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Reduced Vitamin D levels are associated with oxidative stress and inflammation in type 2 diabetes.

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Abstract

Introduction: India, with 32 million diabetic individuals, currently has the highest incidence of diabetes worldwide and 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 inflammatory markers and oxidative stress markersin type 2 diabetes mellitus.

Materials & 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. 5ml of blood was collected and allowed to clot. Estimation of vitamin D levels, inflammatory markers 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 markers and inflammatory markers were negatively correlated with Vitamin D in newly diagnosed type 2 diabetics.

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

Key words: Type 2 diabetes, inflammatory markers, oxidative stress.

Introduction: 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).

There are many studies emphasizing the presence and importance of the inflammatory component in the

pathogenesis of Diabetes mellitus. A very important role is played by adipose tissue, which releases various pro-inflammatory cytokines, such as, tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), C Reactive Protein (hs CRP), intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) (2) (3)(4).

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 (5). Increased oxidative stress is a widely accepted participant in the development and progression of diabetes and its complications (6). A well established correlation exists between the development of macro and micro vascular disease in diabetes mellitus (7).

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. 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 (8).

Based on available clinical and epidemiological data, the positive effects of vitamin D seem to be primarily related to its action on in sulin 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 in order to provide a more robust link between vitamin D, inflammation and type 2 diabetes (9). Deficiency of vitamin D has been associated with increased risk of developing Type 2 diabetes mellitus (DM) and cardiovascular diseases (10). 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 (11)(12).

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 inflammatory and oxidative stress markers in type 2 diabetes mellitus.

Materials and methods: 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 Dept of Biochemistry, Varun Arjun Medical College, Shahjahanpur. This cross sectional study was carried out with Group 1 (n=127): Newly diagnosed type 2 diabetics and Group 2 (n=127): 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. 5ml of blood was collected and allowed to clot. Serum was separated and stored in refrigerator to estimate the inflammatory markers and oxidative stress markers. Estimation of vitamin D levels and oxidative stress markers were carried out by commercially available kits.

Data Analysis: The data was expressed as mean ± SD. Normality was tested with Kolmogorov–Smirnov test. To study the between group differences, independent t test was used. To study the association of vitamin D levels with inflammatory markers and oxidative stress markers, pearson's correlation was used. The null hypothesis will be rejected at $P \leq 0.05$.

Results

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

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 ($p < 0.000$).

The between groups comparison of TNF alpha, IL 1 beta, IL 6, ICAM 1, VCAM 1 and hsCRP are depicted in Table 3. The levels of these parameters are significantly high in newly diagnosed type 2 diabetics when compared to controls TNF alpha ($p < 0.000$), IL 1 beta ($p < 0.000$), IL 6 ($p < 0.000$), ICAM 1 ($p < 0.000$), VCAM 1 ($p < 0.000$) and hsCRP ($p < 0.000$).

Table 4 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 ($p < 0.000$).

Correlation analysis showed significant association of Vitamin D with inflammatory markers and oxidative stress markers (Fig 26-35) in newly diagnosed type 2 diabetics. The levels of Vitamin D is negatively correlated with inflammatory markers TNF alpha ($r = - 0.79$; $p < 0.000$), IL 1beta ($r = - 0.78$; $p < 0.000$), IL 6 ($r = - 0.70$; $p < 0.000$), hs CRP ($r = - 0.89$; $p < 0.000$), ICAM 1 ($r = - 0.82$; $p < 0.000$), VCAM 1 ($r = - 0.81$; $p < 0.000$). 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.

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

Sl. No	Parameter	Controls(n=127) Mean ±SD	Newly diagnosed type 2 DM (n=127) Mean ±SD	P -value
1	Age(yrs)	44.11 ± 3.30	45.12 ± 3.21	0.516
2	Height (cm)	173.50 ± 6.2	170.75 ± 5.22	0.941
3	Weight(kg)	69.99 ± 3.67	79.57 ± 6.44	0.000
4	Gender (M/F)	111/16	108/19	0.000
5	SBP(mmHg)	116.58 ± 5.350	127.15 ± 3.41	0.000
6	DBP(mmHg)	77.26 ± 4.32	84.35 ± 8.58	0.000
7	HR (bpm)	79.15 ± 3.65	84.27 ± 6.38	0.000

Data expressed as mean ± SD. BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic pressure, HR: Heart rate.

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

Sl. No	Parameter	Controls(n=127) Mean ±SD	Newly diagnosed type 2 Diabetes mellitus (n=127) Mean ±SD	P -value
1	Vitamin D (ng/ml)	17.19 ± 3.18	8.17 ± 1.19	0.000
2	FBG (gm/dl)	91.92 ± 6.06	133.27 ± 2.98	0.000

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

Table 3: Inflammatory cytokine levels of controls and type 2 diabetics.

