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RESEARCH ARTICLE

Insights into the Association of Vitamin D Deficiency with Parathyroid Hormone Levels with Relevance to Renal Function and Insulin Resistance

Iyyapu Krishna Mohan[1,*], Siraj Ahmed Khan[1], Rachel Jacob[1], K.S.S. Sai Baba[1], Tajamul Hussain[2], Salman A Alrokayan[3] and Shaik Mohammad Naushad[4]

[1]Department of Biochemistry, Nizam's Institute of Medical Sciences, Panjagutta, Hyderabad-500082, India; [2]Center of Excellence in Biotechnology Research, King Saud University, PO Box 2455, Riyadh, 11451 Saudi Arabia; [3]Department of Biochemistry, College of Science, King Saud University, PO Box 2455, Riyadh, 11451 Saudi Arabia; [4]Department of Biochemical Genetics, Sandor Life sciences Pvt Ld, Banjara Hills, Hyderabad-500034, India

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Abstract: ***Background*:** In majority of the studies inverse association between vitamin D and parathyroid hormone levels is documented.

***Objective*:** The rationale of the current study was to investigate whether this inverse association is age-dependent and whether it has any role in modulating renal function and insulin resistance.

***Methods*:** To test this hypothesis, we have carried out a hospital based study enrolling 848 subjects (558 men and 290 women) with the mean age of 50.9±15.9 y. Chemiluminometric competitive immune assays were performed using commercial kits to determine 25-OH vitamin D and parathyroid hormone (PTH) levels. Fasting glucose levels and serum creatinine were used to evaluate diabetes and renal function.

***Results*:** Vitamin D deficiency was predominant irrespective of age group (p=0.21) and gender (p=0.12). An inverse association between vitamin D and PTH was observed (r= -0.24) in middle age subjects (p=0.02). The data segregation based on plasma vitamin D levels which were <20 ng/ml, 20.1-30 ng/ml and >30 ng/ml confirmed the inverse association between vitamin D and PTH levels (p_{trend}: 0.007). Subjects with low plasma vitamin D and increased PTH exhibited elevated blood urea, serum creatinine and blood glucose. Subjects with 25-OHD deficiency showed a 3.03-folds (95% CI: 2.26-4.07) and 2.09-fold (1.41-3.10) increased risk for diabetes and renal disease, respectively.

***Conclusion*:** Based on the results of the present study, it is suggested that those with vitamin D deficiency need to be evaluated for possible presence of renal dysfunction, diabetes/insulin resistance in addition to assessing their PTH status.

Keywords: Diabetes, hyperparathyroidism, insulin resistance, parathyroid hormone, vitamin D.

1. INTRODUCTION

The incidence of vitamin D deficiency is high in India despite the fact that it is a tropical country. It is likely that high atmospheric pollution masking the UV radiation prevents conversion of 7-dihydrocholesterol to vitamin D3 thus contributing to vitamin D deficiency rickets [1]. In Asian Indians, the incidence of ergocalciferol (D2) and cholecalciferol (D3) deficiencies was reported to be 94.3%, which is attributed to lesser consumption of leafy vegetables and a high number of vegetarians [2]. Parathyroid hormone (PTH) regulates the conversion of 25-OH vitamin D (25-OHD) to its active metabolites *i.e.* 1,25-dihydroxy vitamin D2 and D3 in the kidneys. 1,25-Dihydroxy vitamin D3 binds to nuclear receptor to influence gene transcriptome pattern of target organs [3].

Lowering of calcium levels in extracellular fluids increases the secretion of parathyroid hormone from the chief cells of parathyroid gland. PTH increases osteoclasts activity resulting in resorption of calcium and phosphate ions. On the contrary, vitamin D increases absorption of calcium and phosphate in the intestinal tract leading to increased plasma calcium and lowering of bone resorption. Hence, primary hyperparathyroidism and 25-OHD deficiency are associated with renal bone disease [4, 5]. This is further supported by another study demonstrating high prevalence (82.1%) of Vitamin D insufficiency in children with chronic kidney disease [6].

Furthermore, parathyroidism in women and 25-OHD deficiency in men were reported to be associated with meta-

*Address correspondence to this author at the Department of Biochemistry, Nizam's Institute of Medical Sciences, Panjagutta, Hyderabad-500082, India; Tel: 91-9505322996; E-mail: iyyapu@gmail.com

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bolic obesity [7]. Increased risk for obesity, hypertriglyceridemia, insulin resistance and metabolic syndrome was observed in subjects with 25-OHD deficiency [8]. Diabetic subjects have diminished 25-OHD levels compared to non-diabetic subjects [9]. Short term vitamin D supplementation was shown to be lower fasting glucose levels in end stage renal disease patients [10].

In view of existing literature documenting an inverse association between PTH and 25-OHD, possible association of these two variables in modulating renal function and insulin resistance, we have aimed to investigate whether the association between PTH and 25-OHD is age dependent and whether 25-OHD levels are associated with markers of renal function and glycemic control.

