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"LOW SERUM 25 HYDROXYVITAMIN D LEVEL PREDICTS PROGRESSION TO TYPE 2 DIABETES MELLITUS IN INDIVIDUALS WITH PRE-DIABETES"

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ABSTRACT

Aim: The objective of this study was to identify the association of vitamin D with insulin resistance in subjects with pre-diabetes and compare to it with the levels in newly diagnosed type 2 diabetes mellitus and healthy subjects.

Material & Methods: It is a cross-sectional descriptive type of study. Total 900 subjects were distributed into three groups (300 pre-diabetic subjects, 300 type 2 diabetic subjects and 300 healthy subjects) as per ADA criteria. The biochemical parameters as FPG, 2-hr glucose (after 75 gm oral glucose intake), HbA1c and fasting insulin were analyzed. HOMA-IR was used to calculate insulin resistance mathematically. Anthropometric measurements were done. The Electrochemiluminescence immunoassay (ECLIA) technique was used to analyse serum vitamin D by cobas e411 by Roche diagnostics.

Results: Vitamin D concentration was significantly reduced in patients with type 2 diabetes mellitus and pre-diabetes (15.10±2.93; 18.7±4.12 ng/mL) in comparison to the control group (28.06±6.63ng/mL), p value<0.001.Vitamin D showed an inverse correlation with HOMA-IR.

Conclusion: The findings of this study illustrates the significance of the impact of the vitamin D in the development of insulin resistance (HOMA-IR) in pre-diabetic (r= -0.47; p value<0.01) as well as type 2 diabetic (r = - 0.71; p value < 0.01) patient.

Clinical Significance: Screening for vitamin D at an early stage might prove fruitful in the early detection of the development of insulin resistance and type 2 diabetes mellitus and positively delay the onset of this non communicable disease. Our data suggests that daily supplementation of vitamin D to people with impaired glucose tolerance can delay progression to overt diabetes and lead to development of new treatment modalities.

KEYWORDS : Inflammation, Pre-diabetes, Type 2 Diabetes, Vitamin D, Insulin resistance, ADA.

INTRODUCTION:

Diabetes is a chronic disease, which occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces. This leads to an increased concentration of glucose in the blood (hyperglycaemia).The number of diabetic patients has greatly increased in the past few decades in the world including Asia. It has been forecasted that by 2030, India would bear maximum burden of this disease in the world [1] Obesity and overweight are the most important risk factors responsible for diabetes. Long term diabetes has been associated with complications as retinopathy, neuropathy and nephropathy. Diabetes also increases the risk of life-threatening diseases including cardiovascular disease and cancer. [2] The prevention of diabetes is thus one of the priority issues.

Pre-diabetes is the progeny of diabetes. It refers to as Impaired Glucose Regulation (IGR) which consist of Impaired Fasting Glucose and/or Impaired Glucose Tolerance (IFG and/or IGT). It is a reversible condition that increases the risk for diabetes which is associated with insulin resistance or decline in insulin sensitivity. [3,4]

Vitamin D plays a crucial role in the endocrine functioning of pancreas due to presence of vitamin D-dependent calcium-binding protein and cytosol receptor for the hormonal form of vitamin D,1,25(OH)2D3 in the pancreas. Studies have reported that vitamin D plays an important role in insulin secretion and insulin resistance. 25(OH)D concentration is independently associated with both insulin sensitivity and beta cell function among individual at risk of type 2 diabetes mellitus, thereby indicating that vitamin D may have an important role in pathogenesis of T2DM. These findings suggest that vitamin D may have an important role in regulating glycaemic control.[5,6]

Presence of vitamin D receptors on pancreatic β cells, vitamin D activating 1 α hydroxylase enzyme expressed in pancreatic β cells, presence of vitamin D response element(VDRE) in the insulin gene, presence of vitamin D receptor(VDR) in skeletal muscle and the fact that 1,25(OH)D increases transcription of insulin receptor genes as well as suppresses the rennin gene. The blockage of rennin angiotensin activity has been proposed as a novel target for diabetes treatment. Vitamin D increases calcium contents of the cells which leads to increased transport of glucose into the muscle. Vitamin D also regulates nuclear PPAR (Peroxisome proliferative activated receptor) that has an important role in the insulin sensitivity. Vitamin D attenuates the expression of proinflammatory cytokines involved in insulin resistance such as interleukins, IL1, IL6, TNFα.[7,8]

The current study was an attempt to assess the vitamin D level among newly detected prediabetic patients and newly detected type 2 diabetic patients of Bhopal region of Madhya Pradesh.