Sl. No	Parameter	Controls(n=127) Mean ±SD	Newly diagnosed type 2 DM(n=127) Mean ±SD	P -value
1	TNF alpha (pg/ml)	130.48 ± 22.45	261.23 ± 81.24	0.000
2	IL 1 beta (pg/ml)	6.42 ± 1.44	16.25 ± 1.33	0.000
3	IL 6 (pg/ml)	4.54 ± 0.24	13.32 ± 1.54	0.000
4	ICAM 1 (ng/ml)	10.25 ± 1.41	26.54 ± 4.24	0.000
5	VCAM 1 (ng/ml)	10.14 ± 1.27	27.37 ± 2.02	0.000
6	hsCRP (ng/ml)	2312.38 ± 810.77	7106.24 ± 1012.11	0.000

Data expressed as mean ± SD. TNF alpha: Tumor necrosis factor alpha, IL 1 beta: Interleukin 1 beta, IL 6: Interleukin 6, ICAM 1: Intracellular cell adhesion molecule 1, VCAM 1: Vascular cell adhesion molecule 1, hsCRP: high sensitivity C reactive protein.

Table 4: Oxidative stress markers of controls and type 2 diabetics.

Sl. No	Parameter	Controls(n=127) Mean ±SD	Newly diagnosed type 2 DM (n=127) Mean ±SD	P-value
1	TAOS (mM)	1.12 ± 0.36	0.48 ± 0.59	0.000
2	MDA (mM)	3.87 ± 1.34	15.25 ± 9.21	0.000

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

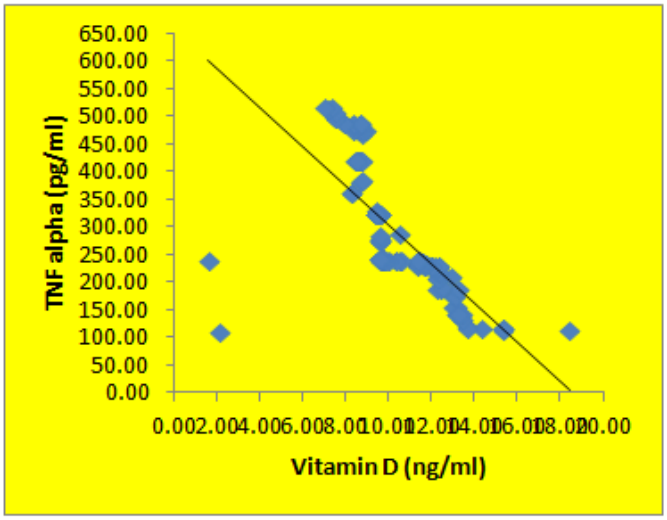

Figure 1: Association of Vitamin D with TNF alpha in type 2 diabetics (r = - 0.79)

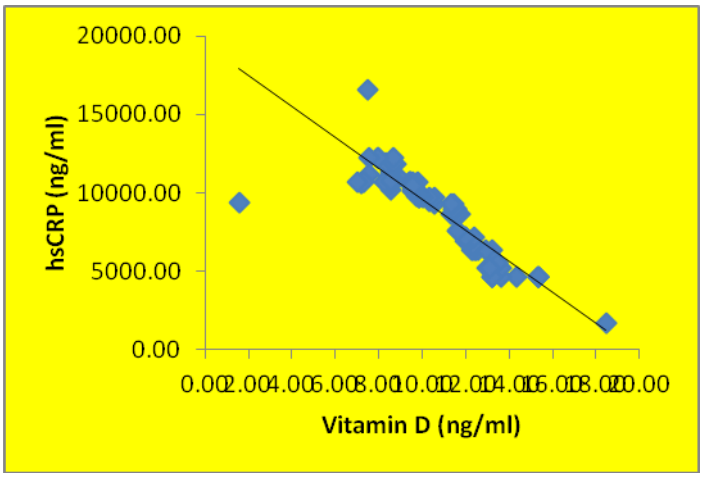

Figure 2: Association of Vitamin D with hsCRP in type 2 diabetics (r = - 0. 89)

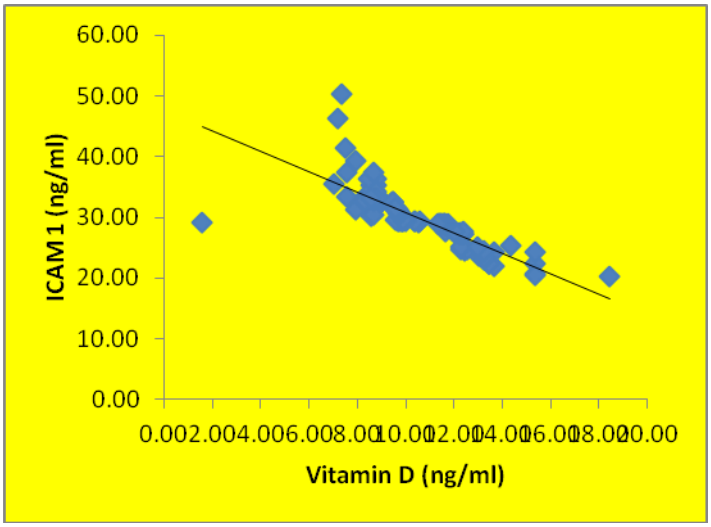

Figure 3: Association of Vitamin D with ICAM 1 in type 2 diabetics (r = - 0. 82)

