VIA MEDICA
RESEARCH PAPER
ISSN 2450–7458
e-ISSN 2450–8187

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Correlation of Vitamin D3, Insulin-Like Growth Factor 1 and Insulin Resistance in Pre-Diabetes and Newly Diagnosed Type 2 Diabetes

ABSTRACT

Background: Vitamin D deficiency is implicated in the pathogenesis of diabetes mellitus, and more importantly, in the progression of 'pre-diabetes' to overt diabetes mellitus. Alterations in circulating insulin-like growth factor 1 (IGF-1) levels to defects in insulin secretion from beta cells. IGF-1 increases 1,25(OH)D level in vitro by stimulating 1α-hydroxylase expression. Interaction between vitamin D and the IGF-1 system provides an explanation of why hypovitaminosis D levels lead to Insulin resistance. This study aims to find the role of vitamin D and IGF-1 in pre-diabetic individuals and their role in the progression of pre-diabetes to clinically overt diabetes mellitus.

Methods: The observational study was done in the Department of Medicine and Department of Biochemistry, ABVIMS & PGIMER, Dr. RML Hospital, New Delhi, after Ethical approval from the institutional review board (IRB). Ninety study participants were enrolled, which included 30 pre-diabetics, 30 newly diagnosed type-2 diabetics, and 30 healthy controls.

Results: Insulin resistance [homeostatic model assessment for insulin resistance (HOMA-IR)] levels increased as vitamin D levels decreased and this negative correlation between vitamin D levels and HOMA-IR was significant in pre-diabetic (p = 0.001) and the newly diagnosed diabetics group (p = 0.011), but not in the controls group (p = 0.067). Whereas, vitamin D and IGF-1 levels showed a similar positive correlation when compared amongst the three groups. The positive association between vitamin D and IGF-1 was statistically significant (p = 0.0012).

Conclusions: Thus, vitamin D and IGF-1 levels should be measured in all individuals with dysglycemia, whether pre-diabetic or overt type 2 diabetic. And, if vitamin D insufficiency/deficiency is found, it should be corrected adequately in these patients. Although, a large population-based study is needed for the same. (Clin Diabetol 2022, 11; 2: 67–72)

Keywords: pre-diabetes, vitamin D3, IGF-1, insulin resistance, newly diagnosed diabetes

Introduction

Pre-diabetes is an early stage in the hyperglycemia continuum where the individual is at an increased risk for the development of diabetes mellitus. Many pre-diabetics progress to overt diabetes within 3 years. The 10-year risk for this progression has been reported to be around 50% [1]. Diagnosis at the pre-diabetic stage provides an excellent opportunity for delaying the onset of diabetes and the complications associated with poor glycemia. The International Diabetes Federation estimates that around 318 million people worldwide have impaired glucose tolerance (IGT) [2]. However, the exact prevalence among the Indian population is not known. Data from a recent Indian Council of Medical Research (ICMR) survey reported 77.2 million pre-diabetic individuals in India, in addition to the 62.4 million existing diabetics [3].

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Clinical Diabetology 2022, 11; 2: 67–72
DOI: 10.5603/DK.a2022.0002
Received: 30.07.2021 Accepted: 24.10.2021

Table 1. Demographic Profile of the Participants

	Group I (controls)	Group II (pre-diabetics)	Group III (NDD)
Total	n = 30	n = 30	n = 30
Age (mean ± SD)	43.6 ± 12.04	45.2 ± 9.55	47.13 ± 10.24
Males	**20** (66.67%)	**16** (53.33%)	**17** (58.89%)
Females	**10** (33.33%)	**14** (46.67%)	**13** (43.33%)

NDD — newly diagnosed diabetic

Vitamin D deficiency is implicated in the pathogenesis of diabetes mellitus, and more importantly, in the progression of "pre-diabetes" to overt diabetes mellitus [4, 5]. Increased insulin resistance is found to be associated with low vitamin D status in various observational study designs including population-based studies in geographically diverse countries like Norway, Australia, and USA [6–10].

Insulin-like growth factors (IGFs) have gained interest among scientists in knowing how the IGF system disruption is related to metabolic disease. IGF is a multipotent growth factor that shares a 50% amino acid sequence with insulin. Alterations in circulating IGF-1 levels lead to Insulin resistance and defects in Insulin secretion from beta cells. IGF-1 increases 1,25(OH)D level in vitro by stimulating 1 -hydroxylase expression [11]. Interaction between vitamin D and the IGF-1 system provides an alternative explanation of the link between hypovitaminosis D levels and Insulin resistance. It has been suggested that patients with Diabetes mellitus and low vitamin D levels have increased Insulin resistance. However, similar observations in pre-diabetics have not been well documented.

