

## Study of Relationship between Serum 25 (OH) Vitamin D and Insulin Resistance in Prediabetic Patients

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Cite this paper as: Tushar Vishnu Tonde, Gaurav A. Chaudhary, Harishchandra Chaudhari (2024) Study of Relationship between Serum 25 (OH) Vitamin D and Insulin Resistance in Prediabetic Patients. *Frontiers in Health Informatics*, 13 (3), 9868-9875

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### ABSTRACT

**Introduction:** Pre-diabetes is a notable predisposing factor for the onset of diabetes and cardiovascular ailments. There is a strong correlation between it and obesity, a condition that is commonly connected to low levels of vitamin D.

**Objective:** To assess and compare the levels of vitamin D in persons with normal glucose levels, pre-diabetes, and diabetes. Additionally, the study intended to investigate the correlation between insulin resistance and vitamin D status in these groups.

**Materials and Methods:** The study comprised a cohort of 50 individuals without diabetes, 50 persons with prediabetes, and 50 individuals diagnosed with type 2 diabetes. Waist-hip ratio and body mass index (BMI) were measured. Analyzed parameters were fasting blood sugar, insulin levels, lipid profiles, calcium, alkaline phosphatase, and serum 25-hydroxy vitamin D. The HOMA2-IR and HOMA2- $\beta$  values were determined using the HOMA 2 calculator to assess insulin resistance and beta cell function, respectively.

**Results:** Among the study participants, 24% of persons with normal health, 42% of those with pre-diabetes, and 52% of those with diabetes were found to have a deficit of vitamin D, defined as having a level below 20 ng/ml. The serum 25(OH) vitamin D levels in diabetics were considerably lower ( $p < 0.0001$ ) compared to both normals and pre-diabetics ( $p < 0.0001$ ). The 25 OH Vitamin D levels showed a significant negative connection with fasting blood sugar (FBS) in individuals with diabetes

( $r = -0.57$ ) and prediabetes ( $r = -0.64$ ), as well as with systolic blood pressure ( $r = -0.46$ ) and diastolic blood pressure ( $r = -0.48$ ) in individuals with diabetes.

**Conclusion:** Individuals in the pre-diabetic stage commonly suffer from a lack of Vitamin D, and those with severe insufficiency (less than 10 ng/ml) have the greatest levels of insulin resistance. The results of our study provide evidence in favor of the notion that vitamin D levels can serve as an early indicator for diabetes. Additionally, our findings indicate that it may be beneficial to consider vitamin D supplementation during the pre-diabetic phase.

**Keywords:** vitamin D, diabetes,

## INTRODUCTION

The term "diabetes mellitus" refers to a collection of metabolic illnesses that are characterized by hyperglycemia as a consequence of insulin insufficiency, whether it be relative or absolute, as well as peripheral insulin resistance (IR) [1].

Among those aged 20–79 years, the global prevalence of diabetes was predicted to be 10.5% (536.6 million) in 2021, according to a recent study conducted by the International Diabetes Federation (IDF) called Diabetes Atlas. It is anticipated that this number would increase to 12.2% (783.2 million) in 2045 [2].

A lack of vitamin D has been the subject of a significant amount of research about the pathophysiology of insulin resistance. It has been discovered that it is linked to an elevated risk of developing type 2 diabetes through a variety of pathways, such as insulin resistance (IR), pancreatic  $\beta$ cell dysfunction, and inflammation [3-7]. It has been discovered that taking vitamin D supplements can reduce insulin resistance in both healthy persons who are under normal conditions and patients who have type 2 diabetes [8]. On the other hand, there is a lack of good documentation about comparable observations made among people who have prediabetes.

With an annual risk of progression to diabetes ranging from 2.5% in the Diabetes Prevention Trial (DPT) to 18% in the Indian Diabetes Prevention Programme-1 (IDPP1) [9], prediabetes is regarded to be a precursor to the development of overt type 2 diabetes mellitus. Many research have demonstrated that there is a connection between a lack of vitamin D and type 2 diabetes. Vitamin D may perform a functional impact on glucose tolerance, according to the findings of several investigations [10, 11]. This is because vitamin D has effects on insulin secretion and insulin sensitivity. Subjects with type 2 diabetes have a considerably reduced circulating concentration of 25 (OH)D [12], in compared to healthy controls. Vitamin D insufficiency has been shown to play many roles in the development of insulin resistance through a variety of processes. One of these mechanisms is the elevation of associated proinflammatory cytokines and acute phase reactants, which are detected in vitamin D deficiency and are responsible for inducing low-grade inflammation [13]. Within the population of prediabetic patients, we investigated the connection between serum 25 (OH) vitamin D and insulin resistance measures.

## METHODOLOGY

The study recruited a cohort of 50 individuals with diabetes, 50 individuals with prediabetes, and 50

healthy control people. The study received permission from the ethical review committee.

