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Original Research Article

Association of vitamin-D deficiency with oxidative stress in newly diagnosed type 2 diabetes

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ABSTRACT

Background: According to a recent World Health Organization (WHO) report, India, with 32 million diabetic individuals, currently has the highest incidence of diabetes worldwide; these numbers are predicted to increase to 80 million by the year 2030. Deficiency of vitamin D has been associated with increased risk of developing Type 2 diabetes mellitus (DM) and cardiovascular diseases. Vitamin D deficiency is highly prevalent in our country. About 70% of adults in both rural and urban areas were found showing manifestations of vitamin D deficiency. Therefore, we designed this study to assess the vitamin D status of the study population by measuring serum 25(OH) D levels, and its association with oxidative stress markers in type 2 diabetes mellitus.
Methods: This is a cross sectional study with Group 1 (n=147): Newly diagnosed type 2 diabetics and Group 2 (n=147): Apparently healthy individuals. Blood was collected by venipuncture. 5ml of blood was collected and allowed to clot. Serum was separated and stored in refrigerator to estimate the oxidative stress markers and vitamin D levels. Estimation of vitamin D levels and oxidative stress markers were carried out by commercially available kits.
Results: Vitamin D levels are significantly low in newly diagnosed type 2 diabetics when compared to controls ($p < 0.000$), whereas the FBG levels are significantly high in newly diagnosed type 2 diabetics when compared to controls ($p < 0.000$). The TAOS levels are significantly low in newly diagnosed type 2 diabetics when compared to controls ($p <0.000$), whereas the MDA levels are significantly high in newly diagnosed type 2 diabetics when compared to controls ($p < 0.000$). The oxidative stress marker TAOS ($r = 0.71$; $p < 0.000$), was positively correlated and MDA ($r = - 0.85$; $p < 0.000$), was negatively with Vitamin D in newly diagnosed type 2 diabetics.
Conclusions: From this study, it is concluded that, lower levels of vitamin D is associated with increased oxidative stress. Therapeutic interventions to increase the vitamin D levels and reduce the oxidative stress should be included as a part of treatment inn newly diagnosed type diabetics.

Keywords: Malondialdehyde, Oxidative stress, Total anti-oxidant status

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia with derangement of carbohydrate, fat and protein metabolism due to absolute or relative deficiency of insulin secretion and action, or both. Diabetes mellitus, especially type-2 diabetes, is a public health problem which has reached epidemic proportions due to the rapidly increasing rates of this disease worldwide. Target organ complications,

secondary to diabetes, are one of the most important medical concerns of the present time.

According to a recent World Health Organization (WHO) report, India with 32 million diabetic individuals, currently has the highest incidence of diabetes worldwide; these numbers are predicted to increase to 80 million by the year 2030.[1]

Hyperglycemia generates reactive oxygen species (ROS), which in turn cause damage to the cells in many ways. Damage to the cells ultimately results in secondary complications in diabetes mellitus.[2] Increased oxidative stress is a widely accepted participant in the development and progression of diabetes and its complications.[3] A well-established correlation exists between the development of macro and micro vascular disease in diabetes mellitus.[4]

Vitamin D deficiency has been shown to alter insulin synthesis and secretion in both humans and animal models. It has been reported that vitamin D deficiency may predispose to glucose intolerance, altered insulin secretion and type 2 diabetes mellitus. Vitamin D replenishment improves glycaemia and insulin secretion in patients with type 2 diabetes with established hypovitaminosis D, thereby suggesting a role for vitamin D in the pathogenesis of type 2 diabetes mellitus. The presence of vitamin D receptors (VDR) and vitamin D-binding proteins (DBP) in pancreatic tissue and the relationship between certain allelic variations in the VDR and DBP genes with glucose tolerance and insulin secretion have further supported this hypothesis. The mechanism of action of vitamin D in type 2 diabetes is thought to be mediated not only through regulation of plasma calcium levels, which regulate insulin synthesis and secretion, but also through a direct action on pancreatic b-cell function.[5]

The initial observations linking vitamin D to type 2 diabetes in humans came from studies showing that both healthy and diabetic subjects had a seasonal variation of glycemic control. Currently, there is evidence supporting that vitamin D status is important to regulate some pathways related to type 2 diabetes developments. Since the activation of inflammatory pathways interferes with normal metabolism and disrupts proper insulin signaling, it is hypothesized that vitamin D could influence glucose homeostasis by modulating inflammatory response. Human studies investigating the impact of vitamin D supplementation on inflammatory biomarkers of subjects with or at high risk of developing type 2 diabetes are scarce and have generated conflicting results.

