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RESEARCH ARTICLE

Role of Vitamin D Receptor in Prediabetes

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Abstract:

Background:

Recent epidemiological evidence points towards the potential association of vitamin D insufficiency with adverse metabolic risk and in the pathogenesis of cancer, cardiovascular diseases, type 2 diabetes and other diseases. Vitamin D exerts its action in a variety of cell types through vitamin D receptors. No reports are available in the literature regarding vitamin D and vitamin D receptor status in prediabetics. The present study was planned to compare serum 25-hydroxy vitamin D [25(OH)D] and vitamin D receptor (VDR) protein levels in prediabetic cases and normoglycemic controls.

Methods:

The present study was conducted in 80 persons who were divided into two groups, Study group (n= 40) comprised of diagnosed cases of prediabetes and control group (n=40) comprised of healthy normoglycemic controls. Serum 25-hydroxy vitamin D [25(OH)D] was analyzed by radioimmunoassay (RIA). Serum vitamin D receptor (VDR) protein was analyzed by sandwich enzyme immunoassay (ELISA).

Results:

Serum 25(OH) vitamin D levels were significantly decreased in prediabetic cases as compared to normoglycemic controls [p<0.001]. Serum Vitamin D receptor protein levels were highly significantly decreased in prediabetic cases as compared to normoglycemic controls [p<0.00]. Serum 25(OH)D levels showed a highly significant positive correlation with serum VDR levels in both the groups [p<0.001 at both levels].

Conclusion:

The findings of the present study indicate that vitamin D and VDR can serve as a possible screening marker and target for modulation of the management and alleviating the progress and complications of diabetes.

Keywords: Vitamin D, Vitamin D receptor, Prediabetes, Normoglycemia, Hyperglycemia, Marker.

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1. INTRODUCTION

Vitamin D deficiency has been linked to impaired glucose tolerance and type 2 DM in humans. Vitamin D has been proposed to play an important role and to be a risk factor in the development of insulin resistance and pathogenesis of type 2 DM by affecting either insulin sensitivity or β cell function or both [1]. Vitamin D exerts its action in a variety of cell types through vitamin D receptors.

Only $1,25(OH)_2D$ form of vitamin D is metabolically active and this molecule exerts its effects by activating the nuclear vitamin D receptor (VDR). The binding of $1,25(OH)_2$-D_3 to VDR leads to the transcription of genes regulated by $1,25(OH)_2D_3$. It is well established that pancreatic β cells express VDR. Johnson et al. have demonstrated the presence of VDR on pancreatic β cells in the islets of Langerhans [2]. Molecular evidence have found that pancreatic β cells express both cytosolic/nuclear VDR, thus enhancing β cells function [3]. Several studies have demonstrated a link between VDR gene polymorphisms and type 2 diabetes, although the findings differ from one population to another [3, 4].

Recent epidemiological evidence points to a potential association of vitamin D insufficiency with adverse metabolic risk and in the pathogenesis of cancer, cardiovascular diseases, type 2 diabetes and other diseases [5]. No reports are available in the literature regarding vitamin D receptor status in

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prediabetics and diabetes. Hence, the present study was planned to analyze serum 25-hydroxy vitamin D [25(OH)D] and vitamin D receptor (VDR) protein levels in prediabetic cases and normoglycemic controls.

2. MATERIALS AND METHODS

The present study was a case control study conducted in the Departments of Biochemistry and Endocrinology and Medicine, Pt. B.D. Sharma PGIMS, Rohtak, Haryana from December 2017 to November 2018 and most of them belonged to Rohtak district and Haryana state at large. The study included 80 persons (in age group: 30-55 years) who were divided into two groups by randomization. Study group (n= 40) comprised of diagnosed cases of prediabetes and control group (n=40) comprised of healthy normoglycemic controls. Sample size was calculated according to the formula [6].

Subjects were selected as per American Diabetes Association (ADA) criteria. Subjects aged ≥18 years, irrespective of their gender, with impaired fasting glucose (IFG) of 100-125 mg/dL and/or impaired glucose tolerance (IGT) of 140-199 mg/dL and/or HbA1c between 5.7-6.4% were included in the study as prediabetic cases.

Pregnant women, women who were breast feeding, critically ill patients, patients with diabetes, tuberculosis, renal/ hepatic impairment, malabsorption syndrome, cardiovascular disease, hypoglycemia, history of cancer, underweight, subjects taking drugs known to alter glucose tolerance, taking vitamin D supplementation for last one year, steroids, oral contraceptive pills, beta blockers, phenytoin and diuretics or fasting serum triglycerides >400 mg/dL (in both the groups) were excluded from the study.