### **Inclusion Criteria**

Individuals with diabetes and those at risk of developing diabetes were diagnosed using the diagnostic criteria established by the American Diabetes Association in 2010. The study patients were randomly recruited from the outpatient department of Medicine & Diabetology using a random sampling procedure.

### **Exclusion Criteria**

Individuals who have acute or chronic liver, kidney, or heart disease, primary hyperparathyroidism, chronic use of drugs such as antiepileptic agents, oral contraceptive pills, or steroids that may affect vitamin-D metabolism, individuals with cancer, pregnant women, and those who have taken calcium or vitamin-D supplements within the past year.

### **Consent**

The study objectives and methods were clearly communicated to patients and/or their attendants, and their informed permission was acquired.

The measurements of height, weight, waist circumference, and hip circumference were taken, and the Body Mass Index (BMI) and Waist-to-Hip Ratio (WHR) were computed using the conventional methods. Standard mercury sphygmomanometer was used to measure blood pressure twice, with a 2-hour interval, in the right arm while the person was sitting and had rested for 10 minutes. A 5 ml sample of fasting venous blood was collected from all participants involved in the research. The examined parameters encompassed FBS (fasting blood sugar), insulin, lipid profile, calcium, ALP (alkaline phosphatase), and serum 25-hydroxy vitamin D.

The calculation of insulin resistance in the basal state will be performed using HOMA2-IR (homeostatic model assessment-insulin resistance), while the estimation of beta cell function will be done using HOMA2- $\beta$  (22). The HOMA2 calculator will be utilized for the computation.

Fasting blood sugar (FBS), lipid profile, calcium, and serum alkaline phosphatase (ALP) were measured using a fully automated biochemistry analyzer. The levels of serum insulin and 25 OH Vitamin D were determined using a chemiluminescent immunometric assay (CLIA).

### **Statistical Analysis**

The collected data was analysed using SPSS version 22.

## **RESULTS**

24% of individuals with normal health, 42% of those with prediabetes, and 52% of individuals with diabetes had a deficit of Vitamin-D, defined as having levels below 20 ng/ml. The prediabetic and diabetic groups exhibited a substantial rise in total cholesterol, triglycerides, LDL, systolic and diastolic blood pressure, and a reduction in HDL when compared to the normal group ( $p < 0.001$ ). Both fasting insulin levels and insulin resistance (HOMA2 IR) showed a substantial increase in individuals with prediabetes and diabetes, compared to those with normal glucose levels ( $p < 0.05$ ). Additionally, those with diabetes exhibited higher fasting insulin levels and insulin resistance compared to those

with prediabetes. The 25 OH Vitamin D levels exhibited a considerable reduction ( $p < 0.05$ ).

Parameters	Normal (n=50)	Prediabetics (n=50)	Diabetics (n=50)
Age (yrs)	48.7+22.5	50.5+17.4	51.2+ 18.6
Systolic BP (mm Hg)	123 + 11.2	137.7+7.7	141.5+12.4
Diastolic BP (mm Hg)	80.7+4.5	90.4+5.8	93.5+8.6
BMI	25.5+2.35	26.7+2.84	27.9+ 2.53
WHR	0.784 +0.43	0.84 +0.11	0.91+0.26
FBS (mg/dl)	87.48+8.0	108.7+9.7	144.8 +30.6
Total Cholesterol (mg/dl)	172 ±16.8	187.7 ±11.74	207.3 ± 34.34
TGL (mg/dl)	103.7 +15.37	129.4+22.1	173.6 +31.13
HDL (mg/dl)	43.8+6.48	37.6+4.74	34.2+6.37
LDL (mg/dl)	97.3+0.85	125.3+ 13.61	134.7+36
S. Calcium (mg/dl)	9.97+0.59	9.86+0.59	9.32+ 0.57
F. Insulin (µIU/ml)	7.68±1.84	12.73± 2.97	18.74±3.23
25 OH Vit D (ng/ml)	26.1+5.46	19.94+3.37	19.2 + 5.42
HOMA2-IR	1.66+0.7	3.52+1.37	6.89+ 3.1
HOMA-B	121.43 +40	100.64+16.6	97.7+36

Table 1: Comparison of Various Anthropometric and Biochemical Parameters in Normal, Prediabetics and Diabetic Groups

There was no substantial alteration in 25 OH Vitamin D levels seen between individuals with prediabetes and individuals with diabetes. There is no substantial disparity in HOMA2-β (beta cell mass) among the groups. There was a significant inverse relationship between 25 OH Vitamin D and HOMA 2 Insulin Resistance in individuals with diabetes ( $r = -0.61$ ) and prediabetes ( $r = -0.73$ ). A significant positive connection was seen between 25 OH Vitamin D and fasting insulin levels in individuals with diabetes ( $r = -0.58$ ) and prediabetes ( $r = -0.74$ ). The 25 OH Vitamin D levels showed a significant negative connection with fasting blood sugar (FBS) in individuals with diabetes ( $r = -0.57$ ) and prediabetes ( $r = -0.64$ ), as well as with systolic blood pressure ( $r = -0.46$ ) and diastolic blood pressure ( $r = -0.48$ ) in individuals with diabetes.

