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Assessment of Vitamin D receptor levels and some physiological and biochemical markers in T1DM and T2DM Patients

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Abstract

Background: Diabetes mellitus is an increasingly serious problem in global health, and both type 1 (T1DM) and type 2 (T2DM) diabetes are correlated to the dysfunction of vitamin D receptor (VDR) as well as oxidative stress. The objective of this study was to determine the levels of VDR and markers of antioxidant status in patients with T1DM and T2DM compared to healthy controls.

Methods: A total of 90 participants were enrolled in this cross-sectional study and randomly allocated into three groups (n=30 each) with two disease groups, normal controls, T1DM patients and T2DM patients. Levels of serum VDR were evaluated by ELISA. Spectrophotometric methods were employed to evaluate oxidative stress indicators such as superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT) and malondialdehyde (MDA). Blood glucose (FBG, HbA1c) were used to assess glycemic parameters.

Results: VDR levels were significantly lower in both T1DM (2.34 ± 0.52 ng/mL) and T2DM (2.89 ± 0.61 ng/mL) groups compared to controls (4.12 ± 0.73 ng/mL, $p<0.001$). Antioxidant enzymes (SOD, GPx, CAT) showed significant reduction in diabetic groups, while MDA levels were significantly elevated (T1DM: 8.76 ± 1.34 nmol/mL; T2DM: 7.92 ± 1.28 nmol/mL vs. controls: 3.45 ± 0.67 nmol/mL, $p<0.001$). There were significant negative correlations between VDR and HbA1c ($r=-0.68$, $p<0.001$) and MDA ($r=-0.71$, $p<0.001$), and positive correlations with antioxidant enzymes.

Conclusion: Decreased VDR together with increased oxidative stress and reduced antioxidant defenses were associated in both types of diabetes (T1DM and T2DM). According to these findings VDR is significantly played on pathophysic of diabetes and might represent an approach to control the oxidative stress.

Keywords: VDR; T1DM; T2DM; Oxidative stress; Antioxidant enzymes; MDA

1. Introduction

The global prevalence of diabetes mellitus (DM) is increasing so rapidly that it has become one of the most serious public health problems in the world, affecting about 537 million adults worldwide by 2021 and projected to affect 783 million people globally by 2045 (Saeedi et al., 2022). Diabetes is primarily of two types of diseases, type 1 diabetes mellitus (T1DM), an autoimmune disease causing destruction of pancreatic β-cells, and type 2 diabetes mellitus (T2DM), characterized by insulin resistance coupled with progressive β-cell failure (Galicia-Garcia et al., 2020). Concrete manifestations of chronic hyperglycemia lead to a number of complications in various organ systems due principally to mechanisms that include oxidative stress, inflammation and metabolic dysregulation for both conditions.

The latest data have highlighted an additional wider dimension of vitamin D beyond the classical mechanisms involving calcium homeostasis and bone metabolism. Vitamin D receptor (VDR), which belonged to a nuclear hormone receptor

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subfamily, has already been detected in the pancreas β-cells, immune cells and metabolic organs, suggesting its significant role in glucose homeostasis and immune regulation (Bouillon et al., 2022). A variety of epidemiological studies have repeatedly correlated vitamin D deficiency to a greater risk for developing diabetes with the factors linking these phenomena mechanistically inadequately comprehended (Zhang et al., 2020). Effect of vitamin D on the biology mediated by its receptor (VDR) is carried out through genomic and non-genomic pathways that result in modifying glucose homeostasis, e.g., insulin secretion, insulin sensitivity, and inflammatory responses (Chagas et al., 2021).

Furthermore, a common pathophysiological mechanism from diabetes complications is the oxidative stress which starts to appear when there is an imbalance between the production of reactive oxygen species (ROS) and antioxidant defense capacity [38]. There are several potential mechanisms underlying the increased generation of ROS in association with hyperglycemia, including glucose autoxidation, enhanced activity of the polyol pathway, formation of advanced glycation end-products (AGEs), oxidative phosphorylation and mitochondrial dysfunction (Brownlee 2005; Rehman & Akash, 2020). Antioxidants in our cells, such as superoxide dismutase (SOD), glutathione peroxidise (GPx) and catalase (CAT), are an essential component of this defense system to scavenge the ROS and protect against cellular damage Fig. 1 a [6,7].

Superoxide dismutase controls the dismutation of superoscide radicals into hydrogen peroxide and molecular oxygen, acting as the first line of defence against oxidative stress (Wang et al., 2018). This is followed by glutathione peroxidase, which uses glutathione as a substrate in the reduction of hydrogen peroxide and lipid hydroperoxides, and catalase it decomposes hydrogen peroxide into water and oxygen (Ighodaro & Akinloye, 2018). Malondialdehyde (MDA), a biomarker of oxidative damage and a product of lipid peroxidation, has been consistently reported to be increased in diabetic patients (Ayala et al., 2014; Tsikas, 2021).

Recent new evidence for a link between vitamin D/VDR signaling and oxidative stress pathways is potentially relevant to understanding diabetes. Through transcriptional regulation by the vitamin D receptor (VDR), vitamin D is known to modulate antioxidant enzyme expression and activity (Cui et al., 2020). Furthermore, vitamin D supplementation studies have shown beneficial effects on glycemic control and oxidative stress markers but were not consistent (Hu et al., 2020; Lemieux et al., 2022). However, the number of studies that evaluated VDR levels along with oxidative stress parameters simultaneously in all groups: T1DM and T2DM is limited.