Hence, this study aims to find the role of vitamin D and IGF-1 in pre-diabetic individuals and their role in the progression of pre-diabetes to clinically overt diabetes mellitus.

Methods

The cross-sectional observational study was done in the Department of Medicine and Department of Biochemistry, PGIMER, Dr. RML Hospital, New Delhi, after ethical approval from the institutional review board (IRB). Ninety study participants were enrolled, which included 30 pre-diabetics, 30 newly diagnosed type-2 diabetics, and 30 healthy controls. 'Pre-diabetic' was defined by the American Diabetes Association 2 criterion [12, 13].
fasting plasma glucose is between 100–125 mg/dL, i.e., impaired fasting glucose (IFG) or
2-hour plasma glucose in 75-g oral glucose tolerance test (OGTT) is 140–199 gm/dL, i.e., impaired glucose tolerance (IGT) or
HbA1c levels between 5.7–6.4.

Newly diagnosed type 2 diabetics have been defined as those diagnosed with diabetes within the last 12 months.

Pre-diabetic/newly diagnosed diabetic patients with associated hyperparathyroidism, abnormal liver function test (LFT) (total bilirubin > 1.0 mg/dL or raised liver enzymes), abnormal kidney function test (KFT) (blood urea > 40 mg/dL, serum creatinine > 1 mg/dL), any type of malignancy, history of oral contraceptive pills intake, intake of steroids or anti-epileptic drugs and with calcium/vitamin D supplementation in last 1 year were exclude from the study.

Statistical tests

Quantitative variables were compared using ANOVA/Kruskal Wallis test (when the data sets were not normally distributed) between the three groups. Qualitative variables were correlated using the Chi-Square test/Fisher's exact test. Pearson correlation coefficient/Spearman's correlation coefficient was used to determine the association between various quantitative parameters. All results were considered significant if $p < 0.05$.

Results

Out of 90 participants, 53 (58.89%) were males, and 37 (41.11%) were females. The average age of participants in the pre-diabetic group was 45.2 years (range 18–65), 47.13 years (range 28–65) in the newly diagnosed diabetic group, and 43.6 years (range 27–65) in the control group. Most of them (33 of 90, 26.67%) were between 41–50 years (Tab. 1).

Regarding personal history (Tab. 2), a total of 31 participants (34.44%) reported a history of alcohol intake. The average blood pressure recorded in these participants was 142/86 mmHg (range 126/80–160/96). A total of 14 participants had a history of drug intake (apart from anti-diabetic drugs in groups II and III). Ten of the fourteen participants were on anti-hypertensive medication, and two females in the control group were taking iron and folic acid tablets. However, there was no history of illicit drug abuse, calcium or vitamin D supplementation in any participant.

Table 2. Personal History of the Participants

	Group I (controls)	Group II (pre-diabetic)	Group III (NDD)
Alcoholics	8 (26.67%)	8 (26.67%)	15 (50.0%)
Smoker	9 (30.0%)	7 (23.33%)	8 (26.67%)
Vegetarian	20 (66.67%)	20 (66.67%)	20 (66.67%)
Non-vegetarian	10 (33.33%)	10 (33.33%)	10 (33.33%)
Previous drug intake	6 (20.0%)	5 (16.67%)	3 (10.0%)
Hypertensive	4 (13.33%)	4 (13.33%)	4 (13.33%)
No family history	29 (96.67%)	26 (86.67%)	27 (90.00%)
Family history present	1 (3.33%)	4 (13.33%)	3 (10.00%)

NDD — newly diagnosed diabetic

Table 3. Showing the Various Parameters in Different Groups

	Group I (controls) (mean ± SD)	Group II (prediabetic) (mean ± SD)	Group III (NDD) (mean ± SD)
BMI [kg/m^2]	23.1 ± 3.84	26.4 ± 3	23.9 ± 3.29
WHR	0.78 ± 0.05	0.83 ± 0.05	0.83 ± 0.05
HbA1c [%]	5.33 ± 0.18	6.04 ± 0.23	9.1 ± 1.84
Insulin [μIU/mL]	14.03 ± 5.09	24.5 ± 5.06	22.79 ± 8.42
HOMA-IR	1.79 ± 0.58	3.31 ± 0.66	4.79 ± 2.06
Vitamin D [ng/dL]	20.25 ± 10.04	16.05 ± 4.31	16.95 ± 8.5
IGF-1 [ng/mL]	199.57 ± 40.03	124.79 ± 27.39	102.03 ± 22.7

