Bangladesh Journal of Medicine (BJM)
ISSN : 1023 - 1986
eISSN : 2408 - 8366

## ORIGINAL ARTICLE

# VITAMIN D DEFICIENCY ASSOCIATED HYPERPARATHYROIDISM MAY BE RELATED WITH IMPAIRED GLUCOSE TOLERANCE WITHOUT ANY ASSOCIATIONS WITH CARDIOVASCULAR RISK FACTORS

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**Abstract**

***Introduction:*** *Secondary hyperparathyroidism due to vitamin D deficiency (VDD) is thought to play a role in glucose homeostasis. The aim of this study was to determine the association of parathormone and vitamin D with prediabetes and its different cardiovascular risk factors.* ***Methods:*** *This cross-sectional study was conducted among 117 adults with newly detected prediabetes. Participants were recruited consecutively from the Department of Endocrinology, BSMMU to measure serum 25-hydroxyvitamin D by high performance liquid chromatography, intact parathormone (iPTH) by chemiluminescent enzyme-labeled immunometric assay; fasting insulin by chemiluminescent microparticle immunoassay and glucose by glucose oxidase method to calculate homeostasis model assessment of insulin resistance (HOMA-IR).* ***Results:*** *Patients with hyperparathyroidism had significantly higher percentages of VDD than those with normal parathyroid status. Only percentages of impaired glucose tolerance (IGT) status had significant association with the combined iPTH and vitamin D groups. Serum iPTH significantly correlated with age, $HbA_{1C}$, vitamin D and HOMA-IR. Hyperparathyroidism had significant predictive association with only IGT and hypovitaminosis D in adults with prediabetes.* ***Conclusion:*** *VDD combined with high PTH may be associated with glycemic dysregulation in adults with prediabetes especially in IGT without any significant associations with its cardiovascular risk factors.*

***Keywords:*** *parathormone, vitamin D deficiency, prediabetes, impaired glucose tolerance, cardiovascular risk factors.*

*Received: 19-12-2021* *Accepted: 06-04-2022*
*DOI: https://doi.org/10.3329/bjm.v33i2.59288*

***Citation:*** *Morshed MS, Hossain MF, Ghani MH, Faisal I, Haq T, Selim S et al. Vitamin D deficiency associated hyperparathyroidism may be related with impaired glucose tolerance without any associations with cardiovascular risk factors. Bangladesh J Medicine 2022; 33: 154-160.*

**Introduction:**

The prevalence of prediabetes, which is the risk factor for diabetes mellitus (DM), has recently increased steadily to 10.1% among Bangladeshi adults with significantly higher in urban area.[1] People living in cities spending a majority of their time in indoors and hardly get enough sunlight exposure for adequate cutaneous production of vitamin D. Thus, VDD has become a major health concern in the modern society. In a recent study, we found that about 70% Bangladeshi adults with prediabetes had VDD (<20 ng/ml).[2] Prediabetes state is associated with the macrovascular complications of DM. Emerging evidence also suggests a role for mineral metabolism in cardiovascular disease (CVD) risk.Parathormone

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(PTH) is a key regulator of mineral metabolism, the homeostasis of calcium, phosphate, vitamin D, and bone turnover[3]. VDD activates the renin-angiotensin-aldosterone system and can predispose to hypertension and left ventricular hypertrophy. Additionally, VDD causes an increase in PTH, which increases insulin resistance and is associated with diabetes, hypertension, inflammation, and increased cardiovascular risk[4]. Furthermore, increased PTH is associated with higher prevalence of metabolic syndrome (MetS), independently of vitamin D status[5]. Some U.S. studies have suggested the importance of initial management in the prevention of MetS as well as CVD in prediabetic adults[6,7].

A regulatory role for PTH in the cardiovascular system is based on the findings that PTH receptors are expressed in the heart and the vessels[8]. Studies also showed the incidence of CVD were reduced after parathyroidectomy in patients with primary or secondary hyperparathyroidism[9,10]. Nevertheless the CVD risks of elevated PTH and the benefits of PTH-lowering in the general population have not been established. However, to date, no studies have established the relationship between PTH status and cardio metabolic risk in Bangladesh. So, the aim of the present study was to determine the association of PTH with cardio-metabolic risk in adults with prediabetes and also to examine whether associations of vitamin D, PTH and calcium with risk factors are independent of each other or not.