Given the distinct pathophysiological mechanisms of both T1DM and T2DM, this indicates that VDR dysregulation and oxidative stress probably varies between both diabetes forms differently. The primary difference between these diseases is that T1DM has an autoimmune-mediated destruction of the β-cells and there are probably roles of VDR in mediating immune pathways while T2DM is a disease characterized by metabolic dysfunction with VDR modulating insulin signaling and adipose tissue function (Sacerdote et al., 2022). Unraveling these differences could offer insights into disease–specific therapeutic avenues.

In light of a heightened interest in vitamin D and its role for diabetes, there are still gaps in knowledge. First, the majority of studies have focused on circulating levels of vitamin D or 25(OH)D rather than expression/levels of VDR which is a direct mediator of biological effects (which includes some biological effects determined by local actions). The second, there are very few comparative studies on oxidative stress profiles of T1DM and T2DM in relation to VDR status. Third, the relationship between VDR and specific antioxidant enzymes in diabetic population should be further explored.

The present study was designed to evaluate the circulating levels of VDR and oxidative stress marker in patients with T1DM and T2DM in relation to controls healthy subjects, thus filling these gaps. In particular, we aimed to evaluate serum VDR levels in parallel with activities of antioxidant enzymes (SOD, GPx, CAT), and lipid peroxidation (MDA), as well as correlate these parameters with glycemic control indices. The hypothesis that diabetics in either cohort would display decreased levels of VDR and impaired antioxidant capacity relative to controls but with magnitude reflectively different between T1DM and T2DM. the aim of this study may shed light on an aspect of VDR in endocrine pathophysiology, especially as it relates to oxidative stress response and ultimately therapeutic targeting modulating vitamin D/VDR pathways to treat diabetes.

2. Materials and Methods

2.1. Study Design and Participants

Cross-sectional analytical study was performed between January 2025 and August 2025 in Al-Qasim Green university labs. The Institutional Ethics Committee (approval no. IEC/2025/145) approved the study protocol, and all procedures

were carried out in accordance with the guidelines set by the Declaration of Helsinki. All participants provided written informed consent before enrollment.

This study suggest that 90 participants were included in current research (Group I: healthy controls, n = 30 (15 males, 15 females; mean age 42.3 ± 8.5 years), Group II: Type1DM Patients) n = 30 (16 males and14 female); mean age 38.7 ±10.2 Yeras.), Group III: type-2 DM patients (n =30) (14 males,16 female mean age48 + /−9.8 Years.) Modelling was performed using GPower software (version 3.1) with $\alpha = 0.05$ and power = 0.80; sample size was determined using expected effect sizes estimated from previous studies.

We recruited type 1 diabetes (T1DM) and type 2 diabetes mellitus patients (T2DM) meeting the inclusion criteria: confirmed diagnosis of T1DM or T2DM based on American Diabetes Association criteria, disease duration ≥ 1 year, aged between 20 years and 60 years, and being under stable medication regimen in the past3 months. Healthy controls were subjects matched on age and sex, with no history of diabetes and fasting glucose levels <100 mg/dL (HbA1c<5.7%). Other exclusion criteria for all groups included pregnancy, lactation, chronic kidney disease (eGFR <60 mL/min/1.73m^2), active liver disease, current vitamin D supplements or antioxidant supplements use, malignancy, acute infections, inflammatory conditions, and circumstances that potentially alter vitamin D metabolism (malabsorption syndromes/hyperparathyroidism).

2.2. Sample Collection and Preparation

A 10 mL fasting venous blood sample was obtained from each participant between 8:00-10:00 AM (to minimize circadian variation effects) after an overnight fasting period of 10–12 hours. A few blood samples are collected in plain and serum separator tubes. Samples were allowed to clot at room temperature for 30 minutes, then centrifuged at 3000 rpm for 15 minutes at 4°C. Serum was separated, aliquoted into multiple cryovials, and stored at -80°C until analysis. All biochemical analyses were performed within 2 months of sample collection to ensure stability of biomarkers.

2.3. Biochemical Analyses

2.3.1. Glycemic Parameters

Fasting blood glucose (FBG) was measured using the glucose oxidase-peroxidase method on a semi-automated clinical chemistry analyzer (Erba Chem-7, Transasia Bio-Medicals Ltd.). Glycated hemoglobin (HbA1c) was determined using high-performance liquid chromatography (HPLC) method with a Bio-Rad D-10 analyzer (Bio-Rad Laboratories, USA).

2.3.2. Vitamin D Receptor Measurement

Serum VDR levels were quantified using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Human VDR ELISA Kit, Elabscience Biotechnology, USA, Catalog No. E-EL-H1481) according to the manufacturer's protocol. The assay utilizes a sandwich ELISA technique with a sensitivity of 0.19 ng/mL and detection range of 0.31-20 ng/mL. Intra-assay and inter-assay coefficients of variation were <5% and <8%, respectively. Samples were run in duplicate, and the mean optical density was measured at 450 nm using a microplate reader (BioTek ELx800, USA).

2.3.3. Antioxidant Enzyme Assays

- **Superoxide Dismutase (SOD):** SOD activity was measured using the nitroblue tetrazolium (NBT) method described by Kakkar et al. (1984) with modifications. The assay is based on the ability of SOD to inhibit NBT reduction by superoxide radicals generated by the phenazine methosulfate-NADH system. One unit of SOD activity was defined as the amount of enzyme causing 50% inhibition of NBT reduction. Results were expressed as U/mL.
- **Glutathione Peroxidase (GPx):** GPx activity was determined using the method of Paglia and Valentine (1967) with cumene hydroperoxide as substrate. The assay measures the rate of NADPH oxidation at 340 nm, which is coupled to the reduction of oxidized glutathione by glutathione reductase. GPx activity was expressed as U/L.
- **Catalase (CAT):** CAT activity was assayed using the method of Aebi (1984), which measures the rate of hydrogen peroxide decomposition at 240 nm. One unit of catalase activity was defined as the amount of enzyme that decomposes 1 μmol of H_2O_2 per minute. Results were expressed as U/mL.