Based on available clinical and epidemiological data, the positive effects of vitamin D seem to be primarily related to its action on insulin secretion and sensitivity and secondary to its action on inflammation. Future studies specifically designed to investigate the role of vitamin D on type 2 diabetes using inflammation as the main outcome are urgently needed to provide a more robust link between vitamin D, inflammation and type 2 diabetes.[6]

Deficiency of vitamin D has been associated with increased risk of developing Type 2 diabetes mellitus (DM) and cardiovascular diseases.[7] Vitamin D deficiency is highly prevalent in our country. About 70% of adults in both rural and urban areas were found showing manifestations of vitamin D deficiency.[8,9]

India is a tropical country, and atmosphere is sunny throughout the year. However, literature search shows that the data regarding the status of vitamin D in adult Indian population is scarcely available. Since, both Type 2 diabetes and deficiency of vitamin D are highly prevalent in Indian population.

Therefore, we designed this study to assess the vitamin D status of the study population by measuring serum 25 (OH) D levels, and its association with oxidative stress markers in type 2 diabetes mellitus.

METHODS

This is a cross sectional study with Group 1 (n=147): Newly diagnosed type 2 diabetics and Group 2 (n=147): Apparently healthy individuals.

Inclusion criteria consists of 18-35 years, both genders, newly diagnosed type 2 diabetics with Fasting blood glucose ≥126mg/dl with symptoms of diabetes mellitus-polyuria, polydipsia, fatigue, weight loss. The participants were excluded if they are Known diabetics, metabolic syndrome, Morbid obese, thyroid dysfunctions and any other condition which alters the glucose homeostasis.

After getting clearance from institute ethics committee. Written and informed consent was obtained from all the participants. All experiments were performed at research laboratory in the Department of Biochemistry, Rohilkhand Medical College, Bareilly. The patients were asked to refrain from heavy physical activity for 24 hours and from consumption of alcohol and caffeinated beverages for 12 hours prior to the measurements. The temperature of the laboratory was kept between 25ºC-28ºC and lights subdued. The patients were asked to void urine before testing and made to sit in the lab comfortably to accustom to the new environment. Baseline and anthropometric parameters were recorded before blood collection. Blood was collected by venipuncture. 5ml of blood was collected and allowed to clot. Serum was separated and stored in refrigerator to estimate the oxidative stress markers and vitamin D levels. Height was measured by using a stadiometer in the upright position and weight will be measured on a weighing machine. BMI will be calculated by weight (Kg) divided by the square of height in meters. After a 30-minute of acclimatization period, BP was measured 3 times to the

nearest of 2 mm Hg in the sitting position, using a mercurial sphygmomanometer and appropriately sized cuffs.

The average of 3 measurements were used to calculate systolic and diastolic BPs; mean BP waist calculated as the diastolic value plus one third of the pulse pressure value. Estimation of vitamin D levels and oxidative stress markers were carried out by commercially available kits.

RESULTS

The baseline and anthropometric parameters of controls, newly diagnosed type 2 diabetics were given in Table 1.

Table 1: Baseline characteristics of controls and newly diagnosed type 2 diabetics.