## Methods:

### *Study design:*

This cross-sectional study was conducted at Department of Endocrinology, BSMMU during the period of July 2018 to June 2019. Newly detected and untreated 117 adults with prediabetes were included in this study by consecutive purposive sampling. Exclusion criteria were: patients with current or past history of intake of vitamin D or calcium within last 120 days of sample collection; taking any medications (anticonvulsant, ketoconazole, glucocorticoids, rifampicin, isoniazid, oral contraceptive etc.) that alter vitamin D level; having any known endocrine disorders (hyperthyroidism, hypothyroidism, hyperparathyroidism, cushing syndrome etc.) affecting vitamin D metabolism; known liver (serum ALT > 2 ×upper limit of normal), renal (eGFR <60 ml/ minute/1.73 $m^2$ of body surface area), autoimmune, inflammatory diseases, malignancy or pregnancy and lactation.The study protocol was approved by Institutional Review Board, BSMMU. Written informed consent was taken from each participant. Data were collected using pretested semi-structured questionnaires and physical examination including blood pressure, waist circumference, height & weight to calculate BMI were done. Blood was taken in fasting state to measure25-hydroxyvitamin D [25(OH)D], intact PTH (iPTH), calcium, phosphate, fasting lipid profile, fasting insulin and fasting blood glucose.

### *Biochemical analysis:*

About 10 ml of venous blood was collected from each participant after an overnight 8 to 10 hours of fasting. Fasting blood glucose was measured by glucose oxidase, 25(OH)D by high performance liquid chromatography (HPLC), iPTH by chemiluminescent enzyme-labeled immunometric assay, fasting insulin by chemiluminescent microparticle immuno-assay method. 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][11]. Serum 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. Serum total cholesterol (TC)along with triglyceride (TG) were analyzed by enzymatic colorimetric assay and high density lipoprotein cholesterol (HDL-C) as well as low density lipoprotein cholesterol (LDL-C) were analyzed using homogeneous enzymatic colorimetric assay.

### *Operational definitions:*

Prediabetes was diagnosed according to American Diabetes Association, 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 $HbA_{1C}$= 5.7 – 6.4%}[12]. Vitamin D status was categorized by Endocrine Society's clinical practice guideline in to vitamin D deficiency or not with a cut-off value of 20 ng/ml[13].The cut-off point to define insulin resistance was by HOMA-IR of 2.6 and hyperparathyroidism was 65.1 pg/ml[14].

### *Statistical analysis:*

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, SD) or median (inter-quartile range, IQR) [HOMA-IR, LDL-C, TG] for quantitative values. Associations among qualitative variables were done by Chi-square or Fisher's exact test. Associations of quantitative variables between two groups were analyzed by independent-samples T test/ Mann-Whitney U test and for more than two groups by One-way ANOVA/ Kruskal-Wallis One-way ANOVA test. Correlation

between iPTH with clinical and biochemical CV risk factors were tested by Pearson's or Spearman's correlation co-efficient test. Multivariate binary logistic regression analysis was done to see the predictive association of clinical and biochemical variables with hyperparathyroid status. A two-sided p <0.05 was set as statistically significant.

**Results:**

Table I is showing the characteristics of prediabetic patients with parathyroid status. Patients with hyperparathroidism had significantly lower corrected calcium (8.94±0.39 vs. 9.27±0.45, mg/dl, p=0.003) and phosphate (3.38±0.71 vs. 3.76±0.44, mg/dl, p=0.040) and higher percentages of VDD (68.4% vs. 40.8%, p=0.042) than those with normal parathyroid status. Other characteristics were statistically similar between the parathyroid status groups.

The patients with prediabetes were divided in to four groups with the combination of parathyroid (cut-off of 65.1 pg/ml) and vitamin D status (cut-off of 20 ng/ml). None of the studied cardiovascular risk factors, were significantly different among the combination groups except IGT status which had significant association with the combined iPTH and vitamin D group [p=0.046] (Table II).

Age was positively correlated with iPTH (r=0.195, p=0.035). Serum corrected calcium (r=-0.476, p<0.001), phosphate (r=-0.414, p<0.001) and vitamin D (r=-0.237, p=0.010) were negatively correlated with iPTH. $HbA_{1C}$ (r=0.185, p=0.046) and HOMA-IR (r=0.182, p=0.049) were positively correlated with iPTH (Table III).