2.3.4. Lipid Peroxidation Assessment

Malondialdehyde (MDA), a marker of lipid peroxidation, was measured using the thiobarbituric acid reactive substances (TBARS) method. The assay is based on the reaction of MDA with thiobarbituric acid under acidic conditions at high

temperature (95°C) to form a pink-colored MDA-TBA adduct, which was measured spectrophotometrically at 532 nm. MDA concentrations were calculated using 1,1,3,3-tetramethoxypropane as a standard and expressed as nmol/mL.

2.4. Statistical Analysis

Statistical analyses were performed using SPSS version 26.0 (IBM Corporation, USA) and GraphPad Prism version 9.0 (GraphPad Software, USA). Data normality was assessed using the Shapiro-Wilk test and visual inspection of Q-Q plots. Continuous variables are presented as mean ± standard deviation (SD) for normally distributed data or median (interquartile range) for non-normally distributed data. Categorical variables are expressed as frequencies and percentages.

One-way analysis of variance (ANOVA) followed by Tukey's post-hoc test was used to compare means among the three groups for normally distributed data. The Kruskal-Wallis test followed by Dunn's post-hoc test was used for non-normally distributed variables. Pearson correlation coefficient was calculated to assess relationships between VDR levels and other biochemical parameters. Multiple linear regression analysis was performed to identify independent predictors of VDR levels, adjusting for potential confounders including age, sex, BMI, and disease duration. A p-value <0.05 was considered statistically significant. Effect sizes were calculated using Cohen's d for pairwise comparisons.

3. Results

3.1. Baseline Characteristics

The demographic and clinical characteristics of the study participants are presented in Table 1. The three groups showed no significant differences in age (p=0.082) and sex distribution (p=0.845), confirming adequate matching. Body mass index (BMI) was significantly higher in the T2DM group (29.3 ± 4.2 kg/m^2) compared to both controls (23.8 ± 2.9 kg/m^2, p<0.001) and T1DM patients (24.5 ± 3.1 kg/m^2, p<0.001). Mean disease duration was 6.8 ± 3.4 years for T1DM patients and 7.2 ± 4.1 years for T2DM patients (p=0.673).

Table 1 Baseline Characteristics of Study Participants

Parameter	Control (n=30)	T1DM (n=30)	T2DM (n=30)	p-value
Age (years)	42.3 ± 8.5	38.7 ± 10.2	48.5 ± 9.8	0.082
Sex (M/F)	15/15	16/14	14/16	0.845
BMI (kg/m^2)	23.8 ± 2.9^a	24.5 ± 3.1^a	29.3 ± 4.2^b	<0.001
Disease duration (years)	-	6.8 ± 3.4	7.2 ± 4.1	0.673
FBG (mg/dL)	88.6 ± 7.4^a	186.4 ± 42.3^b	178.5 ± 38.7^b	<0.001
HbA1c (%)	5.2 ± 0.3^a	8.9 ± 1.4^b	8.5 ± 1.3^b	<0.001

Data presented as mean ± SD. Different superscript letters indicate significant differences between groups (p<0.05) by Tukey's post-hoc test. BMI: body mass index; FBG: fasting blood glucose; HbA1c: glycated hemoglobin; M: male; F: female.

3.2. Glycemic Control

As expected, both diabetic groups showed significantly elevated FBG and HbA1c levels compared to controls (p<0.001 for both). FBG levels were 186.4 ± 42.3 mg/dL in T1DM and 178.5 ± 38.7 mg/dL in T2DM patients, with no significant difference between the two diabetic groups (p=0.427). Similarly, HbA1c values were 8.9 ± 1.4% in T1DM and 8.5 ± 1.3% in T2DM patients (p=0.291), indicating suboptimal glycemic control in both groups.

3.3. Vitamin D Receptor Levels

Table 2 Vitamin D Receptor and Oxidative Stress Markers

Parameter	Control (n=30)	T1DM (n=30)	T2DM (n=30)	F-value	p-value
VDR (ng/mL)	4.12 ± 0.73^a	2.34 ± 0.52^c	2.89 ± 0.61^b	86.34	<0.001
SOD (U/mL)	4.68 ± 0.84^a	2.45 ± 0.58^c	3.12 ± 0.67^b	78.92	<0.001

GPx (U/L)	62.4 ± 9.3[a]	34.8 ± 7.2[c]	42.6 ± 8.5[b]	92.47	<0.001
CAT (U/mL)	28.5 ± 5.2[a]	15.3 ± 3.8[c]	19.7 ± 4.3[b]	81.65	<0.001
MDA (nmol/mL)	3.45 ± 0.67[a]	8.76 ± 1.34[c]	7.92 ± 1.28[b]	195.38	<0.001

Data presented as mean ± SD. Different superscript letters indicate significant differences between groups (p<0.05) by Tukey's post-hoc test. VDR: vitamin D receptor; SOD: superoxide dismutase; GPx: glutathione peroxidase; CAT: catalase; MDA: malondialdehyde.

