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An Observational Study Assessing Vitamin D Levels and Relationship Between Insulin Resistance with Vitamin-D Status among Individuals with Pre-Diabetes and Diabetes

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Abstract

The aim of the present study is to compare Vit D levels between the normals, pre-diabetics and diabetics and study the relationship between insulin resistance and vitamin-D status among individuals with pre-diabetes and diabetes. It was a hospital based cross-sectional study done in multiple tertiary care Hospitals over a period of one year . The study subjects included age and sex matched 300 subjects who were divided into three groups-100 Normal subjects, 100 pre-diabetic subjects and 100 type 2 diabetic subjects. Fasting insulin levels and insulin resistance (HOMA2 IR) were also increased very significantly in pre diabetics and diabetics as compared to normals ($p<0.001$) and in diabetics as compared to pre diabetics. 25 OH vitamin-D levels were significantly decreased ($p<0.001$) in pre diabetics and diabetics as compared to normals ($p<0.001$). There was no significant change in 25OH Vit D levels between pre diabetics and diabetics. There was no significant difference in HOMA2-ß (beta cell mass) between the groups. There was a strong negative correlation between 25 OH vitamin-D and HOMA 2 IR in diabetics. Similar strong correlation was found between 25 OH vitamin-D and fasting insulin levels in diabetics ($r= -0.52$) and pre diabetic ($r= -0.76$). 25 OH vitamin-D had strong negative correlation with FBS in diabetics ($r= -0.58$) and pre diabetic ($r= -0.66$), systolic BP($r = -0.44$) and diastolic BP (-0.46) in diabetics. vitamin-D deficiency is common in pre diabetic state and subjects having severe vitamin D deficiency (<10 ng/ml), had the worst insulin resistance. This study results help in strongly proposing vitamin D levels as an early marker for diabetes and help in recommending vitamin D to be prescribed in the pre diabetic stage to prevent Diabetes in later stage of the life.

INTRODUCTION

Insulin resistance, which is both a cause and a factor that can be changed, affects type 2 diabetes mellitus (T2DM) and other related illnesses[1]. An efficient and suitable substitute for the hyper insulinemic-euglycemic clamp, a method that is laborious, intrusive and costly for assessing insulin resistance (IR), is the homeostasis model of insulin resistance (HOMA-IR), which examines fasting glucose and insulin levels[2]. Vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) are both referred to as vitamin D[3]. Surveys conducted globally indicate that individuals of various age groups and nationalities experience vitamin D insufficiency[3-5].

Diabetes is a highly challenging health problem in the contemporary period. Pre diabetes is a major risk factor for both type 2 diabetes and cardiovascular disease[6,7]. Pre-diabetes is diagnosed when both impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are detected. Pre-diabetes is an intermediary stage that occurs between having normal glucose tolerance and developing type 2 diabetes mellitus. Individuals with pre diabetes frequently have obesity and other symptoms associated with metabolic syndrome. Obesity is frequently associated with hypovitaminosis-D due to the ability of adipose tissue to retain 25(OH) D, making it biologically unavailable [8]. The levels of calcium within adipocytes can increase when there is an increase in parathyroid hormone (PTH) and a reduction in blood levels of 25(OH)D and calcitriol [1,25(OH)2D]. This increase in calcium can then drive lipogenesis, a process that raises the risk of developing diabetes and gaining additional weight[9]. Studies on animals have found a connection between lower levels of serum 25(OH)D and reduced insulin synthesis and secretion. This could potentially contribute to the development of diabetes[10,11]. Pre diabetes is more prevalent than type 2 diabetes worldwide, affecting individuals of all ages, genders, and racial and cultural origins. During the pre diabetes stage, there is compelling evidence that taking preventive actions can delay or potentially prevent the onset of diabetes.

However, limited study has examined the correlation between pre diabetes and blood 25(OH) D levels, especially in the Indian population. The primary objective of this research was to investigate the association between insulin resistance and vitamin-D status in individuals with pre-diabetes and diabetes.

