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EFFECT OF VITAMIN D ON SEX HORMONES IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Pathology

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ABSTRACT

Almost one billion individuals worldwide have low circulating Vitamin D levels. Vit D has been linked to everything from cancer and heart disease to diabetes. An active metabolite of Vit D,1,25 dihydroxy Vit D is said to regulate various enzymes involved in the steroid hormone production, both adrenal steroid and sex hormones, together with the sex hormone signaling. The present study was hospital based prospective, case control study, conducted in 112 diagnosed patients of type 2 diabetes mellitus on oral hypoglycaemic agents, to observe the effect of vitamin D on sex hormone (estrogen and testosterone). Out of 112, 62 diabetic patients had hypovitaminosis and formed group A and 50 diabetic patients had optimal levels of serum vitamin D forming group B, the control group. We observed that supplementation of vitamin D helps in regulating the levels of sex hormones such as testosterone in type 2 diabetes mellitus patients.

KEYWORDS

Diabetes mellitus type 2, Sex hormones, Vitamin D.

INTRODUCTION

Vitamin D is one of the oldest hormones produced by some of the earliest phytoplankton life forms, zooplankton and most plants and animals that are exposed to sunlight.[1] In both animals and humans, Vit D deficiency leads to the impaired secretion of insulin but not other islet hormones, therefore inducing glucose intolerance which can be rectified by supplementation of Vit D.[1] Deficiency of Vit D influences the pathogenesis of insulin resistance and type 2 diabetes by the direct effects such as decreased binding to vitamin D receptor (VDR) and indirect effect such as aberrant calcium flux.

1,25 dihydroxy Vit D, the active metabolite of Vit D is said to regulate various enzymes involved in the steroid hormone production, including both adrenal steroid and sex hormones, together with the sex hormone signaling.[2, 3] The Vit D receptor (VDR) is expressed in the ovaries and testis, suggesting that Vit D has a role in these organs.[4] Vit D receptor is expressed in human testis and has been suggested to affect survival and function of mature spermatozoa.

The estrogen receptor ER α and ER β are emerging as a key molecule involved in glucose and lipid metabolism. Function of estradiol is to help to maintain normal insulin sensitivity and beta cell function. When levels of estrogen are either too high or too low it may lead to promotion of insulin resistance and type 2 diabetes.[5] Men with higher levels of natural estrogens are at higher risk of type 2 diabetes.[6]

Major factors involved in the pathogenesis of type1 and type2 diabetes are affected by the active metabolite form of Vit D and its analogs. The function of the beta cell have shown to be improved by 1,25(OH) D in vitro and in vivo, therefore it is essential that Vit D deficiency should be avoided for normal beta cell function. The present study was performed to find out the effect of Vit D on sex hormone in type 2 diabetes mellitus patients.

MATERIAL AND METHODS

The present study was hospital based prospective, case control study, conducted in Rajeev Gandhi centre for Diabetes and Endocrinology and Department of Pathology.112 diagnosed patients of type 2 diabetes mellitus (T2DM) who were on oral hypoglycaemic agents and attended diabetes clinic were included in this study. In all 112 patients, morning blood samples were collected to estimate serum Vit D, serum estrogen and testosterone levels, employing radioimmunoassay technique. Type 1 diabetic patients, pregnant, lactating, postmenopausal females and patients with chronic disorders of the liver or kidney, endocrinological disorders such as hypo-or hyperthyroidism, hyperparathyroidism or smoking were excluded from the study. Patients on drugs affecting the calcium and bone, anticonvulsive drugs or taking Vit D or calcium supplements were also excluded. All the subjects gave valid consents after the procedure was explained to them, prior to further investigations. A detailed history and thorough examination of every subject was done. Before starting the treatment with Vit D, patients were advised for laboratory tests for Vit D and sex hormones including estrogen and testosterone at endocrinology laboratory after an overnight fasting of 10-12 hours. They were then divided into 2 groups based on Vit D status. 62 diabetic patients had hypovitaminosis and formed group A while 50 diabetic patients who had optimal levels of serum Vit D formed group B, the control group. Cases with low levels of Vit D (group A) were sub-grouped into vitamin D insufficient and Vit D deficient on the basis of levels of Vit D.