Parameter	Controls (n=147) Mean ±SD	Newly diagnosed type 2 diabetes mellitus (n=147) Mean ±SD	P -value
Age (yrs)	46.04 ± 4.30	46.37 ± 4.31	0.516
Height (cm)	171.80 ± 6.2	171.85 ± 6.31	0.941
Weight (kg)	68.19 ± 5.67	76.87 ± 5.44	0.000
BMI (kg/m^2)	23.16 ± 2.32	26.05 ± 1.67	0.000
Gender (m/f)	108/39	112/35	0.000
SBP (mmhg)	113.76 ± 6.00	125.04 ± 4.55	0.000
DBP (mmhg)	79.46 ± 3.00	80.85 ± 2.98	0.000
PP (mmhg)	34.30 ± 6.00	44.19 ± 3.92	0.000
MAP (mmhg)	90.89 ± 3.15	95.58 ± 3.06	0.000
RPP	8880.18 ± 563.92	9910.09 ± 455.79	0.000
HR (bpm)	78.05 ± 2.75	79.25 ± 2.49	0.000

Data expressed as mean ±SD. BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic pressure, PP: Pulse pressure, MAP: Mean arterial pressure, RPP: Rate pressure product, HR, Heart rate.

As shown in Table 1 there was no significant difference between age (p<0.516) and height (p<0.941) of the study participants. Significantly difference in weight (p<0.000), BMI (p<0.000), Heart rate (p<0.000), blood pressure (SBP p<0.000, DBP p<0.000) and rate pressure product (p<0.000) were seen.

Table 2 shows the between groups comparison of Vitamin D and FBG. Vitamin D levels are significantly low in newly diagnosed type 2 diabetics when compared to controls (p<0.000), whereas the FBG levels are significantly high in newly diagnosed type 2 diabetics when compared to controls (p<0.000).

Table 2: Vitamin D and fasting blood glucose levels of controls and newly diagnosed type 2 diabetics.

Parameter	Controls(n=147) Mean ±SD	Newly diagnosed type 2 DM (n=147) Mean ±SD	P -value
Vitamin d (ng/ml)	19.19 ± 2.08	10.47 ± 2.13	0.000
FBG (gm/dl)	95.42 ± 6.06	132.70 ± 3.88	0.000

Data expressed as mean ±SD. FBG: Fasting blood glucose.

Table 3 shows the between groups comparison of TAOS and MDA. The TAOS levels are significantly low in newly diagnosed type 2 diabetics when compared to controls (p<0.000), whereas the MDA levels are significantly high in newly diagnosed type 2 diabetics when compared to controls (p<0.000).

Table 3: Oxidative stress markers of controls and newly diagnosed type 2 diabetics.

Parameter	Controls (n=147) Mean ±SD	Newly diagnosed type 2 DM (n=147) Mean ±SD	P -value
TAOS (mm)	1.04 ± 0.56	0.43 ± 0.19	0.000
MDA (mm)	3.97 ± 2.84	16.37 ± 11.31	0.000

Data expressed as mean + SD. TAOS: Total anti-oxidant status, MDA: Malondialdehyde.

Correlation analysis showed significant association of Vitamin D with oxidative stress markers (Figure 1, 2) in newly diagnosed type 2 diabetics.

The oxidative stress markers TAOS (r = 0.71; p<0.000), was positively correlated and MDA (r= -0.85; p<0.000), was negatively with Vitamin D in newly diagnosed type 2 diabetics.

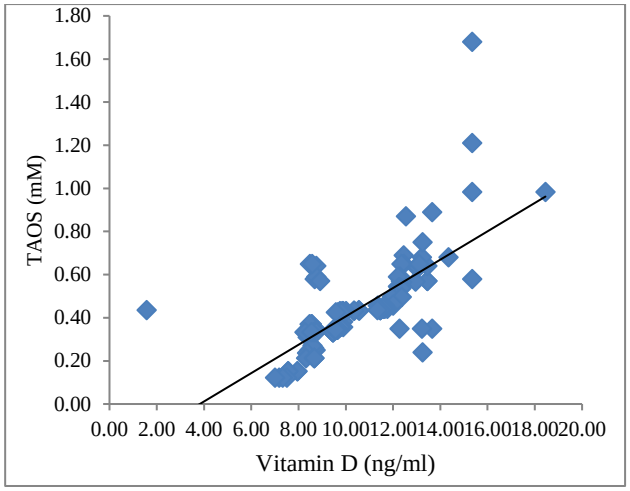

Figure 1: Association of vitamin d with TAOS in newly diagnosed type 2 diabetics (r = 0. 71).

