EC DIABETES AND METABOLIC RESEARCH
Research Article

The Association between Vitamin D and Insulin Resistance among Adults with Prediabetes

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Abstract

Background: Low vitamin D level was observed among adults with prediabetes and diabetes mellitus. Insulin resistance is the hallmark in the pathogenesis of them. Vitamin D deficiency is thought to influence the pathogenesis of type 2 diabetes mellitus by affecting either insulin sensitivity, β-cell function or both.

Aims: To determine the level of serum vitamin D, intact parathyroid hormone (iPTH) and insulin resistance and their association in adults with prediabetes.

Methods: This cross-sectional study was carried out in 115 newly detected adults with prediabetes diagnosed according to American Diabetes Association 2018 criteria. Participants were recruited consecutively from the Department of Endocrinology, BSMMU to measure serum 25hydroxyvitamin D by high performance liquid chromatography method, intact parathyroid hormone was measured by chemiluminescent enzyme-labeled immunometric assay and fasting insulin was measured by chemiluminescent microparticle immunoassay to calculate homeostasis model assessment of insulin resistance (HOMA-IR).

Results: The frequency of vitamin D deficiency was 46.1% in adults with prediabetes. There were no significant association between vitamin D ($p = 0.39$) oriPTH ($p = 0.55$) level with insulin resistance status in adults with prediabetes. No significant correlations were found between vitamin D level ($r = -0.07$, $p = 0.44$) and intact parathyroid hormone level ($r = 0.08$, $p = 0.37$) with HOMA-IR.

Conclusion: A substantial proportion of prediabetes was vitamin D deficient. There was no association or correlation between vitamin D and insulin resistance among adults with prediabetes.

Keywords: *Vitamin D; Prediabetes; HOMA-IR; Intact Parathyroid Hormone*

Abbreviations

iPTH: Intact Parathyroid Hormone; 25(OH)D: 25 Hydroxyvitamin D; DM: Diabetes Mellitus; BSMMU: Bangabandhu Sheikh Mujib Medical University; BMI: Body Mass Index

Introduction

The vitamin D has gained a lot of interest in recent years due to presence of its receptors in different non-classical organs including β-cells of pancreas [1]. Many studies have documented hypovitaminosis D to be associated with many disease conditions such as cancers, cardiovascular disease and diabetes mellitus (DM) [2]. Epidemiologic and animal studies indicate a role of vitamin D in the prevention and treatment of DM, infections, autoimmune and inflammatory diseases [3].

Although the mechanisms are not clear, vitamin D may influence glucose homeostasis by acting on different sites by various direct and indirect possible mechanisms. Along with β-cell dysfunction and apoptosis, low vitamin D increases insulin resistance in target cells by increasing intracellular calcium mediated via compensatory increase of parathormone and reducing expression of insulin receptors [4]. The increased intracellular calcium also promotes adipogenesis predisposing further weight gain and insulin resistance [5]. The immunomodulatory effects of vitamin D is also hampered in hypovitaminosis D state resulting in a low grade inflammation that also reduces insulin sensitivity [6].

As prevalence of hypovitaminosis D is very high in adults with prediabetes, an inverse relationship between vitamin D and insulin resistance is expected. However, cross-sectional studies provide conflicting results between the association of serum vitamin D and insulin resistance [7,8]. A 10 year prospective study showed an inverse relationship between serum 25(OH)D and insulin resistance in non-diabetic people. Baseline 25(OH)D was inversely associated with 10-year risk of hyperglycemia, insulin resistance after adjustment for age, sex, smoking, body mass index (BMI) and season [9]. However, interventional studies demonstrated no improvement of insulin resistance following vitamin D supplementation [10-12] in prediabetes individuals. Similar findings were also found in systematic review and meta-analysis of prediabetes individuals [13]. The scenario may be different in the Indian subcontinent, where an observational study found an inverse relationship between 25(OH) D and insulin resistance in prediabetic individuals [14]. In addition, randomized controlled trials conducted in India showed that vitamin D supplementation improved the glycaemic control and insulin sensitivity in prediabetic individuals [15] and T2DM patients [16]. Genetic and environmental factors may play a role in this regard. In a meta-analysis, an association between insulin resistance related diseases and vitamin D receptor gene polymorphism (ApaI, BsmI, FokI variant) were more obvious in dark-pigmented Caucasians and Asians but not in Caucasian with white skin [17]. An association was also found between vitamin D receptor gene polymorphisms (ApaI variant) and insulin secretion in Bangladeshi Asians, categorized as at risk for T2DM [18].