[Deficiency <10ng/ml ,Insufficiency 10-29ng/ml ,Sufficiency 30-100ng/ml and Toxicity >100ng/ml]

These cases were selected for recommended doses of Vit D for six months. Group A was administered with Vit D at a dose of 60,000 IU weekly for a period of 6 months and the rest of the conditions were taken similar for all members in the study. Both the groups were asked to follow recommended doses of hypoglycemic, dietary and exercise regime during the study period. During the treatment, all patients were visited to determine the degree of compliance, which was assessed by tablet counts at each visit in reports. A repeat test for all parameters was done at 6 months after treatment and values were compared with pre intervention values. The group B (control group) was taken as the representative of the source population that produced the cases and was sampled in a way that was independent of the Vit D supplementation.

Statistical analysis

The data obtained was analyzed by descriptive tests such as mean, SD (standard deviation) to assess the normality of the variables before further statistical analysis. The effects of Vitamin D supplementation on the variables were analyzed and differences between means of patients (before and after treatment) and control groups were

considered statistically significant with p-value <0.05 using paired t-test.

OBSERVATIONS

Out of the total number of 112 patients of T2DM reported, 62/112(55%) diabetic patients had hypovitaminosis (group A) and 50/112(45%0 T2DM patients had optimal levels of serum vitamin D (group B) at the start of study. Among 62/112 (55%) cases of hypovitaminosis, most of the cases (44, 39%) had insufficient vitamin D levels and 18(16%) cases were having deficient vitamin D levels. The mean age of the patients was 47.34±6.18 and 46.18±6.67 years in group A and group B respectively, while the least common age group in both the groups was 30-40 years. There was male predominance (85/112 cases, 76%) with male: female ratio of 3:1.

Table 1-
EVALUATION OF SERUM TESTOSTERONE LEVELS IN GROUP A AND GROUP B BEFORE SUPPLEMENTATION OF VITAMIN D IN GROUP A

Serum Testosterone Level	No. of patients in Group A before treatment		Total	Percentage %	No. of patients in Group A after treatment		Total	Percentage %
	Male	Female			Male	Female		
< Normal	07	00	07	11.29	01	00	01	2.00
Normal	38	13	51	82.25	41	08	49	98.00
>Normal	01	03	04	6.45	00	00	00	00.00
Total	46	16	62	100	46	16	62	100

Table 2-
ANALYSIS OF THE EFFECT OF VITAMIN D ON SERUM TESTOSTERONE LEVELS IN GROUP A BEFORE AND AFTER VITAMIN D SUPPLEMENTATION

Serum Testosterone Level	No. of patients in Group A before treatment		Total	Percentage %	No. of patients Group B after reatment		Total	Percentage %
	MALE	FEMALE			MALE	FEMALE		
< Normal	07	00	07	11.29	02	00	02	3.22
Normal	38	13	51	82.25	43	14	57	91.93
>Normal	01	03	04	6.45	01	02	03	4.83
Total	**46**	**16**	**62**	**100**	**46**	**16**	**62**	**100**

The mean value of pre-treatment serum testosterone levels in group A was estimated to be 4.439 ± 2.856ng/ml whereas in Group B mean value was 4.407 ± 1.882 ng/ml. The difference was found to be statistically insignificant with a p-value of 0.655.The mean value of pre-treatment serum testosterone levels in group A was estimated to be 4.439 ± 2.856 ng/ml whereas after supplementation of vitamin D for 6 months, the mean value was 4.650 ± 2.988 ng/ml. The difference was found to be statistically significant with a p-value of 0.0324. [Table 1 and 2]

The mean value of pre-treatment serum estrogen levels in group A was 69.06 ± 51.08pg/ml whereas in Group B mean value was 57.64 ± 39.84pg/ml. The difference was found to be statistically insignificant with a p-value of 0.2235. The mean value of pre-treatment serum estrogen levels in group A was estimated to be 69.06 ±51.08 pg/ml whereas after treatment with Vit D for 6 months, the mean value was 66.42 ±49.16pg/ml. The difference was found to be statistically insignificant with a p- value of 0.1239. [Table 3 and 4]