Serum VDR levels showed significant differences among the three groups (F=86.34, p<0.001) (Table 2, Figure 1). Control subjects had mean VDR levels of 4.12 ± 0.73 ng/mL, which were significantly higher than both T1DM (2.34 ± 0.52 ng/mL, p<0.001, Cohen's d=2.89) and T2DM patients (2.89 ± 0.61 ng/mL, p<0.001, Cohen's d=1.89). Notably, T1DM patients exhibited significantly lower VDR levels compared to T2DM patients (p=0.001, Cohen's d=0.96), indicating more severe VDR reduction in T1DM.

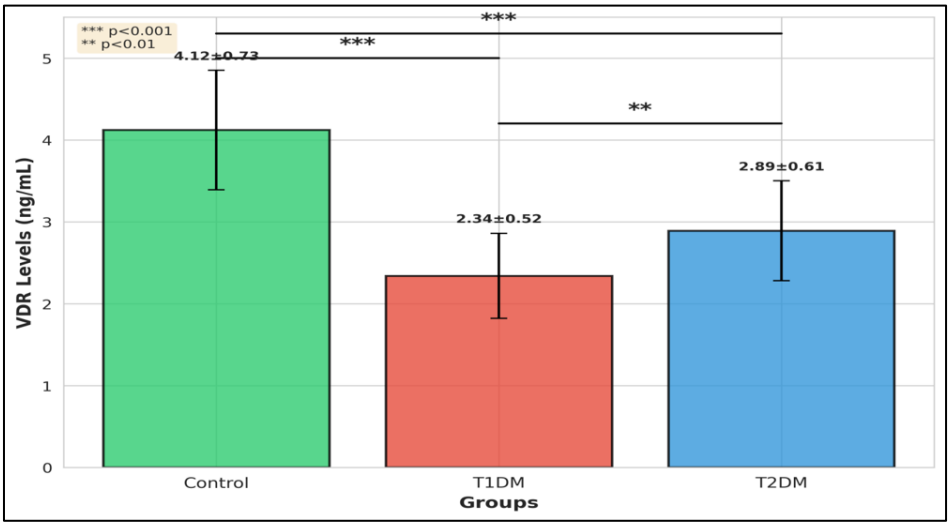

Figure 1 Serum Vitamin D Receptor (VDR) Levels - Shows the significant reduction in VDR levels in both diabetic groups compared to controls, with T1DM showing the lowest levels

3.4. Antioxidant Enzyme Activities

All three antioxidant enzymes showed significant alterations in diabetic patients compared to controls (Table 2) (Figure 2).

- **Superoxide Dismutase (SOD):** Mean SOD activity was significantly reduced in both T1DM (2.45 ± 0.58 U/mL, 47.6% reduction) and T2DM (3.12 ± 0.67 U/mL, 33.3% reduction) compared to controls (4.68 ± 0.84 U/mL, p<0.001 for both). T1DM patients showed significantly lower SOD activity than T2DM patients (p<0.001).
- **Glutathione Peroxidase (GPx):** GPx activity demonstrated a similar pattern, with marked reduction in T1DM (34.8 ± 7.2 U/L, 44.2% reduction) and T2DM (42.6 ± 8.5 U/L, 31.7% reduction) compared to controls (62.4 ± 9.3 U/L, p<0.001 for both). The difference between T1DM and T2DM groups was statistically significant (p=0.001).
- **Catalase (CAT):** CAT activity was significantly lower in both diabetic groups (T1DM: 15.3 ± 3.8 U/mL, 46.3% reduction; T2DM: 19.7 ± 4.3 U/mL, 30.9% reduction) compared to controls (28.5 ± 5.2 U/mL, p<0.001 for both). T1DM patients exhibited significantly lower CAT activity than T2DM patients (p=0.002).

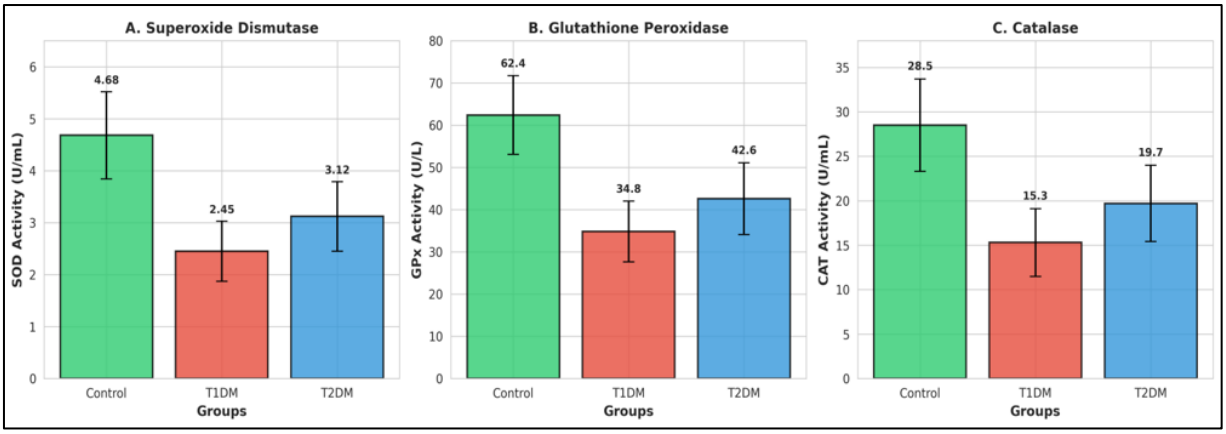

Figure 2 Antioxidant Enzyme Activities - Three-panel comparison showing SOD, GPx, and CAT activities across all groups, demonstrating significant reductions in diabetic patients

3.5. Lipid Peroxidation

MDA levels, reflecting lipid peroxidation and oxidative damage, were significantly elevated in both diabetic groups compared to controls ($F=195.38$, $p<0.001$) (Table 2). Control subjects had mean MDA levels of 3.45 ± 0.67 nmol/mL, while T1DM and T2DM patients showed markedly elevated levels of 8.76 ± 1.34 nmol/mL (154% increase) and 7.92 ± 1.28 nmol/mL (130% increase), respectively ($p<0.001$ for both). T1DM patients demonstrated significantly higher MDA levels compared to T2DM patients ($p=0.014$) (Figure 3).