In binary logistic regression analysis, hyperparathyroidism had significant predictive association with only IGT [â (95% CI):4.296 (1.065, 17.323), p=0.040] and hypovitaminosis D [â (95% CI): 5.012 (1.304, 19.258), p=0.019] in adults with prediabetes (Table IV)

**Table-I**

*Clinical and biochemical profiles of adults with prediabetes according to parathormone status (n= 117)*

| Variables | Normal parathyroid status (n= 98) | Hyperparathyroidism (n= 19) | P |
|---|---|---|---|
| Age (years), mean±SD | 35.60±9.92 | 39.89±9.82 | 0.09 |
| Sex (female), n (%) | 79 (80.6) | 15 (78.9) | 1.00 |
| Smoker, n (%) | 15 (15.3) | 5 (26.3) | 0.315 |
| Physically inactive, n (%) | 47 (48.0) | 10 (52.6) | 0.804 |
| Obesity (BMI ≥25 kg/$m^2$), n (%) | 78 (79.6) | 16 (84.2) | 1.00 |
| Central obesity (M≥90 cm, F≥80 cm), n (%) | 90 (91.8) | 18 (94.7) | 1.00 |
| Hypertension (≥140/90), n (%) | 24 (24.5) | 6 (31.6) | 0.570 |
| Fasting blood glucose (mmol/L), mean±SD | 5.75±0.62 | 5.99±0.56 | 0.11 |
| 2 hours OGTT glucose (mmol/L), mean±SD | 8.14±1.67 | 7.79±1.52 | 0.40 |
| $HbA_{1C}$ (%), mean±SD | 5.72±0.39 | 5.83±0.33 | 0.27 |
| Serum corrected calcium (mg/dl), mean±SD | 9.27±0.45 | 8.94±0.39 | 0.003 |
| Serum phosphate (mg/dl), mean±SD | 3.76±0.44 | 3.38±0.71 | 0.040 |
| Hypovitaminosis D (<20 ng/ml), n (%) | 40 (40.8) | 13 (68.4) | 0.042 |
| Serum HOMA-IR, median (interquartile range) | 2.57 (1.92, 3.66) | 2.45 (1.95, 3.83) | 0.97 |
| Insulin resistance (HOMA-IR ≥2.6), n (%) | 48 (49.0) | 9 (47.4) | 0.90 |
| Hypercholesterolemia (TC ≥200 mg/dl), n (%) | 48 (49.0) | 10 (52.6) | 0.77 |
| Hypertriglyceridemia (TG ≥150 mg/dl), n (%) | 50 (51.0) | 10 (52.6) | 0.90 |
| High LDL-C (≥130 mg/dl), n (%) | 51 (52.0) | 7 (36.8) | 0.23 |
| Low HDL-C, (M<40 mg/dl, F<50 mg/dl), n (%) | 73 (74.5) | 14 (73.7) | 1.00 |
| Metabolic syndrome, n (%) | 71 (72.4) | 16 (84.2) | 0.39 |

Independent-samples T test or Mann-Whitney U test and Pearson's chi-square test or Fisher's exact test were done as appropriate

**Table II**

*The combined effect of iPTH and vitamin D status on characteristics in adults with prediabetes*

| Variables | Hyperparathyroidism | | Normal parathyroid status | | p |
|---|---|---|---|---|---|
| | Hypovitaminosis D (n= 13) | Normal vitamin D (n= 6) | Hypovitaminosis D (n= 40) | Normal vitamin D (n= 58) | |
| Age | 41.38±11.0 | 36.67±6.19 | 36.22±8.82 | 35.17±10.66 | 0.251* |
| Male sex | 4 (30.8) | 0 (0.0) | 9 (22.5) | 10 (17.2) | 0.453† |
| Smoker | 4 (30.8) | 1 (16.7) | 3 (7.5) | 12 (20.7) | 0.118† |
| Physically inactive | 6 (46.2) | 4 (66.7) | 15 (37.5) | 32 (55.2) | 0.282† |
| BMI | 29.24±4.56 | 27.46±1.83 | 28.99±4.07 | 28.89±4.71 | 0.862* |
| WC | 97.31±12.62 | 96.0±7.82 | 99.50±9.29 | 95.59±11.75 | 0.606* |
| SBP | 118.08±14.22 | 117.50±14.748 | 121.30±15.88 | 115.66±14.32 | 0.337* |
| DBP | 81.54±10.68 | 80.83±7.36 | 82.05±11.52 | 78.97±8.84 | 0.484* |
| IFG | 9 (69.2) | 6 (100.0) | 28 (70.0) | 40 (69.0) | 0.536† |
| IGT | 8 (61.5) | 2 (33.3) | 32 (80.0) | 38 (65.5) | 0.046† |
| Raised $HbA_{1C}$ | 9 (69.2) | 5 (83.3) | 27 (67.5) | 29 (50.0) | 0.165† |
| HOMA-IR | 2.45 (1.79, 4.08) | 2.49 (2.01, 3.24) | 2.75 (2.05, 3.98) | 2.41 (1.68, 3.47) | 0.644‡ |
| TC | 212.46±44.52 | 186.17±19.41 | 207.05±39.55 | 201.48±43.47 | 0.558* |
| LDL-C | 127.0 (107.0, 156.0) | 114.0 (99.45, 130.50) | 131.50 (112.0, 148.50) | 131.0 (104.0, 153.05) | 0.266‡ |
| HDL-C | 41.46±12.43 | 41.17±5.85 | 39.95±8.03 | 43.19±9.72 | 0.413* |
| TG | 194.0 (110.0, 212.50) | 136.0 (85.75, 232.0) | 162.50 (138.25, 233.50) | 143.50 (105.75, 190.0) | 0.592‡ |