BMI — body mass index; HbA1c — glycated hemoglobin; HOMA-IR — homeostatic model assessment for insulin resistance; IGF-1 — insulin-like growth factor 1; NDD — newly diagnosed diabetic; WHR — waist-to-hip ratio

The mean body mass index (BMI) and waist-to-hip ratio (WHR) levels were higher in pre-diabetics and newly diagnosed diabetics compared with healthy controls. The difference in BMI was found to be statistically significant when the pre-diabetic group was compared with the control group ($p = 0.001$) or the newly diagnosed diabetics group ($p = 0.015$) as shown in Table 3. Similarly, the difference in the WHR was significant when the control group was compared with the pre-diabetic group ($p < 0.0005$) and the newly diagnosed diabetics group ($p = 0.001$). HbA1c levels also showed a positive correlation with both BMI and WHR. However, statistically, only the association between HbA1c levels and WHR was found to be significant ($p < 0.0001$), whereas the association between HbA1c levels and BMI was not significant ($p = 0.3443$). A negative correlation was observed between serum IGF-1 levels and BMI and serum IGF-1 levels and WHR. It was seen that levels of IGF-1 were lower in overweight/obese patients compared to their counterparts with a normal BMI and WHR. The negative correlation between IGF-1 and WHR was statistically significant ($p < 0.0001$). However, no significant correlation was observed between IGF-1 levels and BMI ($p = 0.063$).

The fasting insulin levels were higher in both the pre-diabetic and the newly diagnosed diabetic groups than in healthy controls. This difference was found to be statistically significant ($p < 0.0005$). The difference in HOMA-IR scores of the pre-diabetic and newly diagnosed diabetic groups was significant compared to the healthy controls ($p < 0.005$). A total of 81 (90%) study subjects displayed inadequate vitamin D levels. Most of these (57.78%) were vitamin D deficient, i.e. levels < 20 ng/mL. Almost half of the subjects who had normal or sufficient vitamin D (30–100 ng/mL) levels were healthy controls. The mean level in this control group was 20.25 ng/mL, which was higher than that in the prediabetic group (mean = 16.05, range = 6–30.5) or the newly diagnosed diabetics group (mean = 16.95, range = 5–41.8). However, the difference in vitamin D levels among the three groups did not show any statistical significance ($p = 0.189$) as shown in Figure 1.

Vitamin D levels decreased as the insulin resistance (calculated as HOMA-IR score) increased. When compared within the three groups, the negative correlation between vitamin D levels and HOMA-IR was significant in pre-diabetic ($p = 0.001$) and the newly diagnosed diabetics group ($p = 0.011$), but not in the