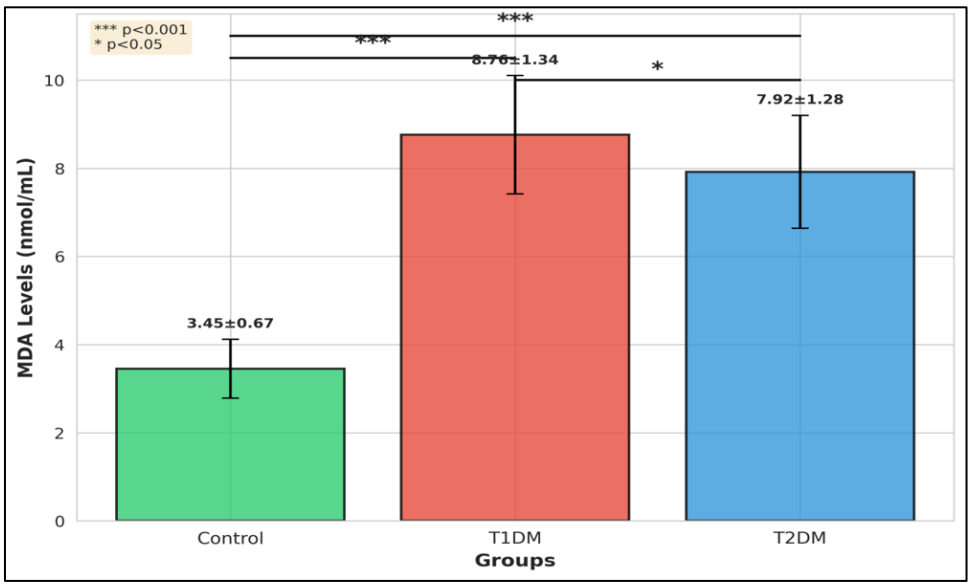

Figure 3 Malondialdehyde (MDA) Levels - Illustrates the marked elevation in lipid peroxidation (oxidative damage) in both diabetic groups

3.6. Correlation Analyses

As shown in Figure 4, VDR level was significantly correlated with several of the biochemical parameters as revealed by Pearson correlation analysis. Reduced VDR levels were significantly and negatively correlated with HbA1c ($r=-0.68$, $p<0.001$) and FBG ($r=-0.62$, $p<0.001$), together suggesting that poor glycemic control was associated with loss of VDR levels in monocyte/macrophages. Negative correlations were found between VDR and MDA($r=-0.71$, $p<0.001$): probably, low values of VDR may indicate high oxidative damage to lipids.

In contrast, VDR levels had positive correlations with all antioxidant enzymes: SOD ($r=0.73$, $p<0.001$), GPx ($r=0.69$, $p<0.001$), and CAT ($r=0.67$, $p<0.001$). These correlations indicate the possible involvement of VDR in preserving antioxidant defense capacity.

MDA was negatively correlated to SOD (r=-0.78, p<0.001), GPx (r=-0.74, p<0.001) and CAT (r=-0.72, p<0.001), all as expected given the inverse relationship between an antioxidant capacity and lipid peroxidation among oxidative stress markers.

