

RESEARCH PAPER

Vitamin D, Parathyroid Hormone and Insulin Resistance among Adults with Prediabetes

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Abstract:

Background: Several studies have found an inverse association among parathyroid hormone (PTH), vitamin D level, and insulin resistance (IR) causing prediabetes and diabetes.

Objective: To assess the level of vitamin D, PTH, and insulin resistance among adults with prediabetes and determine the association of PTH vitamin D and insulin resistance (IR).

Methods : This cross-sectional study was carried out in 140 newly detected adults with prediabetes according to ADA 2019 criteria. 25(OH) D cutoffs to define deficiency and insufficiency were used according to Endocrine Society (USA) criteria, Measurement of intact PTH, vitamin D and insulin (fasting) was done by chemiluminescent microparticle immunoassay (CMIA).

Results: In this study, most of the study population was 30 years and above (73.0%). The male-female ratio was 1:7, the majority of participants came from urban areas (81.0%). 37.0% had raised PTH and most of the participants (79.0%) were vitamin D deficient. A significant association was found between PTH and insulin resistance. Though it was observed that there was an increasing trend of insulin resistance across increasing severity of vitamin D deficiency but statistically it was not significant ($p=0.74$)

Conclusion: Our study results demonstrate an inverse relationship between PTH and insulin resistance but there was no association had been found between vitamin D and insulin resistance in individuals with newly detected untreated prediabetes. The clinical significance of these observations warrants further study to explore these relationships more appropriately.

Keywords: Parathyroid hormone, Vitamin D, Insulin resistance, Prediabetes

Introduction

During the last decades, several studies indicate that there is a role of vitamin D as a biological metabolic regulator.¹ Hypovitaminosis D seems to be implicated in the pathogenesis of prediabetes and diabetes and an inverse association between serum vitamin D and prediabetes prevalence has been reported.²

Prediabetes is an important glycaemic state that predisposes an individual to a high probability of future progression to diabetes and vitamin D deficiency is thought to influence the pathogenesis of type 2 DM by affecting either insulin sensitivity, α -cell function, or both.^{3,4} Activation of adipocytes modulates intracellular calcium concentrations and can affect

changes in lipogenesis and lipolysis. It is therefore assumed that vitamin D is involved in modulating the tissue response to insulin.⁵ One of the hallmarks of type 2 DM is low-grade inflammation which can be a result of an increase in circulating cytokines such as tumor necrosis factor α (TNF- α) and interleukin (IL)-6 which contribute significantly to insulin resistance in muscle and adipose tissue.⁶ Vitamin D tends to down-regulate the transcription of various proinflammatory cytokine genes like IL-2, IL-12, and TNF- α .^{7,8}

On the other hand, vitamin D and parathyroid hormone (PTH) are important physiological regulators of extracellular calcium homeostasis. Studies show that there is some biological plausibility for these relationships because low vitamin D levels and to a lesser extent elevated PTH levels have been associated with insulin resistance and glucose intolerance.⁹⁻¹³

In insulin resistance, there is reduced glucose clearance in skeletal muscles, impaired suppression

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of glucose production by the liver, and decreased rates of lipolysis in adipose tissue or their combination. The longitudinal Whitehall II study described by Tabak et al found 29% lower insulin sensitivity at 13 years before the onset of T2DM.¹⁴ Thus IR represents an early abnormality that is compensated by augmented β -cell function for a long time before the insulin-glucose feedback loop fails.¹⁵

According to IDF atlas, the incidence and prevalence of prediabetes and diabetes are increasing progressively despite various preventive and therapeutic approaches adopted at government and NGO levels in our country. On the other hand, the level of vitamin D is low in most of the population, shown in different studies on Bangladeshi population.^{16,17}

So, the objective of this study was to assess PTH, Vitamin D, and insulin resistance in newly detected untreated prediabetes adults in hospital and find out the cross-sectional associations of vitamin D and PTH levels with insulin resistance which may be of good help for the clinician to address the situation more appropriately.