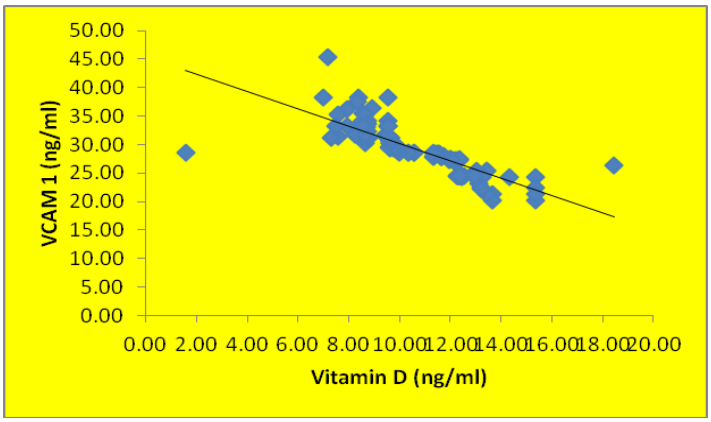

Figure 4: Association of Vitamin D with VCAM 1 in type 2 diabetics (r = - 0. 81)

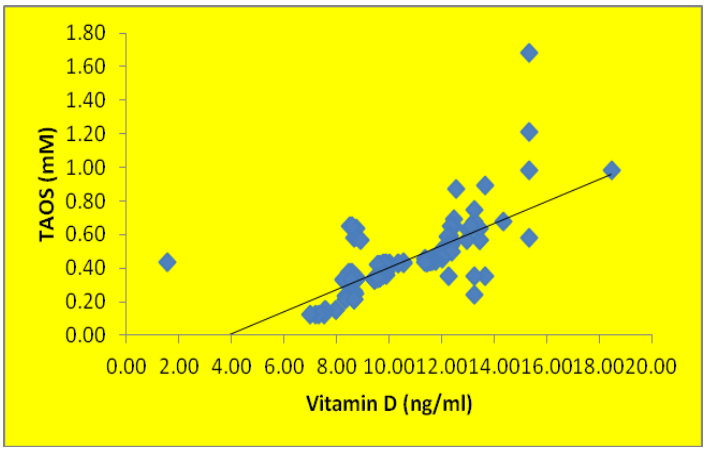

Figure 5: Association of Vitamin D with TAOS in type 2 diabetics (r = 0. 71)

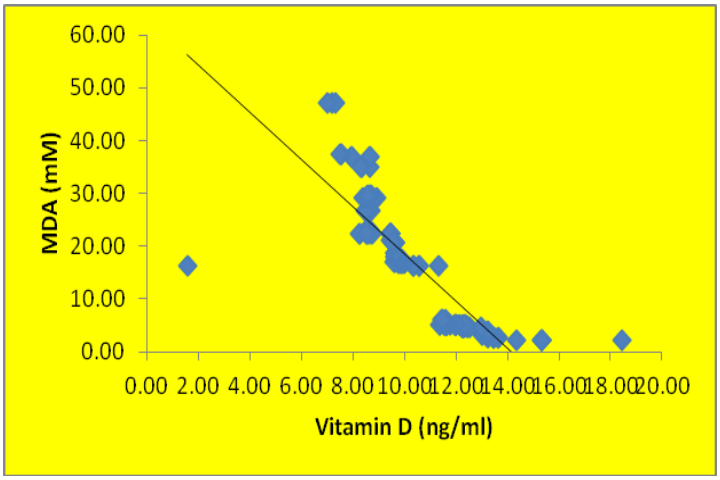

Figure 6: Association of Vitamin D with MDA in type 2 diabetics (r = - 0. 85).

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

In our study, the weight was 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. 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 (13)

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 ($p < 0.000$).

In T2DM, the role of vitamin D was suggested from the presence of vitamin D receptors (VDR) in the pancreatic β-islet cells. 106 In these cells, the biologically active metabolite of vitamin D (ie, 1,25-dihydroxy-vitamin D; 1,25(OH) 2 D) (14) enhances insulin production and secretion via its action on the VDR .

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 (15).

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 .511 IU/day of vitamin D reduced the risk of developing T2DM compared to ingesting 159 IU/day (16).