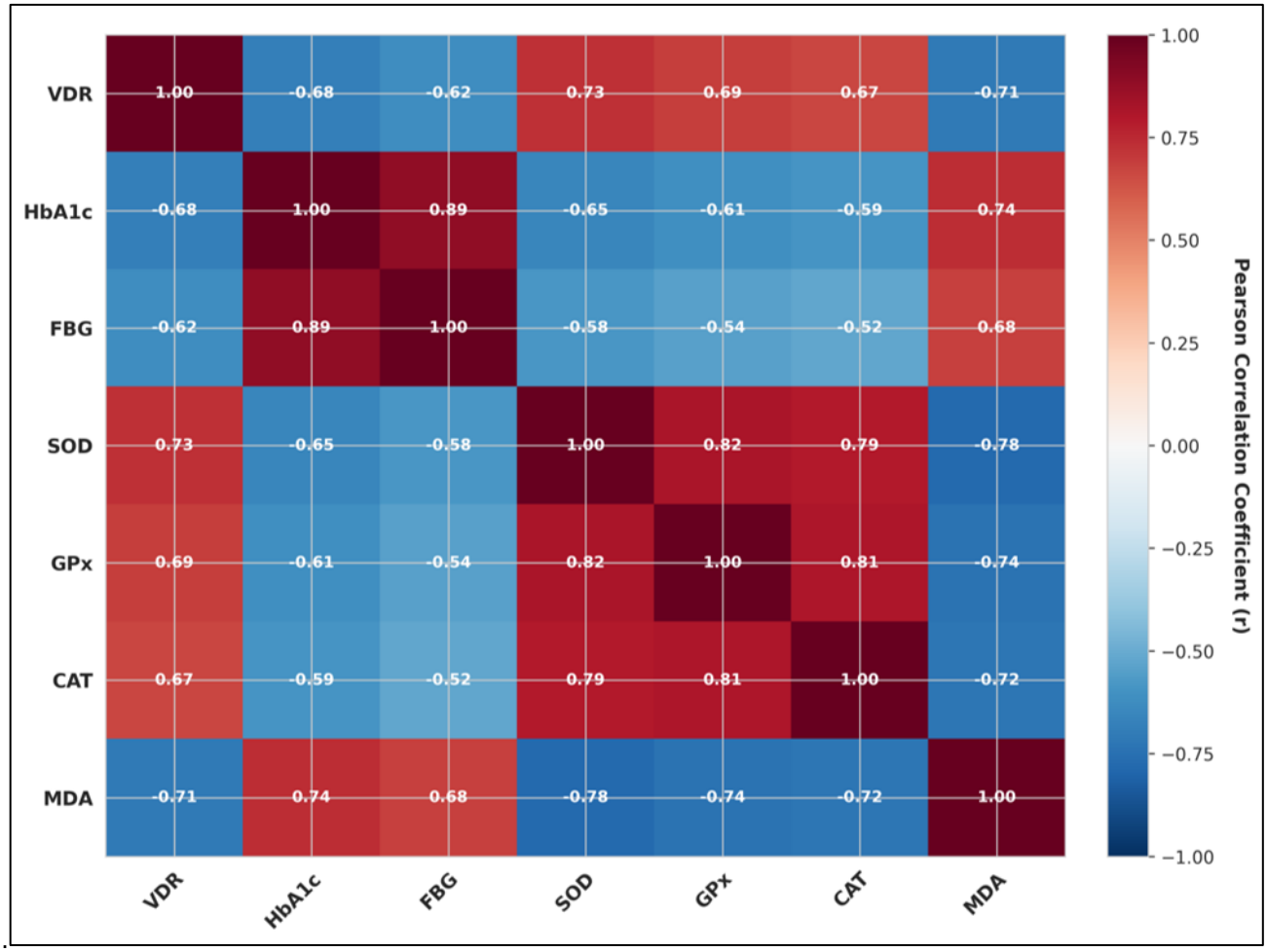

Figure 4 Correlation Heatmap - Comprehensive visualization of all correlations between VDR and biochemical parameters, using color intensity to show the strength and direction of relationships

3.7. Multiple Regression Analysis

To identify independent predictors of VDR levels, we used multiple linear regression analysis with adjustment for age, sex, BMI, disease duration and HbA1c (Figure 5). Model adjusted R^2=0.683, F=28.45,p<0.001 indicated that the model explained 68·3% of variation in VDR levels. ConclusionHbA1c was the most significant independent determinant of insulin sensitivity (β=-0.412, p<0.001) followed by disease duration (β=-0.287, p=0.002), and BMI (β=-0.231, p=0.008). VDR levels were not significantly predicted by either age (p=0.342) or sex (p=0.518).