Approval for the study was taken from the Ethical committee of the institution and written informed consent was taken from all the subjects. No new procedures were performed in these persons and standard treatment protocols were followed and ethical guidelines of Helsinki declaration were followed.

Five ml venous sample was drawn, and serum was separated by centrifugation. For blood urea, urease glutamate dehydrogenase method; for serum creatinine, Jaffe's Kinetic method; for serum uric acid, enzymatic method; for serum calcium, Arsenazo method; for serum phosphorus, colorimetric without precipitation; for serum AST and ALT, UV Kinetic method; for serum ALP, PNP-AMP kinetic method; for serum bilirubin, Evelyn- Malloy method; for serum triglycerides, enzymatic method; for serum cholesterol, CHOD-PAP method; for blood sugar, GOD-POD method; for serum HDL, direct method were used in autoanalyzer (make: RX Suzuka Randox laboratories ltd., County Antrim town, United Kingdom).

Samples were taken after overnight fasting of 8-10 hours and in the morning, study samples were drawn at 8-9 am. Serum 25-hydroxy vitamin D [25(OH)D] was analyzed by radioimmunoassay (RIA) from Beckman Coulter [7]. Serum vitamin D receptor (VDR) protein was analyzed by sandwich enzyme immunoassay (ELISA) from Elabscience [8]. With 95% confidence interval, the population means for vitamin D in cases was between 22.2 and 26.8; and for vitamin D in controls was between 28.4 and 34 (based on 40 samples in each group). With 95% confidence interval, the population means for VDR in cases was between 2.63 and 3.57; and for VDR in controls is between 12.5 and 15.8 (based on 40 samples).

Statistical Package for Social Sciences (SPSS) version 23 was used for analysis, data was normalized and two tailed Pearson correlation test between variables was applied. Data so obtained were expressed as mean with standard deviation (Mean± SD), student's t-test, chi square (χ^2) test and regression analysis were carried out; significance was considered as $p<0.05$.

3. RESULTS

The mean age was comparable in two groups, in the study group, it was 40.9±10.43 years as compared to 38.72 ± 12.10 years in the control group. There were 42.5% females and 57.5% females in the study group and 45% females and 55% males in the control group.

Serum calcium levels were significantly lower in prediabetic group as compared to normoglycemic controls [$p<0.05(0.040)$]. Mean values of blood urea, serum creatinine, ALT, AST, ALP levels were higher in prediabetic cases as compared to normoglycemic controls [$p<0.05$ at all levels], (Table **1**).

Mean values of serum triglyceride, serum cholesterol, LDL and VLDL were significantly higher in prediabetic cases as compared to normoglycemic controls [$p=0.043$, $p=0.021$, $p=0.032$, $p=0.034$ respectively, $p<0.05$ at all levels], (Table **2**).

Serum 25(OH) vitamin D levels were significantly decreased in prediabetic cases as compared to normoglycemic controls [$p<0.001$. Serum Vitamin D receptor protein levels were highly significantly decreased in prediabetic cases as compared to normoglycemic controls [$p<0.001(2.06x\ 10^{-20})$], (Table **3**), (Fig. **1**)].

A significant positive correlation was noted between serum 25(OH)D levels and serum VDR levels in both the groups [r = 0.83 *vs* r = 0.88 respectively; $p=2.16x10^{-11}$ *vs* $p=3.71x\ 10^{-14}$, $p<0.001$ at both levels]. No significant correlation could be found between vitamin D and fasting blood sugar and 2 hours plasma glucose after 75 grams glucose load in prediabetes cases, though it was negative [r= -0.085, r= -0.073 respectively, $p= 0.59$, $p=0.65$ respectively, $p<0.05$ at both levels].

4. DISCUSSION

Prediabetes can develop at any age, but the risk of prediabetes is thought to rise after the age of 45 years. This may be due to inactivity, poor diet and a loss of muscle mass, which typically declines with age. But, now a days, prediabetes and diabetes are becoming more common in children and adolescents due to an increase in fast food consumption and decrease in physical activity, which leads to overweight and obesity.