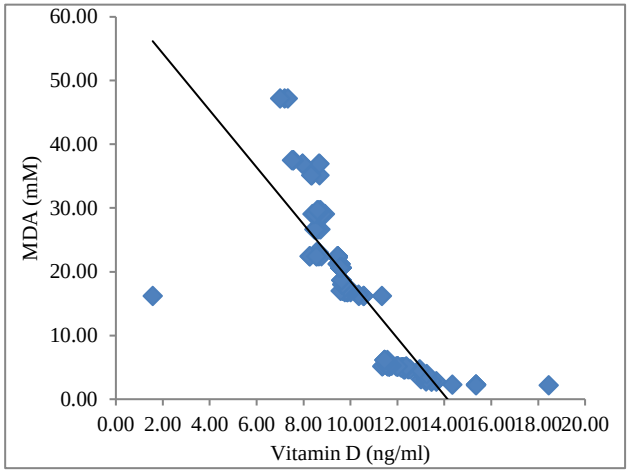

Figure 2: Association of vitamin d with MDA in newly diagnosed type 2 diabetics (r = - 0. 85).

DISCUSSION

In developed countries T2DM mostly affects elderly; but in developing countries like India, the working lives of the younger population are affected causing threat to their health.[10] Diabetes patients often feel challenged by their disease, day-to-day management and its substantial demands. Diabetics have higher risk for cardiovascular disease (CVD) and metabolic dysfunctions.

Although the management of diabetes and its impacts is expensive, cost effective measures prevent their occurrence. Instead of merely aiming at the glycemic control, paying attention to the reduction of cardiovascular risk in diabetes is the most compelling aspect of management for the risk reduction globally.[11]

Very few studies have addressed the relationship between weight change, closely associated with BMI, and incidence of CVD in diabetes patients.

In our study, the weight and BMI were significantly high in newly diagnosed type 2 diabetics. The blood and pressure and heart rate were also significantly high in newly diagnosed type 2 diabetics.

Further, the rate pressure product which is noninvasive myocardial oxygen consumption marker is increased which indicates the cardiovascular risk in newly diagnosed type 2 diabetics. CVD is elevated in type 2 diabetes mellitus due to a complex combination of various traditional and non-traditional risk factors, that have an important role to play in the beginning and the evolution of atherosclerosis over its long natural history from endothelial function to clinical events.[12]

The role of vitamin D in calcium and phosphorous homeostasis and bone metabolism is well understood. However, more recently, vitamin D and calcium homeostasis have also been linked to a number of conditions, such as neuromuscular function, cancer, and a wide range of chronic diseases, including autoimmune diseases, atherosclerosis, obesity, cardiovascular diseases, diabetes, and associated conditions such as the metabolic syndrome and insulin resistance.[13,14]

In T2DM, the role of vitamin D was suggested from the presence of vitamin D receptors (VDR) in the pancreatic β-islet cells. In these cells, the biologically active metabolite of vitamin D (i.e.1,25-dihydroxy-vitamin D; 1,25(OH) 2 D) enhances insulin production and secretion via its action on the VDR.[15]

Indeed, the presence of vitamin D binding protein (DBP), a major predictor of serum levels of 25 (OH) D and response to vitamin D supplementation and VDR initiated several studies demonstrating a relationship between single-nucleotide polymorphisms (SNPs) in the genes regulating VDR and DBP and glucose intolerance and insulin secretion.[16]