Parameters	Parameter adjusted for	Correlation coefficient(r) Total	Correlation coefficient(r) Pre diabetics	Correlation coefficient(r) Diabetics
VITD &FBS	BMI	-0.57	-0.64	-0.58
VITD& HOMA2 IR	BMI	-0.61	-0.73	-0.63
VITD& INSULIN	BMI	-0.58	-0.74	-0.52
VITD &SBP	BMI	-0.50	-	-0.46
VITD &DBP	BMI	-0.52	-	-0.48

Table 2: Univariate Analysis by Spearman Linear Regression

## DISCUSSION

Our study revealed a high prevalence of vitamin-D insufficiency/deficiency among persons diagnosed with prediabetes. In our investigation, we found that patients with prediabetes who had a significant shortage of vitamin D (less than 10 ng/ml) had the highest degree of insulin resistance (measured by HOMA2-IR) compared to those with greater vitamin D levels. Furthermore, we observed a negative relationship between vitamin D status and insulin resistance, even after accounting for BMI.

The serum 25(OH) D is a highly responsive indicator of the vitamin D level and is the primary form of vitamin D found in the bloodstream, indicating the quantity of vitamin D acquired from both food sources and synthesis in the skin. Research has demonstrated that vitamin D has both direct and indirect impacts on many pathways associated with the pathophysiology of type 2 diabetes mellitus (T2DM). According to pre-clinical and animal studies, vitamin D supplementation has been shown to improve insulin resistance and regulate insulin secretion and the survival of beta cells [14-16]. Conversely, a deficiency in vitamin D appears to hinder glucose-stimulated insulin secretion and the function of pancreatic beta cells [17-19].

Further evidence suggests that vitamin D has a role in regulating the levels of calcium outside of the pancreatic beta cell, as well as controlling the movement of calcium through the cell [20]. Additionally, vitamin D affects the activity of calbindin, a calcium-binding protein found in the cytoplasm of pancreatic beta cells, which in turn modulates the release of insulin [21, 22]. Given that insulin secretion relies on calcium-dependent mechanisms [23], any long-lasting changes in calcium flow might impact the ability to secrete insulin [24, 25]. Several extensive correlational investigations have consistently shown that there is a substantial negative correlation between the blood level of vitamin D and insulin resistance (IR) [26-28]. This indicates that individuals with greater levels of vitamin D tend to have higher IR index, which aligns with the findings of this study. Other cross-sectional investigations have yielded inconsistent findings, failing to establish a meaningful correlation [29, 30]. The occurrence of insulin resistance (IR) has been identified as the primary cause of increased risk for type 2 diabetes mellitus (T2DM) in individuals with vitamin D deficiency. However, this risk decreases after receiving external vitamin D supplementation [31]. Research conducted on persons with prediabetes revealed that the addition of vitamin D to their diet resulted in a decrease in the development of diabetes and an increase in the reversal of normoglycemia in subjects with prediabetes [32, 33]. Furthermore, observational studies have indicated that there is a clear and substantial negative

correlation between blood vitamin D levels and several other insulin resistance (IR) diseases, as well as the reported risk of type 2 diabetes mellitus (T2DM) up till now [34, 35]. It is a credible hypothesis that Vitamin D deficiency plays a significant role in speeding up the occurrence and progression of insulin resistance (IR) and, as a result, type 2 diabetes mellitus (T2DM).

The findings of our investigation revealed a significant inverse relationship between vitamin D levels and insulin resistance, as measured by HOMA 2 IR, in individuals with prediabetes ( $r=-0.77$ ) and diabetes ( $r=-0.63$ ). The focus of our study primarily is on individuals with pre-diabetes, as it serves as a prelude to diabetes. Recent studies have indicated that vitamin D can affect insulin sensitivity by directly impacting the cells that respond to insulin and the beta cells in the pancreas. Vitamin D has the potential to augment the quantity of insulin receptors, boost the functioning of transcription factors, and control the concentration of calcium in cells, so enhancing insulin sensitivity [36, 37].

## CONCLUSION

Individuals with a prediabetic state often experience Vitamin D insufficiency, and those with a severe shortage ( $<10$  ng/ml) show the greatest levels of insulin resistance. The results of our study provide compelling evidence that vitamin D levels might act as an early predictor for diabetes, therefore supporting the suggestion to provide vitamin D during the prediabetic phase.

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