterase inhibitors Sildenafil and Tadalafil were FDA approved in 1998 and 2003 respectively for successful treatment of ED patients.

McCormick et al.³ discovered vitamin D in 1922, that cures Rickets. Previously its importance was assumed for bones only but now it has been considered for other organs also including penis. Vitamin D receptor is a steroid receptor, present in almost all the cells and helps in cell differentiation and function.^{4,5} Vitamin D attached to its receptors, moves to the nucleus where it triggers up the genes and results in transcription of nearby genes also.⁶

Vitamin D deficiency is strongly associated with atherosclerotic cardiovascular diseases like peripheral vascular disease, hypertension, metabolic syndrome, coronary artery disease.⁷ As penile erection is maintained due to normal penile vasculature, ED is used as marker of systemic vascular disorder.^{8,9}

Normal levels of vitamin D range between 30-80 ng/ml. The Endocrine society defines vitamin D deficiency as Vitamin D <30 ng/ml and severe deficiency if <20ng/ml.¹⁰ Patients with severe vitamin D deficiency have increased risk of ED particularly arteriogenic ED and risk decreases if level is >35ng/ml.^{11,12}

It has been proven that vitamin D act as anti-inflammatory agent and decreases factors IL-1, IL-6, TNF-A, IL-8^{13,14} involved in inflammation. Oxidative stress of

endothelial cells decrease with Vitamin D supplementation and its deficiency also contributes to ED.

Molinari et al.¹⁵ demonstrated that Vitamin D induces NO production in cultured human umbilical vein endothelial cells through eNOS stimulation. NO is an important factor for maintaining penile erection through vascular dilatation and thus preventing ED.

Canguven O et al. recently demonstrated that Vit D treatment improves sexual hormones, metabolic parameters and erectile function in middle-aged Vit-D deficient man.¹⁶ Rafiq R, et al. demonstrated that serum Vitamin D status was positively associated with total and bioavailable testosterone levels.¹⁷ Pilz et al.¹⁸ investigated the effect of Vitamin D supplementation on androgens in men and they observed significant increase in total testosterone, bioactive and free testosterone levels in vitamin D supplemented groups.¹⁸

Although there are many studies showing association between Vitamin D, atherosclerotic disease and ED, till date there is no prospective study evaluating Vitamin D supplementation in patients with ED. Therefore, this study was undertaken to evaluate the effect of Vitamin D supplementation in ED patients with severe Vitamin D deficiency.

Materials and Methods

This study was carried out in Department of Urology, S.M.S. Medical College and attached Hospitals between March 2018 to April 2019 after getting approval of the Institutional ethics review board.

Patients in the age group 20-60 years presenting with ED and having severe Vitamin D deficiency were enrolled. Patients taking vitamin D, antiandrogens, antipsychotics, antidepressants, antihypertensive, having history of diabetes, prior penile surgery and penile trauma were excluded. Detailed history, physical examination, blood investigations like random blood sugar, complete blood count, serum testosterone, lipid profile, serum Vit D level

and International Index of Erectile Function Questionnaire scoring were done.

After taking informed consent from each one, patients were randomized into three groups. First group was treated with Tadalafil 10mg once a day while the second group had Tadalafil 10mg once a day plus Vitamin D 60,000 IU once a week, and third group was given Vitamin D 60,000 IU once a week only. Drugs were given for a specific period of 12 weeks.

Efficacy of drugs was evaluated at base line and after 12 weeks on the basis of International Index of Erectile Function Questionnaire scoring.

Statistical analysis

Data was collected and analyzed by Paired t-test and Anova test.

Results

The study included 75 patients and three groups were compared regarding improvement of IIEF-5 scoring and toxicity of drugs used in the study.

After 12 weeks of treatment IIEF-5 scoring was nearly same as that of the base line with no significant difference in group C patients. On the other hand, IIEF-5 scoring was significantly improved in group A and B patients ($P < 0.001$). On comparing group A and B patients there was significant improvement in group B compared to group A ($P < 0.05$).

Table 1:

	Group A	Group B	Group C	One-Way ANOVA	Post-Hoc test significant pairs
Age	37.44±10.85	39.08±9.78	37.96±9.66	F=0.171 P>0.05	A Vs B P>0.05 A Vs C P>0.05 B Vs C P>0.05
IIEF-5 scoring at 1 st visit	11.12±1.76	10.76±2.4	12.41±2.12	F=4.14 P<0.05 (P=0.020)	A Vs B P=0.055 A Vs C P=0.549 B Vs C P=0.008
IIEF-5 scoring at 3 month	16.84±3.6	19.2±3.98	12.21±1.41	F=29.73 P<0.001 (P=0.000)	A Vs B P=0.012 A Vs C P=0.000 B Vs C P=0.000
Paired test	t=9.79 P=0.000	t=10.78 P=0.000	t=0.643 P=0.527		