Materials and Methods

This cross-sectional study was conducted in the department of endocrinology of Bangabandhu Sheikh Mujib Medical University (BSMMU) from March 2019 to February 2020. A total of 140 Adults (age group of 18yrs and above) with prediabetes according to ADA 2019 criteria, were enrolled in this study after getting ethical approval from the institutional review board (IRB) of BSMMU. Patients currently on vitamin D and calcium or who had received any one of them within the last 120 days and patients receiving any medications that may alter vitamin D level and glucose tolerance (anticonvulsant, ketoconazole, glucocorticoids, rifampicin, isoniazid, oral contraceptive) and patient having endocrine disorders (hyperthyroidism, hypothyroidism, hyperparathyroidism, cushing syndrome) or chronic disease like CKD, CLD were excluded from this study. Informed written consents were obtained from all subjects. Measurement of Intact PTH, vitamin D, and insulin (fasting) was done by chemiluminescent microparticle immunoassay (CMIA) in the department of biochemistry and molecular biology, Bangabandhu Sheikh Mujib Medical University (BSMMU). Insulin resistance was determined by the homeostasis model assessment of insulin resistance (HOMA-IR). The 25(OH) D cut-offs to define deficiency and

insufficiency were used according to Endocrine Society (USA) criteria.¹⁸ Data were analysed using SPSS and presented as table and figure. p value ≤ 0.05 was considered as significant.

Results

In this study, most of the population was 30 years and above (73.0%). Male female ratio was 1:7, majority of participant came from urban area (81.0%) most of them have an occupation that belonged to manual, unskilled, and unemployed, middle class was the main socio-economic category in the study population (table I).

Table I: Socio-demographic characteristics of the study population (N = 140).

Parameters	Frequency (%)
Age of the respondent	
Less than 30 years	38 (27.1)
30 years and above	102 (72.9)
Region	
Urban	114 (81.4)
Rural	26 (18.6)
Gender	
Male	52 (37.1)
Female	88 (62.9)
Occupation	
Managerial and professional	24 (17.1)
Nonmanual	4 (2.9)
Manual	26 (18.6)
Manual unskilled	6 (4.3)
Institutionalized, retired, unemployed	80 (57.1)
Socio-economic status	
Lower	56(40)
Middle	65(46.4)
Higher	19(13.6)
Physical Activity	
Low	12 (9.1)
Moderate	116 (87.9)
High	4 (3.0)

Within parentheses are percentages over column total

Within parentheses are percentages over column total Overweight and obese were (85.0%), most of the participants were vitamin D deficient group (79.0%) and insulin resistance present about 79.0% participants, 37.0% of the participants had raised PTH (table II)

Table II: Clinical and biochemical characteristics of the study population

Parameters	Frequency (%)
BMI	
Underweight & Normal	20 (14.3)
Overweight & Obese	120 (85.7)
Acanthosis nigricans	
Present	6 (4.4)
Absent	132 (95.7)
Vitamin D	
Deficiency (< 20 ng/ml)	110 (78.6)
Insufficiency (20-29.9)	28 (20.0)
Sufficiency (\geq 30 ng/ml)	2 (1.4)
Insulin resistance	
IR absent (HOMA-IR < 2.6)	30 (21.4)
IR present (HOMA-IR \geq 2.6)	110 (78.6)
PTH	
Normal (18.5-88 pg/ml)	88(62.8)
Increased (> 88 pg/ml)	52(37.1)
Serum calcium corrected	
Normal(8.5-10.5mg/dl)	132(98.6)
Low (<8.5mg/dl)	8 (5.7)

Within parentheses are percentages over column total

Mathematically it was observed that there was an increasing trend of insulin resistance across increasing severity of vitamin D deficiency though it was not statistically significant ($p=0.74$). There was a significant association between PTH level and insulin resistance ($p = 0.028$), about 89% of the participant was insulin resistant among the increased PTH group while it was 73% among the normal PTH group. There was a significant association between physical activity and insulin resistance and those who were highly physically active had low insulin resistance ($p<0.001$). A significant association between BMI and insulin resistance ($p=0.001$) was found about 83.0% of participants with overweight and obese had insulin resistance. In this study, it was also found that gender has a significant association with insulin resistance ($p<0.001$) (table III).

Distributions of PTH and insulin resistance among the participants were recorded (figure 1). This figure depicts that there was high insulin resistance among the high PTH group and there was a significant association between these two variables ($p=0.028$).