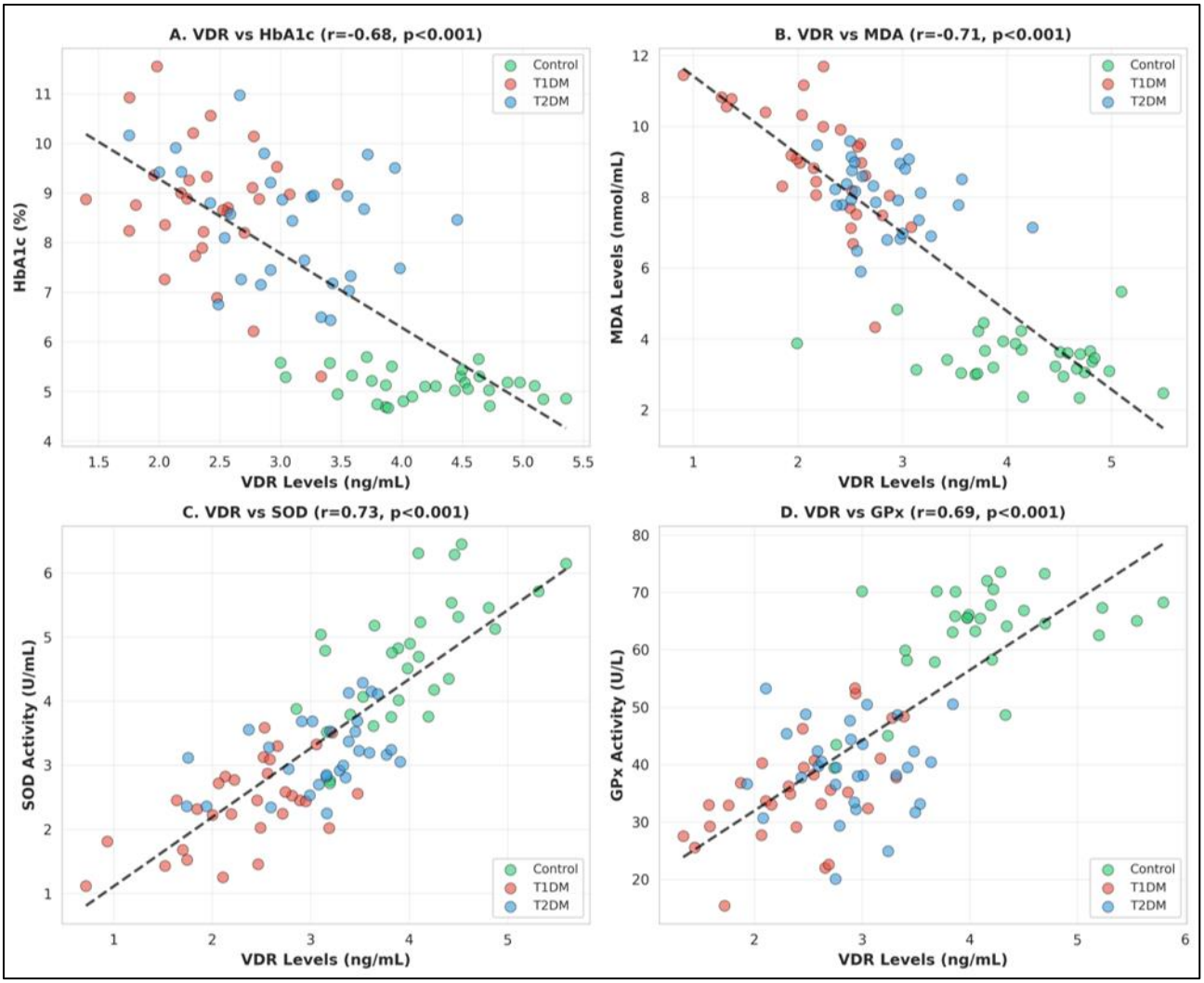

Figure 5 Scatter Plot Correlations - Four panels showing key relationships between VDR and HbA1c, MDA, SOD, and GPx, with regression lines and color-coded groups

4. Discussion

This large cross sectional analysis provides new information on the relationships between vitamin D receptor, antioxidant status and oxidative stress in T1DM and T2DM patients. Our study demonstrated significant decrease in VDR, oxidant and lipid peroxidation level at the time of diagnosis between both groups of diabetic rats as compared with healthy control. Importantly, T1DM patients had significantly exaggerated changes in these parameters versus the T2DM group which may reflect either a new common pathophysiological pathway or more severe metabolic derangement of T1DM. The pronounced reduction of serum VDR in the diabetic groups supports a growing body of evidence that suggests dysregulation of the vitamin D receptor (VDR) is an integral component of diabetes pathophysiology. One of the most remarkable observations was observed between T1DM and controls with a greatest reduction of VDR (43.2% by normalization) compared to T2DM and controls where only 29.9% reduction in VDR was found. This observation may indicate an autoimmune nature of T1DM, since VDR plays critical roles in immune regulation and tolerance (Chagas et al., 2021; Infante et al., 2022). VDR plays roles in T-cell differentiation, regulatory T-cell differentiation and cytokine production which are particularly important in autoimmune disease (Mora et al., 2020).

The high negative correlation regarding VDR levels and HbA1c (r=-0.68, p<0.001), which we observed in our study, confirm that VDR status is related with glycemic control. This association remained significant in multivariate analysis and HbA1c was determined to be the most potent independent predictor of VDR levels. The results are consistent with previous experimental studies showing that VDR activation increases insulin secretion of β-cells and enhances peripheral sensitivity to insulin (Bouillon et al., 2022). These mechanisms include VDR-mediated regulation of insulin

receptor expression, glucose transporter function and pro-inflammatory pathways which modulate insulin signaling (Zhang et al., 2020). Whether vitamin D was indeed associated with diabetes risk observed in epidemiological or as a result of Intervention (randomized) studies has yielded inconclusive results until recently, with positive meta-analysis revealed for the first time [Hu et al., 2020; Lemieux et al., 2022]. We expand upon these findings with a focus on VDR, as opposed to circulating vitamin D metabolites which are not necessarily reflective of functional vitamin D. Genetic polymorphisms, epigenetic modulation as well as vitamin D-independent post-translational modifications could affect VDR expression and function (Sacerdote et al., 2022) and explain the metabolic dysfunction of some patients with normal serum levels of vitamin D.

The markedly reduction of antioxidant enzymes (SOD, GPx and CAT) enzyme from diabetic patients validate the oxidative stress and deficient ability of antioxidant defence. SOD activity was decreased 47.6% in T1DM, and 33.3% in T2DM versus controls, reflecting a fi¬nite impairment of the essential antioxidant defense pro-gram against superoxide radicals [15]. Moreover, decreases in GPx (44.2% in T1DM, 31.7% in T2DM) and CAT (46.3% in T1DM, 30.9% in T2DM) were of comparable magnitude [0]. These findings are in agreement with previous reports showing that depletion of the antioxidant enzymes in diabetes (Newsholme et al., 2021; Volpe et al., 2024). These observations may have several potential explanations. Chronic hyperglycaemia induces overproduction of ROS via several signalling pathways, could eventually saturating antioxidant systems (Brownlee, 2005; Rehman & Akash, 2020). Glycation of antioxidant enzymes is also known to decrease catalysis (Wang et al., 2018), and decreased level of the enzyme can result from impaired synthesis or increased degradation. The tendency for greater enzyme depletion in T1DM patients may represent a more sustained or severe oxidative stress, but duration of diabetes did not differ significantly between the 2 diabetic groups in our study. The strong positive correlations in VDR levels (r=0.67-0.73) and activities of antioxidant enzymes hint mechanistic potential. VDR activation is well established to increase antioxidant enzyme expression via direct transcriptional regulation and Nrf2 pathway activation (Cui et al., 2020). VDR has vitamin D response elements within the promoter regions of genes responsible for antioxidant enzymes providing direct transcriptional control (Infante et al., 2022). In addition, vitamin D/VDR signaling regulates inflammatory pathways impacting oxidative stress such as nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways (Mora et al., 2020).