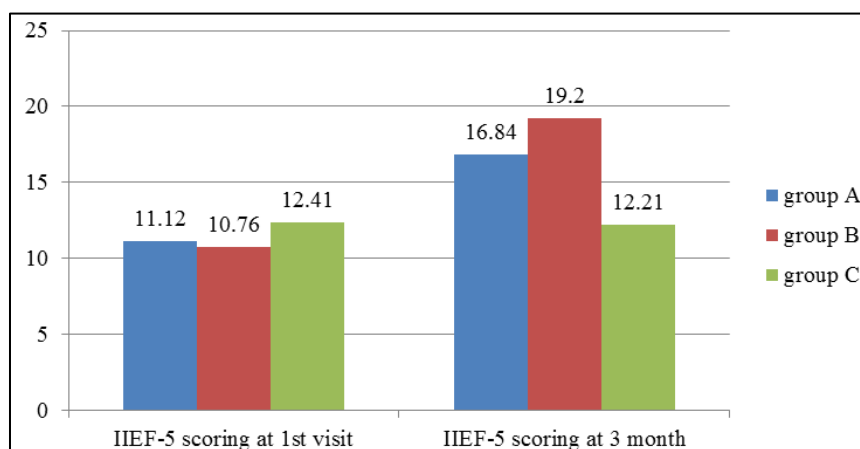


Fig. 1:

In all three groups the administered drugs were well tolerated by the patients with no serious side effects and no patient discontinued the prescribed medications.

In group A, 6 patients complained of dyspepsia, 4 patients had mild headache, 6 patients had backache and myalgia, and 4 patients had nasal congestion and facial flushing.

In group B, 5 patients complained of dyspepsia, 6 patients had mild headache, 4 patients had backache and myalgia, and 4 patients had nasal congestion and facial flushing.

In group C, 4 patients complained of nausea and dyspepsia.

In comparison to group C, group A and group B patients had more side effects ($P < 0.05$), but of mild intensity and prescribed medications were well tolerated. Group A and B patients had no significant difference in side effects. ($P > 0.05$).

Group	Dyspepsia	Headache	Backache & myalgia	Nasal congestion	Total
A	6	4	6	4	20
B	5	6	4	4	19
C	4	0	0	0	4
Total	15	10	10	8	43

Group	Mean	Sd	Versus		Significance
A	5	1.15	A vs B	P >0.05	insignificant
B	4.75	0.96	A vs C	P <0.05	significant
C	1	1.73	B vs C	P <0.05	significant

Discussion

In our study 25 (OH) vitamin D measurements was conducted by chemo luminescence assay. A total of 110 ED patients were examined of which 75 patients had severe vitamin D deficiency (68%) and they were enrolled in the study.

Sexual function assessment was done by IIEF-5 (Rosen et al, 1999)¹⁹ scoring system which had 5 items: 5, 15, 4, 2 and 7 from IIEF-15 scoring system.

IIEF-5 instruments classified ED severity into 5 categories: severe (5 to 7), moderate (8 to 11), mild to moderate (12 to 16), mild (17 to 21) and no ED (22 to 25).

IIEF-5 scoring system

Over the past 6 months					
1. How do you rate your confidence that you could get and keep an erection?	Very low 1	Low 2	Moderate 3	High 4	Very high 5
2. When you had erections with sexual stimulation, how often were your erections enough for penetration?	Almost never 1	Few times (much less than half the times) 2	Sometimes (about half the times) 3	Most times (more than half the times) 4	Almost always 5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?	Almost never 1	Few times (much less than half the times) 2	Sometimes (about half the times) 3	Most times (more than half the times) 4	Almost always 5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Extremely difficult 1	Very difficult 2	Difficult 3	Slightly difficult 4	Not difficult 5
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Almost never 1	Few times (much less than half the times) 2	Sometimes (about half the times) 3	Most times (more than half the times) 4	Almost always 5

Several studies were conducted in the past which showed mixed result of vitamin D in relation to sexual function . Kidir et al.²⁰ in 2015 suggested that sexual dysfunction in dialysis patients is related to low level of vitamin D. Bellastella and colleagues²¹ showed no correlation between severity of ED and vitamin D.

Study conducted by Canguven et al.¹⁶ suggested improved erectile function score after vitamin D supplementation in vitamin D deficient patients but in contrary Blumberg & colleagues²² did not find any improvement in sexual function after 4 months of vitamin D supplementation in vitamin D deficient patients on hemodialysis.

In our study there is significant improvement in sexual function in patients taking vitamin D along with Tadalafil in comparison to Tadalafil alone in vitamin D deficient patients, but there is no improvement in patient taking only vitamin D.

In group B patients, after 3 month we continued vitamin D 400IU once a day along with reduced dose of Tadalafil (5 mg OD) and till date there is no deterioration in erectile function, which showed consistency of effect of vitamin D.

No severe side effects of the drugs were noted and there was no dropout of patients in our study.

Conclusions

This study showed that the use of Tadalafil in combination with Vitamin D in Vit D deficient ED patients act better than Tadalafil or Vit. D alone. The combined therapy was well tolerated with no major side effects. However, more studies are needed to identify the best duration of this treatment and larger study of patients before the final conclusion can be made.

Source of funding

None.

Conflict of interest

None.