2. MATERIALS AND METHODS

A total of 848 subjects (558 men and 290 women) with the mean age of 50.9±15.9 y were enrolled for this study at Nizam's Institute of Medical Sciences, a tertiary care hospital in Hyderabad, India. The subject enrollment happened in out-patient units where in patients visited the hospital for regular health checkups. The subjects volunteered for a blood draw and not received any compensation. Informed consent was obtained from all the subjects prior to enrollment. The study protocol was approved by the Institutional Ethical Committee.

Intact PTH and 25-OHD levels were measured using commercially available kits (Simens Healthcare Diagnostics Inc., U.S.A) on ADVIA Centaur® XP Immunoassay system, which utilize sandwich and competitive immunoassays, respectively based on chemiluminometric technology. PTH in the sample reacts with the first antibody which is a polyclonal goat anti-human PTH (N-terminal 1-34) antibody labeled with acridinium ester. This complex is then captured by the solid phase (a second antibody which is a biotinylated polyclonal goat anti-human PTH (39-84 region) antibody that is preformed to streptavidin coated paramagnetic latex particles). Vitamin D assay uses an anti-fluorescein monoclonal mouse antibody covalently bound to paramagnetic particles (PMP), an anti-25(OH) vitamin D monoclonal mouse antibody labeled with Acridinium Ester (AE), and a vitamin D analog labeled with fluorescein. A direct and inverse relationship exists between the amount of PTH and Vitamin D present in the patient sample and the amount of Relative Light Units (RLUs) detected by the system.

Blood glucose, urea and creatinine were measured using commercial kits based on hexokinase, GLDH and Jaffe's methods on Roche cobas c501 fully automated chemistry analyzer (Roche Diagnostics, U.S.A.). Creatinine assay uses "rate-blanking" to minimize interference by bilirubin.

Serum electrolytes (Na, K, and Cl) were analyzed using Ion-Selective Electrode (ISE) indirect method.

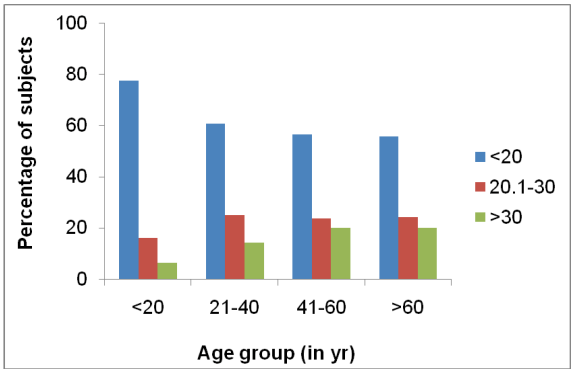
3. STATISTICAL ANALYSIS

Chi square test was carried out to evaluate the effect of age and gender on vitamin D deficiency by segregating the data as deficient (<20), borderline insufficiency (20-30) and sufficient (>30) in each age group. The association was assessed based on P value. Correlation coefficients were used to evaluate correlation between two variables. Analysis of variance (ANOVA) was used to assess whether PTH levels vary across three categories of 25-OHD ranges. Fisher exact test was carried out by computing the data based on presence or absence of variable in 25-OHD deficient vs. sufficient subjects. The data is represented in the form of odds ratio (OR) and 95% confidence interval (CI). All the statistical analyses were carried out using computational website www.statpages.org.

4. RESULTS

4.1. 25-OHD Levels Across Different Age Groups

Out of the 848 subjects enrolled for the study, 486 subjects (57.3%) had 25-OHD levels <20 ng/ml. As shown in Fig. (**1**), age wise distribution of 25-OHD categories revealed no significant association (p=0.21).



$\chi 2$: 8.42, p=0.21

No significant association with age was observed. Data was segregated into 3 groups based on 25-OHD levels (<20, 20.1-30, and >30). However, no age dependent association in 25-OHD was observed ($\chi 2$: 8.42, p=0.21).

Fig. (1). Age wise distribution of vitamin D deficiency.

4.2. Association of 25-OHD with PTH

An inverse association was observed between 25-OHD and PTH levels (r = -0.13, p<0.0001). As shown in Table **1**, segregation of data based on different age groups revealed that an inverse association is prominent in the age group of 21-40 y (p<0.001). The inverse association was further confirmed by comparing PTH levels across three groups of 25-OHD: <20 ng/ml, 20-30 ng/ml and >30 ng/ml (Table **2**).

As shown in Table **3**, inverse association was observed between PTH and 25-OHD. PTH levels showed positive association with fasting glucose, blood urea, serum creatinine and potassium while exhibiting inverse association with sodium and chloride. The 25-OHD levels correlated inversely with fasting glucose, blood urea and serum creatinine.

4.3. Association of 25-OHD with Diabetes and Renal Disease

The incidence of diabetes was higher in 25-OHD deficient group (306/486) compared to 25-OHD sufficient group (130/362). The 25-OHD deficiency is associated with 3.03 folds increased risk for diabetes (95% CI: 2.26-4.07, p<0.0001). The incidence of renal disease was higher in 25-

Table 1. Inverse association of PTH with 25OHD across different age groups.