MATERIALS AND METHODS

This is a hospital based multi-centric cross-sectional study which is conducted in two tertiary care hospitals attached with medical colleges in south India over a period of one year (2023). The study involved data of 300 subjects who were matched for age and sex. These subjects were separated into three groups: 100 normal (non-diabetic) subjects, 100 pre-diabetic subjects and 100 type 2 diabetic subjects. 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 participants and the samples were collected through simple random technique from the General medicine department and samples collected were processed in biochemistry department of the central laboratory available in both the tertiary care hospitals.

The exclusion criteria is the individuals with acute or chronic liver, kidney and heart disease, primary hyperparathyroidism, chronic use of drugs such as anti epileptic agents, oral contraceptive pills and steroids that may disrupt vitamin-D metabolism.

Additionally, patients with cancer, pregnant women and individuals who had taken calcium or vitamin-D supplements within the past year were also excluded.

The study objectives and methods were clearly communicated to patients and/or their attendants and their informed consent was obtained.

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 established methods. Blood pressure was measured using a conventional mercury sphygmomanometer on the right arm while the person was sitting. The measurements were taken twice, with a 2-hour interval between them, after the person had rested for 10 minutes. A 5ml sample of fasting venous blood was collected from all participants involved in the study. The assessed parameters included fasting blood sugar (FBS), insulin levels, lipid profile, calcium levels, alkaline phosphatase (ALP) levels and serum 25-hydroxy vitamin D levels.

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-ß (22). The HOMA2 calculator will be utilized for the computation. The FBS, lipid profile, calcium and serum ALP were analyzed using the fully automated biochemistry analyzer. The levels of serum insulin and 25 OH Vitamin D were determined using a chemiluminescent immunometric assay (CLIA).

RESULTS AND DISCUSSIONS

Fasting insulin levels and insulin resistance (HOMA2 IR) were also increased very significantly in prediabetics and diabetics as compared to normals ($p<0.001$) and in diabetics as compared to prediabetics. 25 OH Vit D levels were significantly decreased ($p<0.001$) in prediabetics and diabetics as compared to normals ($p<0.001$). There was no significant change in

Table 1: Comparison of various anthropometric and biochemical parameters in normal, prediabetics and diabetic groups

Parameters	Normal (n = 100)	Pre diabetics(n = 100)	Diabetics(n = 100)
Age (yrs)	49.6+21.2	51.2+18.5	51.8 +18.2
Systolic BP (mm Hg)	124+10.5	139.5+7.6	142+12.4
Diastolic BP (mm Hg)	82.6+5.6	90.7+5.8	94.6+8.4
BMI	24.3+2.02	25.5 +2.38	26.4+2.42
WHR	0.744+0.16	0.820+0.07	0.906+0.128
FBS (mg/dl)	87.24+7.8	108.6+9.5	144.6 +44
Total Cholesterol (mg/dl)	161+16.1	187.3+11.65	207.1+33.98
TGL (mg/dl)	103.4+15.05	128.6+20	173.7+31.08
HDL (mg/dl)	43.5+6.25	37.2+4.42	33.9+6.36
LDL (mg/dl)	96.8+0.55	124 +13.5	138+33
S. Calcium (mg/dl)	9.94+0.55	9.83+0.56	9.52+0.47
F. Insulin(µIU/ml)	7.58+1.85	12.62+2.96	18.88+2.93
25 OH Vit D (ng/ml)	26.2+5.12	19.9 +3.31	19.2+5.42
HOMA 2-IR	1.65+0.5	3.43+1.04	6.89+3.1
HOMA-B	121.39+39	100.46+16.5	97.7+36

Table 2: Univariate analysis by spearman linear regression

Parameters	Parameter adjusted for	Correlation coefficient(r) Total	Correlation coefficient(r) Prediabetics	Correlation coefficient(r) Diabetics
VIT D and FBS	BMI	-0.59	-0.66	-0.58
VITD and HOMA2 IR	BMI	-0.63	-0.77	-0.63
VIT D and INSULIN	BMI	-0.62	-0.76	-0.52
VIT D and SBP	BMI	-0.50	-	-0.44
VIT D and DBP	BMI	-0.52	-	-0.47

25 OH Vit D levels between prediabetics and diabetics. There was no significant difference in HOMA2-ß (beta cell mass) between the groups. There was a strong negative correlation between 25 OH Vit D and HOMA 2 IR in diabetics.