In the present study, 25 (62.5%) prediabetic cases were in the age group of 40 to 59 years and 15 (37.5%) cases were below the age of 40 years. Whereas, 19 (47.5%) normoglycemic controls were in the age group of 40 to 59 years and

21(52.5%) controls were below 40 years. Age distribution of both the groups was comparable and the difference was not statistically significant [p>0.05 (0.39)]. No statistically significant difference was observed in the gender distribution of both the groups, though the prevalence was more in males in both the groups [$\chi 2 = 0.051$; p>0.05 (0.82)]. Type 1 diabetes prevalence has been reported to be in favor of males in USA and Denmark but in females in Japan and Australia. Diabetic females have reported to have higher levels of antibodies to glutamic acid decarboxylase [9]. A study showed higher prevalence of prediabetes and diabetes was higher in women compared to men [10]. A similar finding was reported by Sajjai *et al.* with a higher prevalence of prediabetes and diabetes among women [11]. In contrast, a higher prevalence of prediabetes and diabetes was noted in men compared to women by other workers [12, 13].

In the present study, 17 (42.5%) prediabetic cases were females and 23 (57.5%) were males. Whereas, 18 (45%) controls were females and 22 (55%) were males.

Akter *et al*. reported a significant and positive association for prediabetes with high body weight among Bangladeshi adults [14]. Similarly, in the present study, body weight was higher in prediabetes cases as compared to controls and a statistically significant difference was present between both the groups [p<0.05 (0.001). In the present study, BMI was higher in prediabetes cases as compared to controls and this difference was statistically highly significant [p<0.001 (2.92x 10-05). Also, in prediabetes, 26 (65%) cases had high BMI whereas in controls, 8 (20%), had high BMI (26.57 ± 4.10 *vs* 22.98 ± 3.05 kg/m^2). The odds ratio for developing prediabetes in people with high BMI was 7.42 [95% CI: 2.7- 20.42, p<0.001 (0.0001)].

A potentially important role for calcium status in the development of type 2 DM has been suggested in case control studies where calcium intake was found to be lower in patients with diabetes compared with controls. In many prospective studies, low calcium intake was consistently found to be inversely associated with incident type 2 DM [15]. In the present study, mean serum calcium level was significantly lower in the prediabetic group as compared to normoglycemic controls [p<0.05(0.040)].

Dyslipidemia frequently occurs in diabetic patients and plays a critical role in the acceleration of macrovascular atherosclerosis and contribute to the excess risk of CVD. In the present study, mean values of serum triglyceride, serum cholesterol, LDL and VLDL were significantly higher in prediabetic cases as compared to normoglycemic controls [p=0.043, p=0.021, p=0.032, p=0.034 respectively, p<0.05 at all levels], (Table **2**). The findings of the present study are in agreement with the previous studies [16 - 18].

Among many non-calcemic functions are the induction of differentiation in Peripheral Blood Mononuclear Cells (PBMCs) and antiproliferative effects in many cancers, as well as its immunosuppressive properties; vitamin D also acts as a necessary adjunct for insulin secretion [4]. Some of the immune non-classical actions of vitamin D point towards its role in the pathogenesis of type 2 DM through down-regulation of cytokines (IL-6). Vitamin D can modulate insulin secretion and also possesses pleiotropic effects on the pathogenesis of diabetes mellitus [19].

Serum 25(OH) vitamin D levels significantly decreased in prediabetic cases as compared to normoglycemic controls [p<0.001] in the present study. Lower serum vitamin D levels affect glucose homeostasis and parathyroid hormone concentrations in patients with prediabetes. Gupta *et al*. reported low 25(OH)D levels in prediabetic patients [20]

Twenty eight cases (70%) showed vitamin D inadequacy (<30 ng/mL) whereas 18 (45%) controls had vitamin D inadequacy. The odds ratio for developing prediabetes in people with vitamin D inadequacy was 2.85 (95% CI: 1.13-7.15, p<0.05 (0.025. The findings of the present study are in agreement with other studies [21].

1,25(OH)2D, an active vitamin D metabolite, binds to vitamin D receptor (VDR) in the intestinal cell and stimulates active calcium transport from the intestine to the circulation.

Vitamin D exerts action in a variety of cell types through vitamin D receptor. Serum vitamin D receptor protein levels significantly decreased in prediabetic cases as compared to normoglycemic controls [p<0.001] in the present study. No reports are available regarding vitamin D receptor protein in prediabetes. A significant positive correlation was noted between serum 25(OH)D levels and serum VDR levels in both the groups [p<0.001 at both levels].