Data were expressed in mean±SD or median (IQR) or frequency (%) as appropriate

*One-way ANOVA test was done; ‡Kruskal Wallis one way ANOVA test was done; †Fisher's exact test was done

**Table III**

*Correlation of clinical and biochemical variables with serum iPTH in the study population*

| Variables | r | p |
|---|---|---|
| Age (years) | 0.195 | **0.035** |
| BMI ($kg/m^2$) | 0.116 | 0.214 |
| WC (cm) | 0.165 | 0.076 |
| SBP (mm-Hg) | 0.128 | 0.168 |
| DBP (mm-Hg) | 0.124 | 0.183 |
| FBG (mmol/L) | 0.045 | 0.630 |
| 2H after OGTT glucose (mmol/L) | 0.122 | 0.191 |
| $HbA_{1C}$ (%) | 0.185 | **0.046** |
| Serum corrected calcium (mg/dl) | -0.476 | **<0.001** |
| Serum phosphate (mg/dl) | -0.414 | **<0.001** |
| Serum vitamin D (ng/ml) | -0.237 | **0.010** |
| HOMA-IR | 0.182 | **0.049**[i] |
| TC (mg/dl) | 0.049 | 0.603 |
| TG (mg/dl) | 0.063 | 0.503[i] |
| LDL-C (mg/dl) | -0.050 | 0.592[i] |
| HDL-C (mg/dl) | -0.039 | 0.680 |

Pearson's correlation test or [i]Spearman's correlation test was done

**Table IV**

*Binary logistic regression analysis of PTH status as dependent variable*

| Independent variable | Odds ratio | 95% confidence interval | p |
|---|---|---|---|
| High CV risk age (M>55, F>65 years) vs. low risk age | 0.494 | 0.059, 4.164 | 0.517 |
| Male vs. female | 1.924 | 0.255, 14.528 | 0.526 |
| Smoker vs. nonsmoker | 0.227 | 0.037, 1.374 | 0.106 |
| Physically inactive vs. active | 0.417 | 0.116, 1.496 | 0.180 |
| Obese (e”25) vs. nonobese | 0.460 | 0.061, 3.477 | 0.452 |
| Centrally obese (Me”90, Fe”80) vs. centrally nonobese | 1.522 | 0.049, 47.707 | 0.811 |
| Hypertensive (e”140/90) vs. normotensive | 0.981 | 0.242, 3.984 | 0.979 |
| IFG (e”5.6) vs. non-IFG | 0.628 | 0.125, 3.165 | 0.573 |
| IGT (e”7.8) vs. NGT | 4.296 | 1.065, 17.323 | **0.040** |
| $Hb_{A1C}$: raised (e”5.7%) vs. normal | 0.491 | 0.133, 1.818 | 0.287 |
| Vitamin D: Deficiency (<20 ng/ml) vs. not deficiency | 5.012 | 1.304, 19.258 | **0.019** |
| Total cholesterol: high (e”200) vs. optimal | 5.238 | 0.682, 40.256 | 0.112 |
| LDL-cholesterol: high (e”130) vs. optimal | 4.884 | 0.768, 31.068 | 0.093 |
| HDL-cholesterol: low (M<40, F<50) vs. optimal | 1.015 | 0.182, 5.671 | 0.987 |
| Triglyceride: Hypertriglyceridemia (e”150) vs. optimal | 1.495 | 0.358, 6.240 | 0.581 |
| Metabolic syndrome vs. non-metabolic syndrome | 1.097 | 0.107, 11.225 | 0.938 |
| Insulin resistance (e”2.6) vs. insulin sensitive | 1.365 | 0.385, 4.838 | 0.630 |
| Constant | 0.814 | – | 0.910 |