References

- Sorenson M, Grant WB. Does vitamin D deficiency contribute to erectile dysfunction? *Dermatoendocrinol* 2012;4:128-36.
- Tostes RC, Carneiro FS, Lee AJ, Giachini FR, Leite R, Osawa Y, et al. Cigarette smoking and erectile dysfunction: focus on NO bioavailability and ROS generation. *J Sex Med* 2008;5:1284-95.
- McCollum E, Siammonds N, Becker J, Shipley P. An experimental demonstration of the existence of a vitamin which promotes calcium deposition. *J Biol Chem* 1922;53:293-8.
- Niruban SJ, Alagiakrishnan K, Beach J, Senthilselvan A. Association between vitamin D and respiratory outcomes in Canadian adolescents and adults. *J Asthma* 2015;52:653-61.
- Kerley CP, Elnazir B, Faul J, Cormican L. Vitamin D as an adjunctive therapy in asthma. Part 2: A review of human studies. *Pulm Phaemacol Ther* 2015;32:75-92.
- Deeb KK, Trump DL, Johnson CS. Vitamin D signaling pathways in cancer: potential for anticancer therapeutics. *Nat Rev Cancer* 2007;7:684-700.
- Vacek JL, Vanga SR, Good M, Lai SM, Lakkireddy D, Howard PA et al. Vitamin D deficiency and supplementation and relation to cardiovascular health. *Am J Cardiol* 2012;109:359-63.
- Meluzin J, Vasku A, Kincl V, Panovsky R, Sramkova T. Association of coronary artery disease, erectile dysfunction, and endothelial nitric oxide synthase polymorphisms. *Heart Vessels* 2009;24:157-63.
- Montorsi P, Montorsi F, Schulman CC. Is erectile dysfunction the "tip of the iceberg" of a systemic vascular disorder? *Eur Urol* 2003;44:352-4.
- Bischoff-Ferrari HA, Gionvannucci E, Willette WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr* 2006;84:18-28.
- Farag YM, Guallar E, Zhao D, Kalyani RR, Blaha MJ, Feldman DI, et al. Vitamin D deficiency is independently associated with greater prevalence of erectile dysfunction: National Health Nutrition Examination Survey (NHANES) 2001-2004. *Atheroscler* 2016;252:61-7.
- Barassi A, Pezzilli R, Colpi GM, Corsi Romanelli MM, Melzi d'Eril GV. Vitamin D and erectile dysfunction. *J Sex Med* 2014;11:2792-2800.
- Almerighi C, Sinistro A, Cavazza A, Ciaprin C, Rocchi G, Bergamini A et al. 1 α ,25Dihydroxyvitamin D3 inhibits CD40L-induced pro-inflammatory and immunomodulatory activity in Human Monocyte. *Cytokine* 2009;45:190-7.
- D' Ambrosio D, Cipitelli M, Coccio MG, Mazzeo D, Di Lucia P, Lang R, et al. Inhibition of IL-12 production by 1,25-dihydroxyvitamin D3. Involvement of NF-kappa B downregulation in transcriptional repression of the p40 gene. *J Clin Invest* 1998;101:252-62.
- Molinari C, Uberti F, Grossini E, Vacca G, Carda S, Incernizzi M, et al. 1 α ,25-dihydroxycholecalciferol induces nitric oxide production in cultured endothelial cells. *Cell Physiol Biochem* 2011;27:661-8.
- Conguven O, Talib RA, El Ansari W, Yassin DJ, Al Naimi A. "Vitamin D treatment improves levels of sexual hormones, metabolic parameters and erectile function in middle-aged vitamin D deficient men." *Aging Male* 2017;1:9-16.
- Rafiq R, Van Schoor NM, Sohl E, Zillikens MC, Oosterwerff MM, Schaap L, et al. associations of vitamin D status and vitamin D-related polymorphisms with sex hormones in older men. *J Steroid Biochem Mol Biol* 2016;164:11-7.
- Pilz S, Frisch S, Koertke H, Kuhn J, Dreier J, Obermayer-Pietsch B, et al. Effect of vitamin D supplementation on testosterone levels in men. *Horm Metab Res* 2011;43: 223-5.
- Rosen R.C, Cappelleri JC, Smith MD, Lipsky J, Pena BM. Development and evaluation of an abridged ,5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool of erectile dysfunction. *Int J Impotence Res* 1999;11:319-26.
- Kidir V, Altuntas A, Inal S, Akpınar A, Orhan H, Sezer M.T et al. Sexual dysfunction in dialysis patients: does vitamin D deficiency have a role? *Int J Clin Exp Med* 2015;12:22491-6.
- Bellastella G, Maiorino M.I., Olita L. Vitamin D deficiency in type 2 diabetic patient with hypogonadism. *J Sexual Med* 2014;2:536-42.
- Blumberg A, Wildbolz A, Descoedres C. Influence of 1,25 dihydroxycholecalciferol on sexual dysfunction and related endocrine parameters in patients on maintenance hemodialysis. *Clin Nephrol* 1980;5:208-14.

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