Table 1. Routine investigations in both the groups [MEAN±SD]

Parameter (Normal Range)	Cases (n=40) Mean ± SD (Range)	Controls (n=40) Mean ± SD (Range)	*p* Value
Hb (12-15.5 gm/dL in females, 13.5-17.5 gm/dL in males)	12.69 ± 1.80† (9.2-16.1)	13.06 ± 2.6 (9.2-16.7)	0.45
Blood urea (10-50 mg/dL)	25.85 ± 9.20† (15-58)	24.02 ± 7.04 (14-52)	0.32
Serum creatinine (0.5-0.9 mg/dL in females. 0.6-1.1 mg/dL in males)	0.91 ± 0.22† (0.5-1.6)	0.84 ± 0.17 (0.6-1.4)	0.11
Serum uric acid (2.4-5.7 mg/dL in females, 3.4-7.0 mg/dL in males)	4.65 ± 1.34† (2.8-9.2)	4.47 ± 1.28 (2.0-6.9)	0.55

(Table 1) cont.....

Parameter (Normal Range)	Cases (n=40) Mean ± SD (Range)	Controls (n=40) Mean ± SD (Range)	*p* Value
ALT/SGPT (upto 40 U/L)	40.05 ± 17.77† (15-83)	38.12 ± 17.55 (15-74)	0.62
AST/SGOT (upto 40 U/L)	40.3 ± 17.9† (19-84)	34.3 ± 12.81 (15-66)	0.088
Serum ALP (30-90 U/L)	77.97 ± 19.65† (27-109)	76.15 ± 17.50 (39-105)	0.66
Serum bilirubin (upto 1.0 mg/dL)	0.69 ± 0.22† (0.4-1.2)	0.65 ± 0.16 (0.4-1.1)	0.46
Serum calcium (8.1-10.4 mg/dL)	**9.54 ± 0.84*** (8.0-11.2)	9.91 ± 0.70 (7.9-11.5)	0.040
Serum phosphorus (2.7-4.5 mg/dL)	3.61 ± 0.60† (2.4-5.2)	3.58 ± 0.54 (2.3-4.8)	0.80

†Not significant ($p>0.05$) as compared to controls
*$p<0.05$ when compared to controls

Table 2. Lipid profile in both the groups

Parameter (Normal Range)	Cases (n=40) Mean ± SD (Range)	Controls (n=40) Mean ± SD (Range)	*p* value
Serum triglyceride (upto 150 mg/dL)	**145.3 ± 54.50*** (51-246)	118.9 ± 60.77 (35-261)	0.043
Serum cholesterol (upto 200 mg/dL)	**189.95 ± 41.82*** (92-255)	170.22 ± 32.83 (99-230)	0.021
Serum HDL (40-60 mg/dL)	45.15 ± 9.96† (23-59)	45.12 ± 8.33 (22-59)	0.99
Serum LDL (upto 160 mg/dL)	**121.87 ± 38.85*** (47-182)	105.47 ± 27.60 (46-157)	0.032
Serum VLDL (16-32 mg/dL)	**23.07 ± 7.26*** (13-42)	19.82 ± 6.23 (11-33)	0.034

*$p<0.05$ when compared to controls
†Not significant ($p>0.05$) as compared to controls