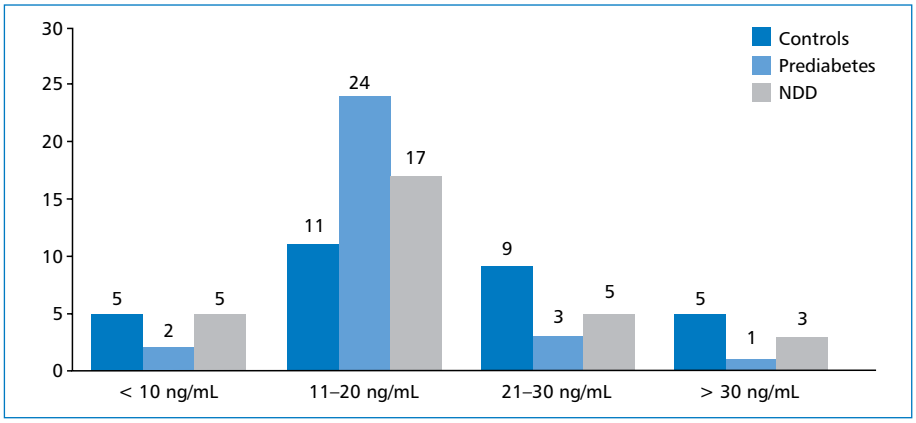

Figure 1. Vitamin D Insufficiency/Deficiency in Various Groups

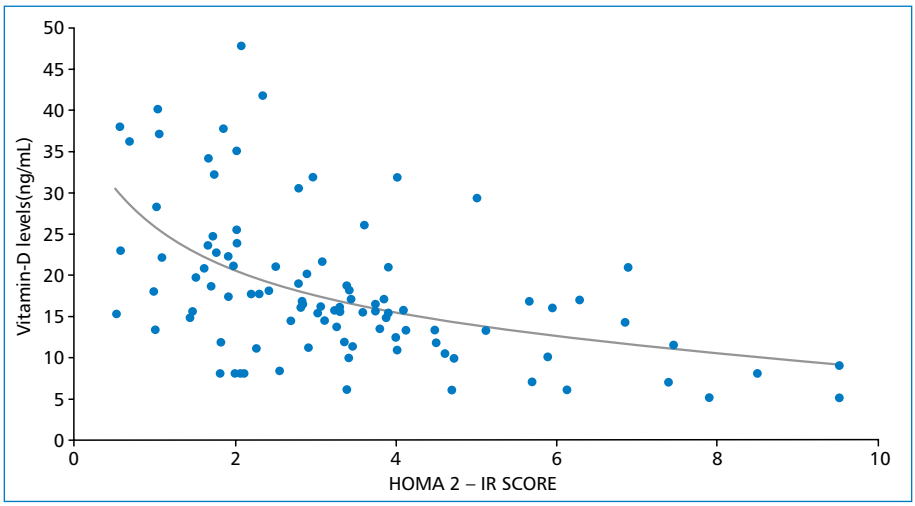

Figure 2. Relationship of Vitamin D Levels with Insulin Resistance (p = 0.0001)

controls group (p = 0.067) as shown in Figure 2. The negative correlation was found to be significant (95% confidence interval [CI] –0.557 to –0.206, p = 0.0001, Spearman's coefficient of rank correlation = –0.396).

Vitamin D and IGF-1 levels showed a similar positive correlation when compared amongst the three groups. Most of the study participants with higher vitamin D levels had higher serum IGF-1 levels.

Newly diagnosed diabetics had the lowest IGF-1 levels, and these patients also showed the lowest levels of vitamin D as shown in Figure 3. The positive correlation between vitamin D and IGF-1 was statistically significant (95% CI = 0.138–0.507, p = 0.0012, Spearman's coefficient of rank correlation = 0.335).

Discussion

This study was performed to observe the vitamin D, and IGF-1 levels in individuals with pre-diabetes and newly diagnosed diabetes where as most of the studies have evaluated the relationship between vitamin D and IGF in healthy subjects or diabetic patients.

The mean age in the control group, the pre-diabetic group, and the newly diagnosed diabetic group were 43.6, 45.2, and 47.13 years, respectively, with no statistically significant difference. In our study, hypovitaminosis-D was observed in 90% of our study population. Out of these, 71.1% had vitamin D deficiency, i.e. levels < 20 ng/mL. The presence of vitamin D insufficiency/deficiency in controls, pre-diabetics and newly diagnosed diabetics was 83.3% (n = 25), 96.6% (n = 29) and 90% (n = 27) respectively. Similar values in the study by Deep Dutta were 78.57 % (n = 22), 73.25 % (n = 115) and 66.6 % (n = 28) [14]. Vitamin D levels in pre-diabetics were slightly less as compared to the newly diagnosed diabetics. However, when median and mode values were taken into account,