The downregulation of MDA levels in both diabetic models (⬆ 154% all structures from T1DM, ⬆ 130% all structures from T2DM) indicates the increased lipid peroxidation, and oxidative damage to cell membranes. MDA is an end product of lipid peroxidation which reliably represent in diastere herable biomarker of oxidative stress and has been shown to correlate consistently with diabetic complications (Tsikas, 2021) Increased MDA levels induce cellular dysfunction through different mechanisms such as reaction with (de)proteins, oxidative damage of DNA and changing membrane permeability (Ayala et al., 2014).

Also, an inverse correlation of VDR with MDA (r=-0.71, p<0.001) implies VDR could provide protection against oxidative damage. This relationship probably indicates the regulatory influence of VDR on antioxidant defence as indicated by high negative correlations between antioxidant enzymes and MDA (r=-0.72 to -0.78). Moreover, vitamin D/ VDR signaling decreased oxidative stress by anti-inflammatory mechanism (Bouillon et al.

It is worth noting the higher level of MDA in T1DM compared to T2DM patients. This could possibly be due to the differences in disease characteristics, where full insulin deficiency seen in T1DM may lead to more profound metabolic derangement and oxidative stress. In addition, the autoimmune inflammatory aspect of T1DM may increase oxidative stress by immune cell activation and cytokine production (Galicia-Garcia et al., 2020). There are several potential clinical implications based on our findings. Our findings point to an important association between VDR levels and glycemic control and oxidative stress markers, suggesting that interventions targeting vitamin D/VDR pathways could represent a therapeutic option beyond classical diabetes therapy. Studies that assess the impacts of vitamin D supplementation on glycemic outcomes have had little utility due to mixed results when circulating levels are measured, not VDR function (Lemieux et al., 2022). Future research may focus on strategies that can boost VDR expression or function, which could be achieved via VDR agonists and/or interventions targeting VDR regulation. Secondly, the rationale for antioxidant-based therapeutic strategies is supported by the severe oxidative stress and depletion of antioxidants in patients with diabetes. That being said, the results from prior antioxidant supplementation trials have been disappointing, likely due to bioavailability and/or dosing & targeting issues (Ighodaro & Akinloye 2018). The presence of correlations between VDR and antioxidant status indicates a potential synergy effect of approaches targeting both pathways, combining these strategies may generate more promising outcomes than applying one or the other. Lastly, the differences in T1DM and T2DM patients observed would suggest disease-specific management of VDR dysregulation and oxidative stress may be appropriate. With more pronounced changes seen in T1DM patients, perhaps should be prompt at earlier to vigorous interventions from protective strategies.

This study has multiple strengths: (1) A thorough evaluation of several oxidative stress parameters in the same patient samples as VDR measurements enabling insightful comparisons; (2) Inclusion of both T1DM and T2DM with possibilities for comparison between the two types of diabetes; (3) Methodical exclusion criteria to minimize confounding due to other factors; (4) Application of standardized biochemical assays validated by prior peer-reviewed publications. The study was designed to assess the relationships between VDR and oxidative stress markers controlled for key demographic and clinical variables. Several limitations should be considered, however. The cross-sectional design prevents from establishing the cause-and-effect or time-order relationship between VDR dysregulation and oxidative stress. Whether oxidative stress is the cause or consequence of VDR deficiency requires longitudinal studies. Although we would expect to find at least moderate effects given the study size, the relatively smaller sample size results in lower power for all but the most important subgroup analysis. Additionally, we quantify VDR levels in circulation but not in tissues and these circulating concentrations do not necessarily reflect tissue-specific VDR actions, especially since such effects are expected to occur in pancreatic β-cells or immune cells.

There are a number of pathways through which future research can address some of the limitations identified in this regard. Studies evaluating changes in VDR in relation to the initiation of oxidative stress, particularly longitudinal studies of patients from diabetes diagnosis may provide additional insights. Well-controlled intervention studies assessing the impact of vitamin D supplementation or VDR agonists with full characterization of VDR, anti-oxidant activity, and clinical benefits will better elucidate causation versus therapeutic promise. Assessment of VDR expression in tissues from patients with type 2 diabetes may provide mechanistic insights which reflect local rather than systemic function. Studies investigating genetic polymorphisms of the VDR may identify those at greatest risk and who are most likely to benefit from vitamin D–based interventions. Research that examines whether or not glycemic control reinstates VDR expression and oxidative stress markers will aim to distinguish primary pathologic processes from secondary ones. Moreover, a possible cooperation of vitamin D/VDR targeted treatment with standard antioxidative strategies was evaluated and could disclose superior combinatory approaches.

Additional mechanistic investigation using in vivo and/or in vitro approaches will certainly improve our understanding of the molecular pathways involved by which VDR modulates antioxidant enzyme activity to protect against oxidative stress under both healthy and diabetic conditions. So you definitely must analysis epigenetic adjustments that regulate VDR expression in diabetes that may very well be new therapeutic targets.

5. Conclusion

Therefore, the finding of this current study that BMD and VDR are significantly lower in T1DM and T2DM patients than controls along with unfavorable antioxidant systems (decreased SOD, GPx, and CAT activities) status might reflect higher oxidative stress condition (increased MDA level). Importantly, the level of these changes was more pronounced in T1DM patients than controls indicating that different mechanisms and/or severity of disease may underlie these two forms of diabetes. Given the strong correlations we found between the abundance of VDR and various measures of glycemic control and oxidative stress, further mechanistic studies may also be warranted.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

Ethical approval was obtained from ethical committee in Al-Qasim Green university (#1231-2025)

Statement of informed consent

The written acceptance was obtained from all subjects participants in this research

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