MATERIAL & METHODS:

This cross sectional study was carried out in the Department of Biochemistry, People's College of Medical Sciences & Research Centre and Centre for Scientific Research & Development (CSRD), People's University, Bhopal during July 2017 to July 2019. The blood sample was collected from the outpatient department (OPD) and inpatient department (IPD) of People's Hospital. The study was designed taking 300 human subjects in each arm, in which, 300 age matched healthy subjects were considered as control group, 300 as pre-diabetic subjects and 300 as type 2 diabetic subjects. Ethical principles such as respect for the persons, beneficence and justice were adhered. Ethical clearance was obtained from the research committee and the Institutional Review Board of People's University. Written informed consent was taken from all the subjects. The evaluation involved a full medical history and anthropometric measurements (weight, height, BMI, waist and hip circumferences, waist hip ratio) and arterial blood pressure.

INCLUSION CRITERIA:

- Patients diagnosed with pre-diabetes according to the ADA (American Diabetes of Association) values of FPG (100-125mg/dl), 2 hr glucose (140-199mg/dl) and HbA1c (5.7-6.4%) were taken into consideration for selection of patient.
- Patients newly diagnosed with type 2 diabetes mellitus as per ADA criteria (FBG ≥126 mg/dl , 2-hr glucose ≥ 200 mg/dl, HbA1c ≥ 6.5%) and
- Patients aged between 30-60 years were taken up into the study.

EXCLUSION CRITERIA:

- Patients with diagnosis of any other disease other than pre-diabetes & type 2 diabetes mellitus (based on their medical history and physical examination) were excluded.
- Patients on antidiabetic drugs, insulin, corticosteroids, vitamin D and Ca supplementation were excluded from the study.
- Patients below 30 years and above 60 years were excluded from the study.

All the biochemical parameters as FBG, 2-hr Glucose and HbA1c are estimated by Standard Kit method by using Cobas c311 fully automated analyzer (Roche diagnostics). Serum Insulin and vitamin D are assayed on Cobas c411 fully automated immunoassay analyzer (Roche diagnostics) by using Cobas kits. Serum Insulin resistance was estimated by the **Homeostasis model assessment (HOMA-IR)** and calculated as Fasting Insulin (microU/L) x Fasting glucose (mg/dl)/405. Biochemical parameters are analysed by the following methods as: (Table 1)

Table 1: Biochemical Parameters and Methods:

Sr. No.	Biochemical parameters	Methodology
1.	Glucose	Hexokinase
2.	HbA1c	Turbidimetric inhibition Immunoassay(TINIA)
3.	Insulin	Electrochemiluminiscence(ECL)
4.	Vitamin D	Electrochemiluminiscence(ECL)

Calculation and Statistical analysis:

The data was entered into Microsoft Excel software package. The entered data were transferred to SPSS 24.0 software (SPSS Inc., Chicago, Illinois, USA) package for analysis. ANOVA test was applied to proportions to test the level of significance. Pearson's correlation was used to study the strength of association. The level of significance was fixed at 0.05 and Confidence interval (CI) was set at 95%.

RESULTS:

In our study we have compared anthropometric and biochemical parameters in pre-diabetic, type 2 diabetic and healthy control groups. Anthropometric parameters (BMI, waist circumference, waist to hip ratio) as well as systolic and diastolic blood pressure are statistically significantly differed in pre-diabetic and diabetic group compared to control group. (Table 2)

Table 2: Comparison between the three groups selected for the study:

Parameter	Control	Pre-diabetes	T2DM	p-value
WC (cm)	74.87±7.4	79.95±5.7	84.2±5.4	<0.001
WHR	0.82±0.09	0.87±0.06	0.98±0.23	<0.001
BMI(Kg/m2)	22.22±2.79	24.89±2.4	29.25±3.06	<0.001
SBP(mmHg)	120±8.03	131±6.4	145.5±15.45	<0.001
DBP(mmHg)	76.28±6.9	83.04±7.5	96.33±9.4	<0.001
FBG(mg/dl)	83.62±7.7	114.58±7.3	149.78±30.27	0.001
2-hr Glucose	120.72±10.05	163.2±14.77	255.58±40.07	<0.001
HbA1c(%)	4.5±0.63	6.10±0.25	8.85±1.39	<0.001
Fasting Insulin (µU/mL)	6.09±2.13	7.19±3.63	29.006±5.06	<0.001
HOMA-IR	1.48±0.80	2.04±0.98	10.67±2.7	<0.001
Vitamin D (ng/mL)	28.06±6.63	18.7±4.12	15.10±2.93	<0.001

*** p value significant < 0.001**

The mean vitamin D biomarker value is least for diabetes 15.10 ±2.93 as compared to pre-diabetes 18.7 ± 4.12 and healthy controls 28.06±6.63. The difference is statistically significant. (Figure 1)

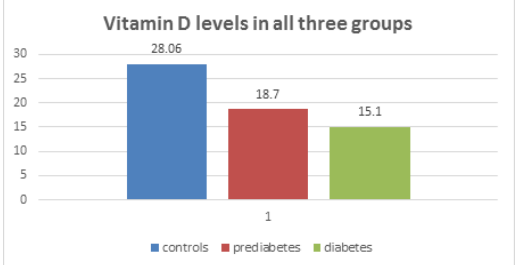

Figure 1. Bar chart showing Vitamin D levels in controls, pre-diabetes and diabetes