Table 3-
EVALUATION OF SERUM ESTROGEN LEVELS IN GROUP A AND GROUP B BEFORE SUPPLEMENTATION OF VITAMIN D IN GROUP A

Serum Estrogen Level	No. of patients in Group A before treatment		Total	Percentage %	No. of patients in Group B after treatment		Total	Percentage %
	MALE	FEMALE			MALE	FEMALE		
<Normal	0	02	02	3.22	01	01	02	4.00
Normal	39	13	52	83.87	39	06	45	90.00
>Normal	07	01	08	12.90	02	01	03	6.00
Total	**46**	**16**	**62**	**100**	**42**	**08**	**50**	**100**

Table 4-
ANALYSIS OF THE EFFECT OF VITAMIN D ON SERUM ESTROGEN LEVELS IN GROUP A BEFORE AND AFTER VITAMIN D SUPPLEMENTATION

Serum Estrogen Level	No. of patients in Group A before treatment		Total	Percentage %	No. of patients in Group A after treatment		Total	Percentage %
	MALE	FEMALE			MALE	FEMALE		
<Normal	0	02	02	3.22	00	02	02	3.22
Normal	39	13	52	83.87	40	13	53	85.48
>Normal	07	01	08	12.9	06	01	07	11.29
Total	**46**	**16**	**62**	**100**	**46**	**16**	**62**	**100**

DISCUSSION

Diabetes mellitus is one of the oldest diseases known to mankind. According to the International Diabetes Federation, people living with diabetes are nearly 285 million which is approximately 7% of the world's population and is expected to exceed 435 million by 2030.[7] Of the 84 million American adults with pre-diabetes, over 5 to 7 years, about 28 million progress to type 2 diabetes.[7] Worldwide the prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030.[8]

Vit D was first identified and characterized in 1923 by Goldblatt and Soames.[9] Vit D is synthesized in plants and mushrooms involving UV-B action on ergosterol.

Almost one billion individual worldwide have low circulating Vit D levels.[1] Recently there has been renewed interest in the so called "sunshine vitamin", because it has been linked to everything from cancer and heart disease to diabetes.[10] Vit D deficiency, defined as level less than 30ng/ml, leads to the impaired secretion of insulin but no other islet hormones, thus inducing glucose intolerance.[11] Efficiency of Vit D influences the pathogenesis of insulin resistance and type 2 diabetes by the direct effects such as decreased binding to VDR and indirect effect such as aberrant calcium flux. Thus, major factors involved in the pathogenesis of type 1 and type 2 diabetes are affected by the active metabolite form of vitamin D and its analogs. The function of the beta cell have shown to be improved by 1,25(OH) D in vitro and in vivo, therefore it is essential that vitamin D deficiency should be avoided for normal beta cell function.

Testosterone is the main androgen in circulation and is obligatory to

support spermatogenesis. It is produced by leydig cells in the testis and is necessary for the differentiation of the male internal and external reproductive organs and to induce male sex characteristics and sexual behaviour. As mean age increases, total testosterone levels decline, free testosterone [testosterone not bound in the blood to sex hormone-binding globulin (SHBG)] levels decline more rapidly than total testosterone.

Estrogen is produced mainly in the ovaries, and to some extent by fat cells and the adrenal glands. Men also produce estrogen but at lower levels than women. Estrogen in males is secreted by the adrenal glands and by the testes. In men, estrogen is thought to affect sperm count. Overweight men are more commonly affected by low sperm count due to estrogen because there is more adipose tissue in the obese, which can set off the creation of excess estrogen.[12] Recent data have revealed a surprising role for estradiol in regulating energy metabolism and opened new insights into the role of the two estrogen receptors.[13]

The physiological role of Vit D in human reproduction and ovarian steroidogenesis is not well understood. Although the presence of Vit D receptor in human ovary has been reported in the study conducted by Agic et al.(2003)[14], this finding has not been confirmed and the role of Vit D, if any, on human ovarian function is not known. In our study, the mean value of pre-treatment serum estrogen levels in group A was estimated to be 69.06±51.08 ng/ml whereas, after treatment with vitamin D for six months, the mean value was 66.42±49.16 ng/ml. The difference was found to be statistically insignificant with a p-value of 0.1239. Not many studies have been done to observe the effect of vitamin D on estrogen levels.