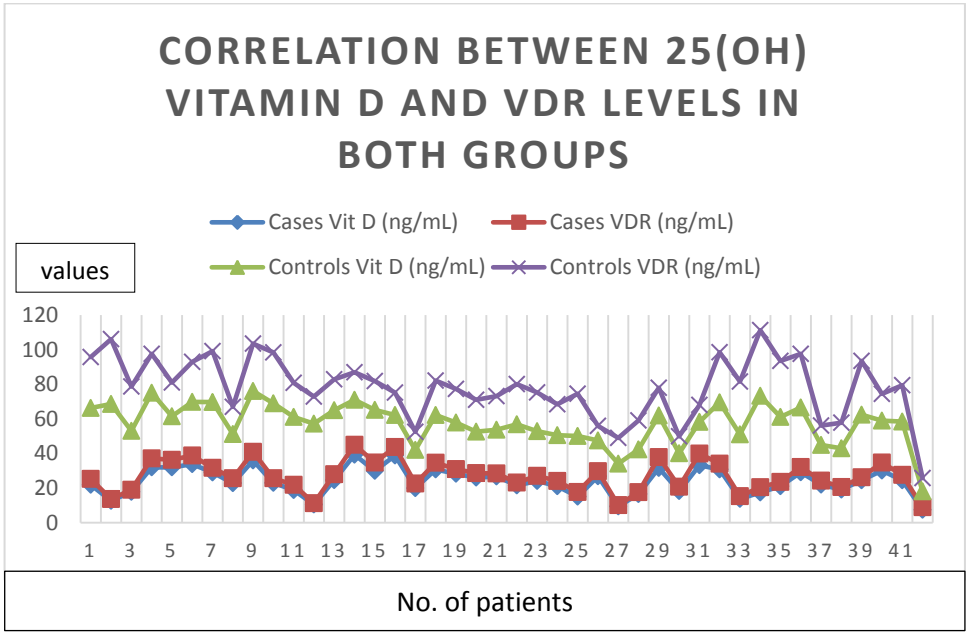

Fig. (1). Correlation between serum 25(OH) vitamin D and serum VDR levels in both groups

Table 3. Serum 25(OH) vitamin D levels and Vitamin D Receptor Protein (VDR) Levels in both the groups [MEAN ± SD, ng/mL]

Parameter (Normal Range)	Cases (n=40)	Controls (n=40)
Serum 25(OH)D (30-100 ng/mL)	24.51 ± 7.48**	31.19 ± 9.12
Range	9.4-39.3	17.7-55.0
Serum VDR (ng/mL)	3.10 ± 1.51**	14.12 ± 5.34
Range	0.74-6.71	5.89-25.89

**$p<0.001$ when compared to controls

Vitamin D and its receptor complex play a key role in regulating the β cell insulin secretion. In the present study, a negative correlation was observed between vitamin D and fasting blood sugar and 2 hours plasma glucose after 75 grams glucose load in prediabetes cases, but the difference was statistically insignificant. Forouhi *et al.* demonstrated a negative correlation between insulin resistance and 25(OH)D levels [22]. During the early phase of prediabetes, pancreatic insulin release is impaired and together with increased serum insulin levels it accelerate the development of insulin resistance and overt diabetes in prediabetic patients. Recent studies support a role for vitamin D as a vascular protective agent against the effects of advanced glycation end products, which mediate the devastating consequences of diabetes on cardiac complications [19].

Few observational studies have suggested that low blood 25-hydroxyvitamin D levels are associated with the risk of type 2 diabetes. However, this is still not known whether vitamin D supplementation lowers the risk of diabetes. Conflicting reports are available in the literature [23 - 25].

Pittas *et al.* in their *Vitamin D and Type 2 Diabetes (D2d) trial* to test whether vitamin D supplementation (dose of 4000 IU per day) reduces the risk of type 2 diabetes among adults, reported that this supplementation did not lower the risk of diabetes than placebo in their study population [20]. Also, another study reported no differences between placebo and vitamin D supplementation groups in terms of fasting plasma glucose, 2-h glucose, or insulin secretion and sensitivity or percent developing diabetes or returning to normal glucose tolerance [21]. In contrast, one study has reported that vitamin D supplementation in prediabetes subjects significantly lowered FPG, 2-h plasma glucose and A1C levels [22]. These differences could be due to ethnic population differences in the relationship between vitamin D and glucose metabolism. No study is available regarding the effect of vitamin D supplementation on vitamin D receptor in prediabetes.

CONCLUSION

The findings of the present study indicate that vitamin D and VDR can serve as a possible screening marker and target for modulation the management and alleviating the progress and complications of diabetes. In the future, vitamin D supplementation may have a role in the diagnosis of impending diabetes, and prevention of complications of prediabetes.

Further work is needed to define the mechanisms by which such variations in VDR synthesis lead to variation in cellular function and to determine whether such variation is abolished by adequate vitamin D repletion.

Identifying people with prediabetes and creating awareness on the prevention of diabetes by lifestyle modification and development of cost-effective strategy to prevent or delay, the progression of the prediabetic stage to diabetic stage is the need of the hour for prevention of diabetes in a country like India, which experiencing the epidemiological transition of chronic non-communicable diseases.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics approval for the study was taken from the institutional ethical committee of the Pt. B.D.Sharma PGIMS/ UHS. Rohtak. The ethical code number is IEC/17/488.

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

Written informed consent was taken from all the subjects.

AVAILABILITY OF DATA AND MATERIALS

The data sets analyzed during the current study are available from the corresponding author upon request.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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