Age group (y)	n	PTH vs vitD ® Rho	P value
0 to 20	31	-0.28	0.06
21 to 40	175	-0.23	0.001*
41 to 60	357	-0.10	0.03*
>60	285	-0.14	0.01*

n: number of subjects; Rho: correlation coefficient;

Table 2. Inverse association of PTH with 25-OHD levels.

25-OHD	n	PTH
<20 ng/ml	486	131.97±141
20.1-30 ng/ml	206	98.22±125
>30 ng/ml	156	81.24±129

n: number of subjects; F: 10.34, P_{anova}=0.0001

Table 3. Association of PTH and 25-OHD with glucose, urea, creatinine and electrolytes.

Pair	Pearson r	Spearman rho	Kendall tau
PTH;25-OHD	-0.1373	-0.2416	-0.1652
PTH;Glucose	0.166	0.2035	0.1368
PTH;Urea	0.4919	0.4906	0.3483
PTH;Creatinine	0.3689	0.4565	0.3194
PTH;Na	-0.1658	-0.2849	-0.1981
PTH;K	0.0124	0.227	0.1539
PTH;Cl	-0.205	-0.245	-0.1713
25-OHD; Glucose	-0.17	-0.3591	-0.243
25-OHD;Urea	-0.0702	-0.1366	-0.0942
25-OHD;Creatinine	0.0179	-0.1814	-0.1268
25-OHD;Na	0.0133	0.0889	0.0616
25-OHD;K	0.0151	-0.0436	-0.0302
25-OHD;Cl	0.0875	0.1238	0.0862

Green color suggests strong positive association while red color suggests strong inverse association.

OHD deficient compared to 25-OHD sufficient group (111/486 vs. 35/362). The 25-OHD deficiency is associated with 2.09 folds increased risk for renal disease (95% CI: 1.41-3.10, p<0.0001).

5. DISCUSSION

The current study demonstrates very high incidence of 25-OHD deficiency in Indian population, which is probably the prime contributing factor for the high incidence of osteopenia (52%) and osteoporosis (29%) in Indian women. This deficiency is predominant in all age groups [11]. The observed inverse association between 25-OHD and PTH, is consistent with a study on the Brazilian population [12]. However, our population exhibited higher PTH levels than the Brazilian population.

Several studies were conducted to evaluate the contributing factors towards 25-OHD deficiency. Sahu *et al.* explored the impact of exposure to sun on 25-OHD levels and observed that during summer 25-OHD levels are higher in women compared to their levels in winter [13]. Level of skin

pigmentation was reported to have inverse association with 25OHD [14]. Exposure to sun and percentage body surface area exposed were reported to have positive association with 25-OHD [15].

The importance of 25-OHD is not limited to bone related diseases alone. It is reported that 25-OHD levels are positively associated with adjusted beta cell function and insulin sensitivity index [16]. Furthermore, high level of PTH was reported to be associated with abnormal glucose metabolism resulting in higher prevalence of diabetes mellitus [17]. The binding of PTH to a G-protein coupled receptor stimulates adenylate cyclase enzyme thus increasing the production of cAMP, which results in phosphorylation of Insulin Receptor Substrate 1 (IRS-1) on serine 307 through activation of protein kinases. Reduced expression of IRS-1 and glucose transporter 4 (GLUT4) induces insulin resistance [17]. These studies are consistent with the current observation demonstrating high incidence of diabetes mellitus in subjects with 25-OHD deficiency.

The association of 25-OHD deficiency with renal disease observed in the current study can be explained based on 25-OHD deficiency dependent activation of renin-angiotensin system resulting in multiple fold elevation of angiotensin II [18, 19], which has deleterious effects on blood pressure and vasculature and thus might contribute to renal parenchymal damage.

Apart from diabetes and renal disease, PTH/25-OHD ratio was reported as a determinant of cardiovascular risk and insulin sensitivity in adolescent girls [20]. The combination of lower 25-OHD and higher PTH concentrations appeared to be associated independently with sudden cardiac death risk among older adults without cardiovascular disease [21]. 25-OH vitamin D insufficiency and elevated PTH levels were associated with increased arterial stiffness in postmenopausal women [22]. A strong positive association for leptin with PTH and inverse associations with 25-OH vitamin D and adiponectin was reported [23]. High leptin attenuates gene expression for two hydroxylases that are critical in converting vitamin D to 25-OH-vitamin D as well as 25-OH-vitamin D to $1,25(OH)_{2n}$vitamin D.

The major strength of the current study is its sample size. The limitations of the current study are: i) no documentation of bone related diseases; and ii) lack of data on glycosylated hemoglobin levels.

CONCLUSION

The current study reports high incidence of 25-OHD deficiency among Indians, which is associated with diabetes and renal disease. Based on the present study, we recommend that subjects with vitamin D deficiency need to be evaluated for the possible presence of renal dysfunction and the presence of diabetes mellitus or insulin resistance. In view of high PTH levels in 25-OHD deficient subjects, the possible presence of primary or secondary hyperparathyroidism in these subjects needs to be evaluated.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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