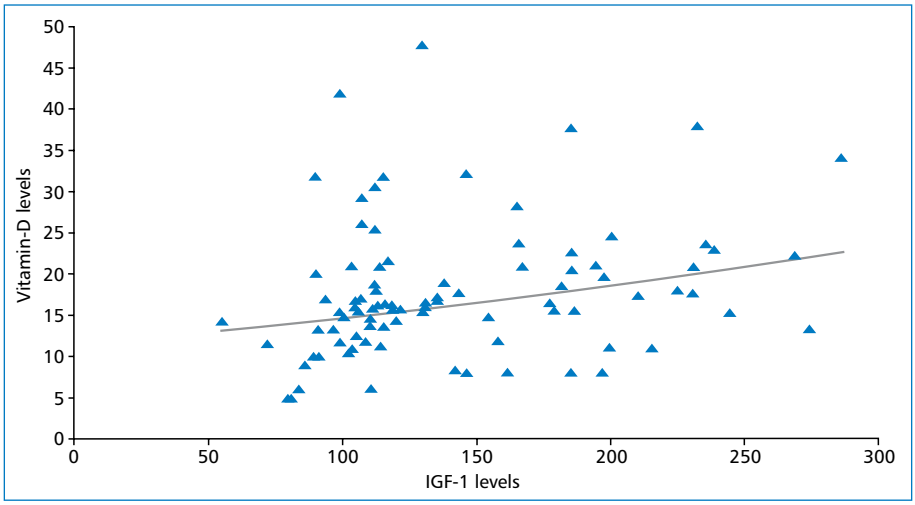

Figure 3. Correlation between vitamin D and IGF-1 levels (p = 0.0012)

vitamin D levels of controls were higher than those of pre-diabetics, which in turn were higher than those of newly diagnosed diabetics.

Serum vitamin D levels are inversely correlated with insulin resistance, decreasing with an increase in the HOMA2-IR score. Thus, the glycemic status of an individual worsened with the decrease in vitamin D levels. The mean IGF-1 levels in controls, pre-diabetics, and newly diagnosed diabetics in our study were 199.57, 124.79, and 102.03 ng/mL, respectively. Serum IGF-1 concentrations were highest in healthy individuals and declined as the glycemic status worsened, and Insulin resistance increased. Our results closely resemble those of Giorgio Sesti et al. [15] who studied the relationship between plasma IGF-1 levels and Insulin resistance in 357 non-diabetic, 54 IGT, and 98 newly diagnosed diabetic individuals. Thus, a strong association between plasma IGF-1 concentration and Insulin sensitivity at different degrees of glucose tolerance can be concluded.

Our study has demonstrated a negative correlation of both serum vitamin D and serum IGF-1 levels with Insulin resistance. Also, the association between vitamin D and IGF-1 levels was positive and significant (p = 0.0012). These findings are per the observations of Elina Hyppönen [16] in the 1958 British birth cohort. Both 25(OH) D and IGF-1 showed inverse associations with metabolic syndrome. It was suggested that the reduction in the prevalence of metabolic syndrome is most significant when both 25(OH)D and IGF-1 levels are high. 25(OH)D was inversely associated with metabolic syndrome regardless of IGF-1 concentration. In contrast, the inverse association between IGF-1 and metabolic syndrome is more pronounced at lower 25(OH) D levels, thus suggesting that the metabolic efficacy of IGF-1 in different body tissues may vary according to the individual's vitamin D status. Our study corroborates the findings of Gómez [17] and Bogazzi [18], who have previously outlined a positive association between vitamin D concentration and serum IGF-1 levels.

A Danish population-based study by Nele Friedrich [19] concluded a U-shaped association between IGF-1 and insulin resistance. Both very low and high normal IGF-1 levels were related to higher odds of insulin resistance. These findings were more pronounced in women rather than men. This difference is possibly due to smaller sample size in our study and the fact that most subjects in the Danish study were normoglycemics (only 3.7% were diabetics).

Our study's strength is that we have included individuals with the whole spectrum of glucose tolerance ranging from normo-glycemia to pre-diabetes to overt diabetes mellitus. We did a detailed anthropometric evaluation in addition to measuring biochemical parameters and were able to evaluate associations between these anthropometric parameters and Insulin resistance, hypovitaminosis-D, and plasma IGF-1 concentration. Though, more randomized controlled trials are required to determine the extent to which prevention of hypovitaminosis-D might lessen the risk of worsening insulin resistance and the progression of pre-diabetes to overt diabetes.

Conclusions

Our study shows that insulin resistance has an inverse relationship with vitamin D and IGF-1 levels in patients with impaired glucose tolerance (pre-diabetes) or overt diabetes. Thus, it is suggested from the study

that vitamin D and IGF-1 levels should be measured in all individuals with dysglycemia, whether pre-diabetic or overt type 2 diabetic. If found, vitamin D insufficiency/deficiency should be corrected adequately in these patients. Similarly, insulin resistance (using the HOMA-IR score) should be used routinely, in conjunction with fasting blood glucose and HbA1c values, to measure an individual's glycemic status.

Conflict of interest

None declared.

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