There is a possibility that hypovitaminosis D may affect insulin resistance adversely contributing to development of prediabetes and diabetes in our population. However, the association in prediabetes is found to be controversial in different studies. Furthermore, it has not been studied previously in Bangladeshi population as per our best knowledge. Therefore, this study was conducted to explore the association of serum vitamin D and intact parathyroid hormone (iPTH) with insulin resistance among adults with prediabetes.

Materials and Methods

Study design

This cross-sectional study was carried out in the Department of Endocrinology, BSMMU during the period of July 2018 to September 2019. In this study, 115 newly detected and untreated adults with prediabetes were included by consecutive purposive sampling. Patients who were taking or had received vitamin D or calcium within last 120 days of sample collection; taking any medications that alter vitamin D level; having any endocrine disorders affecting vitamin D metabolism; known liver, renal, autoimmune, inflammatory diseases, malignancy or pregnancy and lactation were excluded from the study. The study protocol was approved by Institutional Review Board, BSMMU (No. BSMMU/2018/4826). Written informed consent was taken from each participant. Data were collected using pretested semi-structured questionnaires and physical examination including height and weight to calculate BMI was done. Blood was taken for 25(OH) D, iPTH, fasting insulin and fasting blood glucose.

Biochemical analysis

About 10 ml of venous blood was taken from each participant in the fasting state. Fasting blood glucose was measured by glucose oxidase method. Serum was separated from remaining blood and stored in - 20°C until assay. Assay of the collected samples were done for 25(OH)D by high performance liquid chromatography method (HPLC), iPTH by chemiluminescent enzyme-labeled immunometric assay, fasting insulin by chemiluminescent microparticle immunoassay. Values of the fasting insulin and fasting blood glucose were used to calculate the HOMA-IR [{fasting insulin (μU/ml) × fasting blood glucose (mmol/L)} ÷ 22.5] [19]. 25(OH)D was measured by SIL 20 series prominence HPLC analyzer with a coefficient of variability 2.6 - 4.9%. Insulin was measured by ARCHITECT Insulin assay Abbott, USA and iPTH was measured by Immulite 2000 systems Siemens, USA analyzer.

Operational definitions

Prediabetes was diagnosed according to ADA, 2018 criteria {any one from below: fasting blood glucose = 5.6 - 6.9 mmol/L (IFG), 2 hours after 75 gm OGTT = 7.8 - 11 mmol/L (IGT) or HbA1C = 5.7 - 6.4%} [20]. Vitamin D deficiency was categorized by Endocrine Society clinical practice guideline, 2011 into vitamin D sufficiency, insufficiency and deficiency with the cut off value 30 and 20 ng/ml respectively [21]. The cut-off point to define insulin resistance was HOMA-IR of 2.6. This was based on a cross-sectional study conducted among Bangladeshi people [22]. The cut off value to define raised iPTH was 66 pg/ml.

Sample size calculation

The minimum number of sample to be studied was 76 using, n = $(Z^2 \times p \times q) \div d^2$ formula. Here, p = prevalence of vitamin D deficiency in prediabetes (73.25%) = 0.7325 [14], q = 1- p = (1-0.7325) = 0.2675, Z = value of standard normal distribution at a given level of significance or at a given confidence level (1.96 at the level of 95% confidence), d = margin of error (10%). Present study included 115 adults with prediabetes.