Further, the Correlation analysis showed significant association of Vitamin D with inflammatory markers and oxidative stress markers (Fig 1-6) in newly diagnosed type 2 diabetics. The levels of Vitamin D is negatively correlated with inflammatory markers TNF alpha ($r = -0.79$; $p < 0.000$), IL 1beta ($r = -0.78$; $p < 0.000$), IL 6 ($r = -0.70$; $p < 0.000$), hs CRP ($r = -0.89$; $p < 0.000$), ICAM 1 ($r = -0.82$; $p < 0.000$), VCAM 1 ($r = -0.81$; $p < 0.000$). 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. Which indicates the association between Vitamin D levels and inflammatory and oxidative stress markers.

The between groups comparison of TNF alpha, IL 1 beta, IL 6, ICAM 1, VCAM 1 and hsCRP are depicted in Table 3. The levels of these parameters are significantly high in newly diagnosed type 2 diabetics when compared to controls TNF alpha ($p < 0.000$), IL 1 beta ($p < 0.000$), IL 6 ($p < 0.000$), ICAM 1 ($p < 0.000$), VCAM 1 ($p < 0.000$) and hsCRP ($p < 0.000$).

Findings of this study showed higher fasting glucose in diabetic patients compared to non-diabetic subjects. Diabetes, characterized by chronic hyperglycemia, is associated with significant morbidity due to long term complications, such as diabetic nephropathy, atherosclerosis, and hypertension. Endothelial dysfunction, by accelerating glycosylation or sorbitol pathways, is regarded as a key event in the development and progression of atherosclerosis and thought to be the major cause of vascular disease due to hyperglycemia (17).

CRP has been demonstrated to increase the expression of ICAM-1, VCAM-1, and MCP-1 in a concentration-dependent fashion (18). Likewise, CRP has been demonstrated to facilitate native LDL uptake into macrophages, an important step in foam-cell formation (19).

Our results shows that the endothelial dysfunction markers VCAM-1, ICAM-1 levels were higher in diabetic patients than healthy group, which are quite similar to other studies in diabetes (20) and cardiovascular disease (21). The adhesion molecule VCAM -1, ICAM-1 are established markers for endothelial dysfunction and they represent major receptors controlling the influx of monocytes and other inflammatory cells into the arterial wall, their expression is considered as a hallmark in the etiology of atherosclerosis (22).

In present study, we also observed that serum IL-1β concentrations were significantly higher in patients group than in control group. Proinflammatory cytokines secreted by adipose tissue and the other tissues can cause insulin dysfunction in adipose tissue, skeletal muscle and liver by inhibiting insulin signal transduction.

Accumulating evidence indicates that diseases related to metabolic syndrome are characterized by abnormal cytokine production, including elevated circulating IL-1β, increased acute-phase proteins, e.g., CRP and activation of inflammatory signaling pathways (23). IL-1β plays an important role in lipid metabolism by regulating insulin levels and lipase activity under physiological conditions. Previous studies have described a positive association between IL-1β gene polymorphism and obesity, suggesting functional effects on fat mass, fat metabolism and body mass (24). Recent evidence has shown that IL-1β plays a role in various diseases, including autoimmune diseases such as inflammatory bowel diseases and type 1diabetes, rheumatoid arthritis, as well as in diseases associated with metabolic syndrome such as atherosclerosis, chronic heart failure and type 2 diabetes (25). IL-1β production and secretion from pancreatic islets have also been reported (26).

Table 4 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 ($p < 0.000$).

Oxidation is a chemical process whereby electrons are removed from molecules and highly reactive free radicals are generated. Free radicals include ROS such as superoxide and hydroperoxyl and RNS such as nitric oxide and nitrogen dioxide (27), (28). Reactive species arise as natural by-products of aerobic metabolism, and they play a role in numerous signaling cascades and physiological processes, such as phagocytosis, vasorelaxation, and neutrophil function (27), (29).

However, excessive oxidation can trigger cytotoxic chain reactions that are damaging to membrane lipids, proteins, nucleic acids, and carbohydrates (29), (30).

Therefore, the capacity of serum to control production of free radicals is defined as the ‘total antioxidant status'. The signaling transduction role of ROS stems from their ability to activate a number of stress-sensitive kinases

whose downstream effects mediate insulin resistance (28). Activation of these kinases upregulates and activates NFκB and activator protein-1 (AP-1), which subsequently (a) activates c-Jun N-terminal kinase (JNK) and inhibitor of NFκB kinase-β (IKK), (b) transcriptionally upregulates proinflammatory cytokine genes (31), and (c) increases the synthesis of acute phase reactants (32), (33).

Reactive species can play a role directly in insulin sensitivity, secretion, and action in both animal and human models (34). 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 (35) and in men with plasma levels of 8-epi-prostaglandin F2α(PGF2α), a marker for lipid peroxidation (36).

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

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