The associations between insulin resistance with other co-factors were analysed by using an unadjusted and adjusted logistic regression model. The unadjusted

Table III: Association between HOMA-IR and other cofactors

Parameters		HOMA IR status		p value
		(HOMA-IR < 2.6)	(HOMA-IR \geq 2.6)	
Vitamin D status	Deficiency (< 20 ng/ml)	24 (21.8%)	86 (78.2%)	0.74
	Insufficiency (20-29.9)	6 (21.8%)	22 (78.2%)	
	Sufficiency (\geq 30 ng/ml)	0	2 (100%)	
Age of respondent	Less than 30 years	12 (31.6%)	26 (68.4%)	0.074
	30 years and above	18 (17.7%)	84 (82.4%)	
Region	Urban	26 (22.8%)	88 (77.2%)	0.41
	Rural	4 (15.4%)	22 (84.6%)	
Gender	Male	20 (38.5%)	32 (61.5%)	<0.001
	Female	10 (11.4%)	78 (88.6%)	
Physical activity	Low	4 (33.3%)	8 (66.7%)	<0.001
	Moderate	22 (19.0%)	94 (81.0%)	
	High	4 (100.0%)	0 (0.0%)	
BMI	Underweight & Normal	10 (50.0%)	10 (50.0%)	0.001
	Overweight & Obese	20 (16.7%)	100 (83.3%)	
PTH	Normal (18.5-88 pg/ml)	24 (27.3%)	64 (72.7%)	0.028
	Increased (> 88 pg/ml)	6 (11.5%)	46 (88.5%)	
Serum Calcium (Corrected)	Normal (8.5-10.5 mg/dl)	30 (22.7%)	102 (77.3%)	0.128
	Low (<8.5)	0 (0.0%)	8 (100.0%)	

Table IV: Factors associated with insulin resistance, results from univariate and multivariate logistic regression

Parameters	Unadjusted OR	p-value	95% CI	Adjusted OR	p-value	95% CI
Vitamin D status						
Deficiency	ref		-	ref		-
Insufficiency	1.02	0.96	0.37 - 2.81	1.14	0.84	0.33 - 4.00
Sufficiency						
Age of the respondent						
Less than 30 years	ref		-	ref		-
30 years and above	2.15	0.078	0.91 - 5.505	1.28	0.67	0.39 - 4.22
Gender						
Male	ref		-	ref		-
Female	4.87	<0.001	2.05 - 11.56	6.05	0.001	2.03 - 17.97
Physical activity						
Low	ref		-	ref		-
Moderate	2.13	0.24	0.58 - 7.73	0.63	0.56	0.13 - 2.99
High						
BMI						
Underweight & Normal	ref		-	ref		-
Overweight & Obese	5.0	0.002	1.84 - 13.58	2.36	0.018	1.29 - 15.81
PTH						
Normal (18.5-88 pg/ml)	ref		-	ref		-
Increased (> 88 pg/ml)	2.87	0.033	1.08 - 7.59	2.58	0.01	1.66 - 41.29

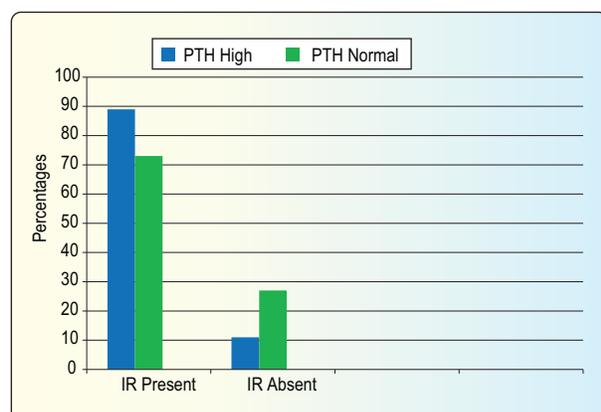
model showed that female participants, BMI, overweight and obese group, and increased PTH group were positively correlated with insulin resistance. On the other hand, the vitamin D status of the participant had no role in insulin resistance. In the adjusted model we found that females were more likely to develop insulin resistance than males [OR 6.05, 95% CI (2.03 – 17.97)]. A similar kind of findings was also found in the overweight and obese group and increased PTH

group where they were 2.36 and 2.58 times more prominent for developing insulin resistance than other counterparts (table IV).