Similar strong correlation was found between 25 OH Vit D and fasting insulin levels in diabetics (r= -0.52) and prediabetic (r= -0.76). 25 OH Vit D had strong negative correlation with FBS in diabetics (r= - 0.58) and prediabetic (r= -0.66), systolic BP (r = -0.44) and diastolic BP (-0.46) in diabetics.

Individuals who have impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) are commonly known as having prediabetes[12]. The Indian diabetes prevention programme-1 (IDPP-1) found that the yearly likelihood of developing overt diabetes from impaired glucose tolerance (IGT) was around 18%, while the diabetes prevention trial (DPT) in the Chinese diabetes prevention research indicated a risk of approximately 2.5%. Prediabetes often correlates with obesity and other elements of metabolic syndrome[13]. Obesity is often linked to hypovitaminosis-D because adipose tissue has the ability to accumulate 25-hydroxy vitamin-D [25(OH)D], which makes it biologically inaccessible[14].

Adjustment for BMI was performed since persons with greater BMI tend to have lower levels of vitamin D in their serum, as it is primarily stored in adipose tissue. The findings of our study provide evidence to suggest that Vitamin-D deficiency/insufficiency may contribute to the onset or progression of insulin resistance in patients with pre-diabetes in our nation. Therefore, it is necessary to conduct more longitudinal prospective studies in order to evaluate whether the aggravated insulin resistance observed in persons with prediabetes and lower levels of vitamin D actually leads to an increased likelihood of developing diabetes. Scragg *et al*. found that the levels of 25-hydroxyvitamin D (25(OH) D) were significantly lower in individuals who were newly diagnosed with impaired glucose tolerance (IGT) or diabetes, compared to individuals who did not have these conditions[15]. Both prediabetics and diabetics showed a substantial rise in fasting insulin levels and insulin resistance (HOMA2 IR) compared to individuals without diabetes (p<0.001). Additionally, diabetics had higher levels of fasting insulin and insulin resistance compared to prediabetics. 25-hydroxy vitamin D The levels of Vitamin D were significantly lower (p<0.001) in those with prediabetes and diabetes compared to those without these conditions (p<0.001). There was no substantial alteration in the levels of 25OH Vitamin D between individuals with prediabetes and individuals with diabetes. There was no notable disparity in HOMA2-ß (beta cell mass) between the groups. A significant inverse relationship was observed between 25 OH Vitamin D and HOMA 2 Insulin Resistance in individuals with diabetes. A significant positive connection was seen between 25 OH Vitamin D and fasting insulin levels in individuals with diabetes (r = -0.52) and prediabetes (r = -0.76). The 25 OH Vitamin D levels showed a significant negative connection with fasting blood sugar (FBS) in individuals with diabetes (r = -0.58) and prediabetes (r = -0.66), as well as with systolic blood pressure (r = -0.44) and diastolic blood pressure (r = -0.46) in individuals with diabetes.

Recent research have indicated that vitamin D can affect insulin sensitivity by directly impacting the cells that insulin acts upon, as well as 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 regulate the concentration of calcium within cells, so enhancing insulin sensitivity[16,17]. Inflammation is a significant physiological and pathological mechanism. Vitamin D has the ability to control the immune response of macrophages and monocytes, leading to a decrease in the levels of interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor- a (TNF-a) and other substances. This, in turn, helps alleviate the inflammatory reaction[18]. Given the correlation between vitamin D and insulin sensitivity and ß-cell activity, the use of vitamin D supplements appears to be a potentially effective method for enhancing insulin resistance and lowering the likelihood of developing diabetes. Research conducted by Mitri *et al.*[19] and other studies have proposed different dosages of 25-hydroxy vitamin D supplements for individuals with Vitamin D insufficiency to enhance insulin resistance and hinder or postpone the advancement of diabetes. However, the dosage of Vitamin D supplementation still varies depending on the geographical region.

CONCLUSION

Vitamin D deficiency is prevalent in individuals with prediabetics conditions and those with severe vitamin D deficiency (less than 10 ng/ml) have the most severe insulin resistance. The findings of our study significantly support the notion that vitamin D levels can serve as an early indicator for diabetes. Additionally, this study results and observations suggest that prescribing vitamin D during the pre-diabetic stage may be beneficial.

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