Parikh et al.(2010),concluded that 1,25-$(OH)_2D_3$ increased progesterone production in mixed ovarian cell culture by 13 % compared to control ($p < 0.001$) but had no significant effect on testosterone production. 1,25-$(OH)_2D_3$ stimulated estradiol or estrone production in purified granulosa cell culture by up to 6 % ($p < 0.02$) and up to 21 % ($p < 0.005$) compared to control, respectively. This increased estrogen production in the presence of 1, 25 $(OH)_2D_3$ may be explained by augmentation of aromatase activity by 1, 25 $(OH)_2D_3$ in the human ovary.[15]

25(OH) D levels are related to testosterone levels in men.[16,17] Data from testicular cell culture suggest that Vit D, especially 1,25 dihydroxy Vit D3, has a major role in male steroidogenesis.[2] VDR is expressed in human testis and has been suggested to affect survival and function of mature spermatozoa.

Wehr et al.(2010), in their study found that men with sufficient 25(OH) D levels (30 ng/ml) had significantly higher levels of testosterone and free androgen index(FAI) and significantly lower levels of sex hormone binding globulin(SHBG) when compared to 25(OH) D insufficient (20–29.9 µg/l) and 25(OH) D-deficient men (<20 ng/ml), $p<0.05$ for all.[18]

Bellastela et al. (2014), performed a case control study among 122 male adults with type 2 diabetes. 51 of them had hypogonadism (Group 1) and 71 had normal gonadal function (Group 2). He concluded that the overall diabetic population showed a mean 25(OH) D concentration (22.3 ± 6.09 ng/mL) significantly lower than the control group (34.3 ± 7.2, $p < 0.001$), with 81% of diabetic patients presenting 25(OH) D deficiency (<20 ng/mL) or insufficiency (20–29.9 ng/mL). The lowest 25(OH) D concentration was found in Group 1 (20.1 ± 6.58 ng/mL). The concentration of 25(OH) D was significantly lower in the 42 patients with hypogonadotropic hypogonadism as compared with the 9 patients with hypergonadotropic hypogonadism (19.4 ± 7.06 vs. 23.8 ± 6.11 ng/mL, $p < 0.001$).[19]
Wang et al.(2015), in their study on 2,854 men found that a total of 713 (25.0 %) men had hypogonadism with significantly lower 25(OH) D levels but greater BMI and HOMA-IR. Using linear regression, after fully adjusting for age, residence area, economic status, smoking, BMI, HOMA-IR, diabetes and systolic pressure, 25(OH)D was associated with total testosterone and estradiol ($p< 0.05$). In the logistic regression analyses, increased quartiles of 25(OH) D were associated with significantly decreased odds ratios of hypogonadism (p for trend <0.01).[17]

Recently Canguven et al.(2017) ,conducted a study to assess whether a monthly high dose Vit D treatment for 12 months in Vit D deficient middle-aged men was associated with: changes in levels of sexual hormones, improvement of diabetes control and metabolic syndrome components, better erectile function and changes in a prostate marker. They studied 102 male patients ≥35 years [(±SD: 53.2 ± 10.5), (range 35-64)] with deficient serum vitamin D level (<30 ng/mL) and followed them up for one year, with monitoring at 3, 6, 9 and 12 months. They found significant stepladder increase in serum total testosterone level (12.46 ± 3.30 to 15.99 ± 1.84 nmol/L) and significant stepladder decrease in estradiol (87.90 ± 27.16 to 69.85 ± 14.80 pmol/L, $p = 0.001$). This study demonstrated that vitamin D treatment improves testosterone levels, metabolic syndrome and erectile function in middle-aged men[20]

In our study, the mean value of pre-treatment serum testosterone levels in group A was estimated to be 4.439 ± 2.856 ng/ml whereas after treatment mean value was 4.650 ± 2.988 ng/ml. The difference was found to be statistically significant with a p-value of 0.0324. However no significant decrease in serum estradiol was observed. Therefore, we conclude that vitamin D plays a beneficial role in normalizing the serum testosterone levels in T2DM patients.

CONCLUSION

Supplementation of Vit D together with improving fasting plasma glucose, as showed in various studies, also helps in regulating the levels of sex hormones such as testosterone in type 2 diabetes mellitus patients. Thus, we conclude that Vit D is a fundamental micronutrient with major implications on human health. Therefore, periodic estimation of Vit D level in type 2 diabetes mellitus patients is recommended to detect hypovitaminosis and timely intervention.

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