Data management

Data were coded, entered and analyzed by computer based SPSS program (version 22.0). Data were expressed as frequencies or percentages for qualitative values and mean (± standard deviation) for quantitative values. Data with skewed distribution (HOMA-IR) were transformed into 10-based logarithmic values. To compare the mean value (vitamin D, HOMA-IR and iPTH level) of subgroups, independent t test, one way ANOVA and factorial designed two way ANOVA were used as appropriate. To test the association between categories (insulin resistance, vitamin D status and raised iPTH status), Pearson's Chi-square test and Fisher's exact test were done as appropriate. Pearson's correlation test was used to correlate HOMA-IR levels with vitamin D and iPTH. $P \leq 0.05$ was considered as statistically significant.

Results

A total of 115 adults with prediabetes were enrolled in this study to explore the association among vitamin D, iPTH and insulin resistance in adults with prediabetes.

Vitamin D level and status in adults with prediabetes

In this study, the mean age of the study population was 36.37 ± 10.06 years with BMI 26.91 ± 2.83 kg/m^2. The female and male ratio was 4:1. Majority of the participants came from urban area. Most of them had an occupation that belonged to manual unskilled. Majority of the study participants had completed their higher secondary education. Lower class was the predominant socio-economic category in the study population (Table 1).

The mean vitamin D level was in the vitamin D insufficiency group. Nearly half of the participants had vitamin D deficiency and insulin resistance. Less than 20% of the participants had raised iPTH level (Table 2a and 2b).

Variables	Frequency (%)
Gender	
Male	23 (20)
Female	92 (80)
Area of residenceƗ	
Urban	89 (77.4)
Rural	26 (22.6)
Occupational classification*	
Managerial and professional	14 (12.2)
Nonmanual	7 (6.1)
Manual	7 (6.1)
Manual unskilled	74 (64.3)
Institutionalized, retired, unemployed	13 (11.3)
Educational status (completed years of schooling)	
Not completed primary (< 5)	15 (13)
Completed primary but not secondary (5 - 9)	39 (33)
Completed secondary but not higher secondary (10 - 11)	15 (13)
Completed higher secondary (≥ 12)	46 (40)
Socio-economic status†	
Lower	51 (44.3)
Middle	46 (40)
Higher	18 (15.7)

Table 1: *Sociodemographic characteristics of the study population (N = 115).*
Within parenthesis are percentages over total.
Ɨ: According to Bangladesh national conservation strategy [23].
**: According to registrar general occupational classification [24].*
†: According to monthly household income [25].

Variables	Frequency (%)
Vitamin D status	
Sufficiency (≥ 30 ng/ml)	24 (20.9)
Insufficiency (20 - 29.9 ng/ml)	38 (33.0)
Deficiency (< 20 ng/ml)	53 (46.1)
Insulin resistance (HOMA-IR ≥ 2.6)	56 (48.7)
Raised iPTH (≥ 66 pg/ml)	19 (16.5)

Table 2a: *Frequency of biochemical parameters in the study population.*

Variables	Mean ± SD	Range	Reference/optimal value
Serum 25(OH)D (ng/ml)	20.79 ± 10.63	2.0 - 45.47	≥ 30
HOMA-IR	3.13 ± 2.92	0.12 - 28.48	< 2.6
Serum iPTH (pg/ml)	46.74 ± 23.82	10.50 - 122.0	10 - 65

Table 2b: *Mean value of the biochemical parameters of the study population (n = 115).*

Associations and correlation of serum vitamin D and iPTH with insulin resistance in the prediabetic population (n = 115)

Although a lower mean vitamin D value was observed in the group with insulin resistance, there was no significant difference between the insulin resistance categories (21.28 ± 11.12 vs 19.91 ± 10.83, p = 0.50) (Figure 1a). Similarly, a higher iPTH level was observed in the insulin resistance present group than the insulin resistance absent group without significant association (50.22 ± 23.50vs 43.10 ± 24.20, p = 0.56) (Figure 1b).