Correlations among variables in control and pre-diabetic group

- HOMA-IR is moderately negatively correlated with vitamin D (r = - 0.47; p value < 0.01) which are statistically significant. (Table 3) (Figure 2)

Table 3: The correlation among the variables chosen for study among controls and pre-diabetes:

Variable	FBG	2hr-glucose	HbA1c	HOMA-IR
Vitamin D	-.626**	-.530**	-.532**	-.464**

**Correlation is significant at the 0.01 level (2-tailed).

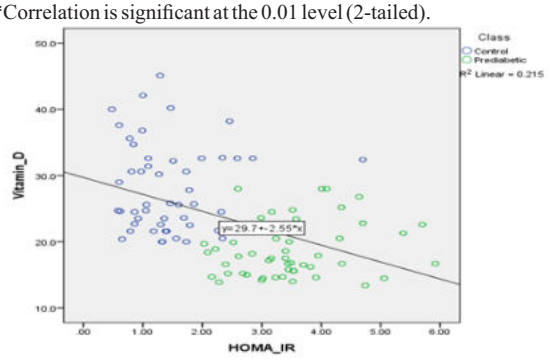

Figure 2. Correlation between HOMA-IR and Vitamin D in pre-diabetes

Correlations among variables in control and diabetic group:

- HOMA-IR is strongly negatively correlated with vitamin D (r = -0.71; p value < 0.01) which are statistically significant.(Table 4 & Figure 3)

Table 4: The correlation among the variables chosen for study among controls and diabetes:

Variables	FBG	2hr-glucose	HbA1c	HOMA-IR
Vitamin D (r)	-.635**	-.735**	-.703**	-.714**

**Correlation is significant at the 0.01 level (2-tailed).

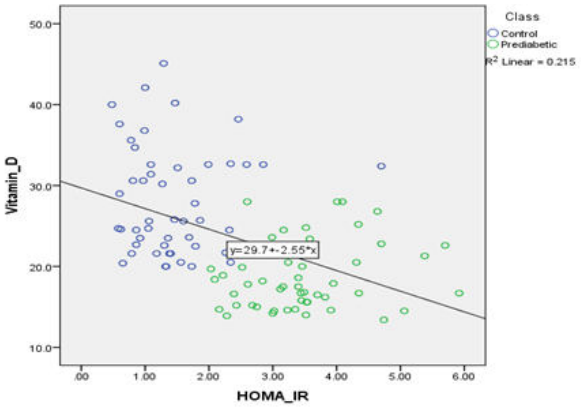

Figure 3. Correlation between HOMA-IR and Vitamin D in Diabetes

DISCUSSION:

From our results, it is evident that vitamin D deficiency in patients with impaired glucose tolerance (pre-diabetes) and type 2 diabetes is high. Therefore, vitamin D deficiency may affect insulin secretion and insulin resistance- the two methods of pathogenesis of type-2 DM. Several cross-sectional and prospective studies in various populations show inverse association between circulating 25(OH)D and fasting plasma glucose (FPG) level, impaired glucose tolerance (IGT), HbA1c, metabolic syndrome, and incidence of prediabetes.

A study conducted by Dutta et al. have investigated the relationship between the vitamin D status and insulin resistance among adult individuals with pre-diabetes, by evaluating the circulating levels of [25(OH)D]. As per the study report from Dutta et.al, the association between vitamin D deficiency among pre-diabetic patients was independent of their BMI status and HbA1c levels.[9] But from our study, we can conclude that there is an association between impaired FPG levels and vitamin D deficiency among pre-diabetic patients.[9] In a study conducted by Holick et al., the authors observed that patients with vitamin D deficiency have the highest insulin resistance.[10] The prevalence of vitamin D deficiency in our study is similar to that reported by Scragg et al., where the circulating 25(OH)D levels was found to be significantly lower in individuals with newly diagnosed impaired glucose tolerance or pre-diabetes as compared to normal individuals.[11] In their study, vitamin D levels were not significantly different in individuals with pre-diabetes as compared to those with diabetes or normoglycemia. But in our study we find a significant difference between prediabetes and diabetes group. Gupta et al,

suggested that 25[OH]D levels were lower in prediabetic patients and affected by age, sex and BMI.[12] In our study also we found a negative correlations between serum 25[OH]D level and BMI and fasting blood glucose. Moreover, low serum 25[OH]D level was strictly correlated with elevated insulin leve. The risk of insulin resistance was increased in patients with vitamin D deficiency. Forouhar et al demonstrated that there is negative correlation between insulin resistance and 25[OH]D level.[13] In prediabetic patients, pancreatic early phase insulin release is impaired, together with increased serum insulin levels.[14,15] This situation accelerates the development of insulin resistance and overt diabetes in prediabetic patients.[16]

CONCLUSION:

Vitamin D deficiency is a risk factor for development of type 2 diabetes mellitus. There might be potential beneficial role of vitamin D supplementation and improving glycemic status in type 2 diabetics.

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