This further supports a role for vitamin D in T2DM and may explain the reduced overall risk of the disease in subjects who ingest 800IU/day of vitamin D.[17] However, an alternative, perhaps related, explanation was recently proposed for the role of vitamin D in the prevention of T2DM based on its potent immunomodulatory functions. 1,25 (OH) 2D modulates the production of the immunostimulatory IL-12 and the immunosuppressive IL-10, and VDRs are present in most types of immune cells. 117 In this respect, supplementation with vitamin-D or its bioactive form 1,25(OH)2D improved insulin sensitivity by preventing the excessive synthesis of inflammatory cytokines.[18] This effect of vitamin D on cytokine synthesis is due to its interaction with vitamin D response elements present in the promoter region of cytokine-encoding genes. This interaction down regulates the transcriptional activities of cytokine genes and attenuates the synthesis of the corresponding proteins. Vitamin D also deactivates NFκB, which

transcriptionally regulates the proinflammatory cytokine-encoding genes.

Down regulating the expression of NFκB and downstream cytokine genes inhibits β-cell apoptosis and promotes their survival. As reviewed by Pittas et al a number of cross sectional studies in both healthy and diabetic cohorts have shown an inverse association between serum 25(OH)D and glycemic status measures such as fasting plasma glucose, oral glucose tolerance tests, hemoglobin A 1c(HbA1c), and insulin resistance as measured by the homeostatic model assessment (HOMA-R), as well as the metabolic syndrome.[14,19]

For example, data from the National Health and Nutrition Examination Survey showed an inverse, dose-dependent association between serum 25(OH)D and diabetes prevalence in non-Hispanic whites and Mexican Americans, but not in non-Hispanic blacks.[20]

The same inverse trend was observed between serum 25(OH)D and insulin resistance as measured by HOMA-R, but there was no correlation between serum levels of vitamin D and β-cell function, as measured by HOMA-β.[21] Data from the same cohort also showed an inverse association between serum 25(OH)D and prevalence of the metabolic syndrome.[21]

In prospective studies, dietary vitamin D intake has been associated with incidence of T2DM. For example, data from the Women's Health Study showed that among middle-aged and older women, taking 511IU/day of vitamin D reduced the risk of developing T2DM compared to ingesting 159 IU/day.[22]

Table 3 shows the between groups comparison of TAOS and MDA. The TAOS levels are significantly low in newly diagnosed type 2 diabetics when compared to controls ($p<0.000$), whereas the MDA levels are significantly high in newly diagnosed type 2 diabetics when compared to controls ($p<0.000$). A number of studies have highlighted a direct link between oxidative stress and diabetes through the measurement of markers of oxidative stress (e.g., plasma and urinary F2-isoprostanes and plasma and tissue levels of nitrotyrosine and superoxide).[23]

Oxidative stress in diabetes arises from various pathways, including nonenzymatic, enzymatic, and mitochondrial processes. Hyperglycemia modifies the redox balance through the polyol pathway (where glucose is reduced to sorbitol, with subsequent decreases in levels of NADPH and reduced glutathione), activates oxidases, and interferes with the mitochondrial electron transport chain.[24,25]

These processes generate by-products that can trigger various signaling cascades, for example activation of protein kinase C to further increase the synthesis of reactive oxidative species.[26] Reactive species can play a role directly in insulin sensitivity, secretion, and action in both animal and human models.[27] Oxidative stress has also been noted to coexist with insulin resistance in patients with type 2 diabetes, in obese subjects, and at various stages of the metabolic syndrome.[28]

For example, insulin resistance has been noted in obese women with reduced total antioxidant status and in men with plasma levels of 8-epi-prostaglandin F2α(PGF2α), a marker for lipid peroxidation.[29,30]

Further, the Correlation analysis showed significant association of Vitamin D with inflammatory markers and oxidative stress markers (Figure 1-2) in newly diagnosed type 2 diabetics. The levels of Vitamin D were positively correlated and MDA ($r = -0.85$; $p<0.000$) and negatively with Vitamin D in newly diagnosed type 2 diabetics. This indicates the association between Vitamin D levels and oxidative stress.

CONCLUSION

From this study, it is concluded that, lower levels of vitamin D is associated with increased oxidative stress. Therapeutic interventions to increase the vitamin D levels and reduce the oxidative stress should be included as a part of treatment in newly diagnosed type 2 diabetics.

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