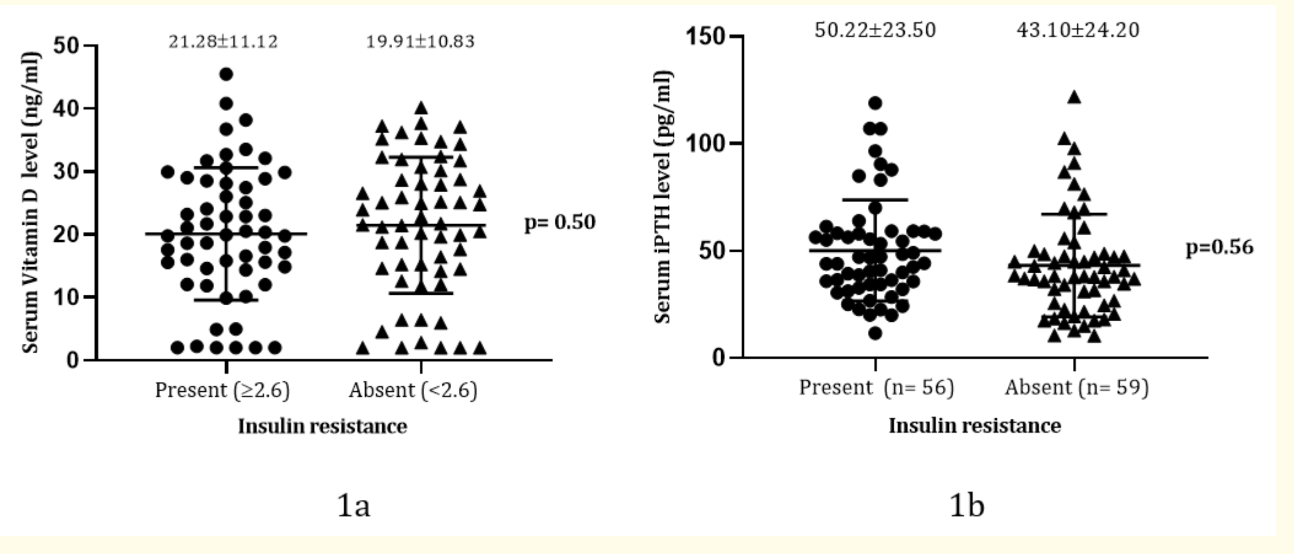

Figure 1: *Distribution of serum 25(OH)D(1a) and iPTH (1b) level according to insulin resistance status. Independent t test was done.*

There was no significant difference of 25(OH)D level among different quartiles of HOMA-IR (p = 0.36) (Table 3).

HOMA-IR quartiles	Vitamin D level (ng/ml)	p
	Mean ± SD	
1st quartile (< 1.93)	22.66 ± 10.50	
2nd quartile (1.93 to < 2.56)	19.70 ± 11.30	
3rd quartile (2.56 to < 3.75)	22.40 ± 9.34	
4th quartile (≥ 3.75)	20.79 ± 10.63	0.36

Table 3: *Distribution of vitamin D level among the HOMA-IR quartiles in the study population (n = 115). One way ANOVA was done.*

Although there was a trend of increasing level of insulin resistance across increasing severity of vitamin D deficiency, there was no significant difference among the mean value of HOMA-IR in three subgroups of vitamin D status (p = 0.62). Similarly, there was no significant difference between the mean values of HOMA-IR in different iPTH categories (p = 0.78) (Figure 2). There was no significant association between interaction of vitamin D status and iPTH status with HOMA-IR level (p = 0.96) (not shown).

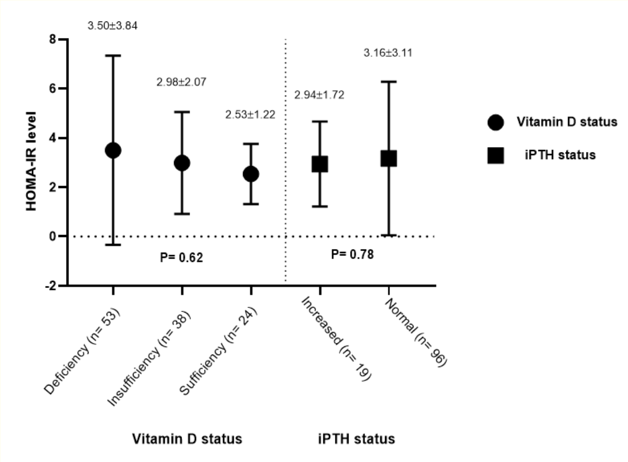

Figure 2: *Distribution of HOMA-IR level according to vitamin D and iPTH status.*
One way ANOVA and independent t test were done respectively.