Discussion

Vitamin D deficiency is a significant problem in this country as has been documented previously.^{16,17} Our study also showed that vitamin D insufficiency/deficiency was common among individuals with prediabetes according to Endocrine Society criteria. In this study, it was found that there was no association between vitamin D and insulin resistance among adults with prediabetes. Similar findings were also observed in other studies done in people with prediabetes.²²⁻²⁴

There are different mechanisms for the effects of vitamin D on the pancreas: the presence of vitamin D receptors on pancreatic β cells, expression of vitamin D activating 1α hydroxylase in pancreatic β cells, the insulin gene having vitamin D response element, and the transcription of insulin receptor genes being increased by vitamin D. The protective role of vitamin D on prediabetes and diabetes, may be due to its well-

**Figure 1:** PTH and IR among the adults with prediabetes

known effects, such as its anti-inflammatory properties, its effects on calcium and phosphorus metabolism and regulation of the insulin receptor gene.²⁵⁻²⁷ It has been observed that vitamin D increases in calcium content of the cells, in turn leading to increased transport of glucose into the muscle.²⁸

Vitamin D also regulates nuclear PPAR (Peroxisome proliferative activated receptor) that has an important role in insulin sensitivity.²⁹ Vitamin D deficiency is associated with increases in inflammation. Vitamin D attenuates the expression of proinflammatory cytokines involved in insulin resistance such as IL-1, IL-6, TNF- α and also downregulates NF-K β (Nuclear factor) activity.³⁰

A review by Mitri et al found that people with higher vitamin D status (>25 ng/ml) had a decreased chance of getting glucose intolerance later in life compared to those with the lowest levels (<14 ng/ml).³¹ After conducting a meta-analysis and review of the impact of vitamin D and calcium on glycemic control in patients with type 2 diabetes, Pittas et al concluded that insufficient vitamin D and calcium appears to hinder glycemic control and that supplementing both nutrients may be necessary to optimize glucose metabolism in these patients.³² This study also found that female gender has an association with insulin resistance and similar findings also observed in another study in by Bhatt et al.³³

The results of this study indicate that PTH status plays an important role in insulin resistance in the patient with prediabetes. The exact pathogenic mechanism between vitamin D/PTH and glucose intolerance is not yet understood. It has been suggested that PTH acts directly on β -cell or indirectly through augmentation of extracellular calcium intake and increase of peripheral insulin resistance.³⁴ PTH increases cytosolic calcium in pancreatic cells and induces adipocyte tissue lipolysis in a dose-dependent manner through protein kinase A phosphorylation of the hormone-sensitive lipase (HLA) results in insulin resistance.³⁵

Conclusion

The cross-sectional nature was one of the major limitations of our study. The present study had certain other limitations. Firstly, the number of study subjects, if higher, would have made the findings more significant. Secondly, the patients were from OPD of

our hospital which was not a true representative of the normal population. Thirdly, presences of confounding effect of unforeseen variables (dietary habit, solar exposure etc.) that influence the variable parameters were not included in the present study). Fourthly, Liquid Chromatography-Tandem Mass Spectrometry (LC/MS) method was not available to measure vitamin D level. To summarise, vitamin-D deficiency/insufficiency is common among individuals with prediabetes in our country. However, this vitamin-D deficiency/insufficiency was not associated with insulin resistance in individuals with prediabetes. A significant association between PTH and insulin resistance has been found. Longitudinal prospective studies are warranted to assess whether this insulin resistance in prediabetes individuals with high PTH and lower vitamin D actually results in increased progression to prediabetes and diabetes in Bangladeshi adults.

Acknowledgements

The authors express their gratitude to to Bangabandhu Sheikh Mujib Medical University (BSMMU) authority for research grant and department of biochemistry & molecular biology, BSMMU for laboratory facilities. The authors also gratefully acknowledge department of endocrinology, BSMMU for technical support.

Conflict of interest: The authors declared no potential conflicts of interest

Funding: BSMMU, Dhaka

Ethical approval: IRB, BSMMU, Dhaka

Submitted: 01 November 2021

Final revision received: 18 November 2021

Accepted: 25 November 2021

Published: 01 December 2021

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