**Discussion:**

This study included 117 newly detected adults with prediabetes to see the association of iPTH and vitamin D with different CV risk factors. This study failed to demonstrate any significant association of iPTH with/without vitamin D with different CV risks in adults with prediabetes. However, iPTH had significant association with glycemic profiles indicating that hyperparathyroidism might be responsible for development of prediabetes- a well known risk factor for CVD. Significant correlation of iPTH with HOMA-IR indicates a plausible mechanism of progression from NGT to prediabetes by hyperparathyroidism mediated insulin resistance. Again significant association between iPTH with vitamin D explains role of vitamin D deficiency in the pathogenesis of prediabetes.

The pathogenic mechanism between vitamin D/PTH and glucose intolerance is not yet clarified. PTH is thought to act both directly on â-cell or indirectly through augmentation of extracellular calcium intake and byreducing peripheral insulin sensitivity[15]. 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, results in IR. Vitamin D status has been also hypothesized to be involved in the regulation of â-cell function[16].

Several large–scale observational and epidemiological data also suggest the positive association of hyperparathyroidism with abnormal glucose metabolism. In a large, epidemiological study, serum PTH was found to be positively correlated with fasting plasma glucose[17,18]. The evidence on the connection between PTH and dysglycemia has come predominately from case-control studies of patients with primary hyperparathyroidism[19]. In a large, population-based study showed, elevated PTH was independently associated with risk for diabetes among white, but not black adults[20].

In the current study, we found that, hyperparathyroidism was significantly associated with only IGT, similar findings that have been reported previously in elderly patients with prediadetes[21]. In contrast, patients with normocalcemic primary hyperparathyroidism (PHPT)do not exhibit insulin resistance and glucose intolerance in another

study[22]. The inconsistency between study results might be attributed to the heterogeneity in study designs, the tiny study samples included, the varied time intervals of follow-up, also because the different techniques used for the evaluation of glucose homeostasis.

Elevated PTH is associated with a greater prevalence of cardiovascular risk factors[23]. The results of our earlier study demonstrated that there have been higher prevalence rates of obesity, hyperlipidemia, hypertension and type 2 diabetes mellitus among PHPT patients compared with the general population and goiter patients[24]. While most evidence suggests that hyperparathyroidism causes CVD risk factors, it is possible that other factors influence both conditions.

In our study we found, no significant association of iPTH with/without vitamin D with other different cardio-metabolic risk factors (obesity, dyslipidemia, hypertension) in adults with prediabetes. The association of increased PTH with cardio-metabolic risk factor may be explained by correlations with individual components, especially high blood pressure, hyperglycemia, and low HDL-C levels[25]. However, the current literature assessing this association is inconsistent. Variations in the study populations may partly support the different results. The majority of the recent data arefrom observational, epidemiological studies that are useful for generating hypotheses but not for proving causality. It is particularly difficult to remove all the confounding variables, especially adiposity. Further research, particularly prospective studies, is needed to determine the role of PTH in the etiology of cardio-metabolic risk factors. Limitations to our study were the small sample size and cross-sectional design, which can not prove a causal relationship. We did not take into consideration of inflammatory markers which are possible intermediate confounders. Despite these limitations, to our knowledge, this is the first study to investigate the relationship between serum vitamin D, PTH and cardio-metabolic risk factors among Bangladeshi adults with prediabetes.

**Conclusion:**

Vitamin D deficiency associated secondary hyperparathyroidism may play a role in the pathogenesis of prediabetes. However, the cardio-metabolic risk factors in patients with prediabetes have no significant associations with PTH.

**Acknowledgement:**

We are grateful to Department of Biochemistry, BSMMU and Center for Advance Research in Sciences (CARS), Dhaka University for technical support.

**Financial Disclosure:**

We obtained a grant from Beximco Pharmaceuticals Limited of Bangladesh for measurement of vitamin D.

**Conflict of Interest:**

The authors stated that there is no conflict of interest in this study.

**Ethical Considerations:**

The study protocol was approved by IRB of BSMMU (*No.BSMMU/2018/4826*).

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