There was no significant association between vitamin D status (p = 0.39) and iPTH (p = 0.55) status with HOMA-IR category in the prediabetic population (Table 4).

Categories of biochemical parameters		**Insulin resistance**		**p**
	Present	**Absent**		
	Frequency (%)			
Vitamin D status	Deficient	29 (51.8)	24 (40.7)	0.39
	Insufficient	18 (32.1)	20 (33.9)	
	Sufficient	9 (16.1)	15 (25.4)	
iPTH status	Increased	9 (16.1)	10 (16.9)	0.55
	Normal	47 (83.9)	49 (83.1)	

Table 4: *Association of vitamin D status and iPTH status with insulin resistance category (by HOMA-IR) in the prediabetic population (n = 115).*
Within parentheses are percentages over total.
Pearson's Chi-square test and Fisher's exact test were done.

Furthermore, there were no significant correlation found between HOMA-IR with vitamin D level and iPTH level (Table 5).

Determinants of r	**r**	**p**
25(OH)D	-0.07	0.43
iPTH	0.08	0.37

Table 5: *Correlation of vitamin D level and iPTH level with HOMA-IR level.*
By Pearson's correlation test.
r: Pearson's correlation coefficient.

Discussion

In this study we found that the mean vitamin D level of the prediabetic population was in the vitamin D insufficiency category. Substantial percentage of the study population was vitamin D deficient according to Endocrine Society's criteria. There was no association and correlation between vitamin D and insulin resistance among adults with prediabetes.

The mean vitamin D level in the study population was in the insufficiency group according to Endocrine society's criteria. Similar findings were also observed in other studies done in people with prediabetes [14,26,27].

In this study, vitamin D deficiency was the predominant vitamin D status among adults with prediabetes. Although similar findings were found by other authors [28,29], some found a very high percentages of vitamin D deficiency [27,30,31]. This might be due to a relatively higher age, greater percentage of smokers and higher BMI in these studies.

We did not find any association and correlation between vitamin D with insulin resistance. Similarly, one study did not find any association with insulin resistance [32] and another one with fasting insulin level [33]. On the contrary, others found negative correlation between vitamin D and HOMA-IR [14,26,29]. However, the strength of the relationship is variable [29,34]. Another study conducted in 60 adults with prediabetes, observed a positive correlation of vitamin D with reciprocal HOMA-IR, but this relationship was lost with multiple linear regression analysis [31]. These different findings might due to different sample size, age, race, latitude, method of vitamin D estimation etc.

These conflicting results may be due to diverse effects of vitamin D on glucose homeostasis at different stages of diabetes development [29]. The relationship between vitamin D level and insulin resistance was found among patients with DM in several studies [35,36]. Therefore, the relationship may be expected in patients with frank DM, where insulin resistance is more profound. This study looked at the relationship between vitamin D and insulin resistance in prediabetes where only 48.7% had insulin resistance and the mean HOMA-IR level was only 3.13 ± 2.92. Similarly, many studies failed to show improvement of insulin resistance after vitamin D supplementation in deficient prediabetic patients [12,37]. The lack of association found in our study may be due to presence of other factors influencing insulin resistance [38]. So, vitamin D deficiency may have a minor role in developing insulin resistance. Several longitudinal prospective studies are warranted to assess whether this worsened insulin resistance in prediabetes individuals with lower vitamin D actually results in increased progression to diabetes.

Conclusion

Vitamin D deficiency was common in adults with prediabetes. However, it was not associated with insulin resistance among adults with prediabetes.

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Conflict of Interest

None of the authors have any conflict of interest.

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