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Original Article

Comparison of Parathyroid Hormone and Vitamin-D Levels in Individuals with Prediabetes, Diabetes and Normoglycemia

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ABSTRACT

Objective: To evaluate levels of Parathyroid Hormone (PTH), Vitamin D and glycaemic control in individuals with diabetes, prediabetes and normoglycemia.

Study Design: Cross-sectional study.

Place and Duration of Study: Department of Chemical Pathology, Combined Military Hospital, Quetta Pakistan from Jan to Jun 2020.

Methodology: We included subjects with diabetes, prediabetes, and normoglycemia and were divided into three groups i.e., normoglycemic, prediabetics, and diabetics based on their Fasting Plasma Glucose and Glycosylated Haemoglobin (HbA1c) levels. They were further divided into subgroups based onsubjects' Vitamin D and Parathyroid Hormone levels.

Results: Vitamin D was deficient in all groups. Patients with prediabetes with Vitamin D deficiency had raised Parathyroid Hormone levels but patients with Vitamin D insufficiency had normal Parathyroid Hormone levels. Patients with diabetes with Vitamin D deficiency had raised Parathyroid Hormone while patients with Vitamin D insufficiency had normal Parathyroid Hormone levels. Healthy subjects with Vitamin D deficiency or insufficiency had normal Parathyroid hormone. About 90% of diabetics had Vitamin D deficiency and raised Parathyroid hormone with HbA1c>7% while 10% were with Vitamin D insufficiency and normal Parathyroid hormone level with good glycaemic control (HbA1c<7%).

Conclusion: Vitamin D was deficient in all groups suggesting the importance of Vitamin D supplementation. Patients having raised Parathyroid hormone levels and Vitamin D deficiency have glycaemic dysregulation in prediabetics and diabetics. It signifies the importance of measuring Vitamin D and PTH levels in Diabetes Mellitus, particularly response of Parathyroid hormone towards diabetics.

Keywords: Diabetes, Glycosylated haemoglobin (HbA1c), Normoglycemic, Parathyroid hormone (PTH), Prediabetics, Vitamin D.

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INTRODUCTION

Diabetes and prediabetes are prevalent world-wide and its prevalence is increasingday by day. In 2017 about 451 million people had diabetes globally and number is to increase to 693 million by the year 2045.[1] Many factors contribute to an increase in diabetes and pre-diabetes, especially in younger age groups. Most important of them include an increase in sedentary lifestyle and increased consumption of processed food. In Pakistan too, its prevalence is on a surge. Inyear 2019 the prevalence of diabetes was about 16.98% and that of prediabetes was 10.91%.[2]

Importance of Vitamin D in bone metabolism is adequately studied and current evidence suggests that it is critical for bone health.[3] But evidence forthe presence of Vitamin D receptors (VDR) in most tissues and cells in the body has provided an insight about role of Vitamin D in important systems of body function like nervous, immune and cardiovascular system, and cell signalling processes.[4] Role of Vitamin D in diabetes, glycaemic controland prevention of micro and macrovascular complications is extensively studied with variable outcome.[5]

Vitamin D deficiency has been implicated in pathogenesis of Diabetes Mellitus (DM) suggesting that it leads to glucose intolerance and improper insulin secretion resulting in the disease.[6] It is also suggested in many studies that Vitamin D supplementation in diabetic patients on treatment results in improving glycemia and secretion of insulin, highlighting the significance of Vitamin D in Diabetes.[7] Moreover, It has been suggested that PTH has a role in the pathogenesis of insulin resistance, metabolic syndrome, B cell dysfunction, and Diabetes , the exact mechanism is still not clear but many researchers point

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towards a causal relationship.[8] Several studies have been conducted showing that low level of Vitamin D results in abnormal HbA1c in Diabetes.Vitamin D supplementation in such patients result in good glycaemic control showing that there is a causal association between Vitamin D levels and glycaemic control.[9,10] However, no significant research has been done on Vitamin D and PTH levels in bothpatients with diabetes and prediabetes.The objective of our study was to compare the levels of Vitamin D and PTH in diabetics, prediabetics and normoglycemic subjects.

METHODOLOGY

The cross-sectional study was carried out at department of Pathology, Combined Military Hospital Quetta Pakistan, for 6 months from January 2020 to June 2020 after approval of the Research protocol by the Institutional Review Board (IRB#042).

Inclusion Criteria: Patients of either gender with prediabetes, diabetes and normoglycemic levels were included in study. Prediabetes, diabetes, and normoglycemicpatients were diagnosed based on American Diabetes Association (ADA) criteria.[11]

Exclusion Criteria: Patients with history of impaired renal function, on Vitamin D supplementation, subjects with history of hormonal disorders like Cushing Syndrome, hyper/hypothyroidism and acromegaly, and conditions that affect Vitamin D metabolisms like malabsorption syndrome and chronic renal failure, were excluded.

Sample was collected using non-probability convenient sampling technique after taking informed written consent from each subject. Sample size of 319 was calculated using given formula of World Health Organization (WHO) sample size estimation [n=z2P(1-P)/d2]. A panel of biochemical tests was used, including serum total calcium, phosphorus, albumin, alkaline phosphatase (ALP), 25(OH)D, plasma iPTH, fasting plasma glucose and HbA1c. Serum creatinine and ACR were analysed to rule out kidney disease. Serum ALP was done to rule out liver and bone disease. A self-generated questionnaire was used to assess demographic data. Venous blood samples were collected after overnight fasting (10-12 hours) to standardise sample collection and to cater for diurnal variation and dietary effects. About 12ml blood was collected in serum gel separator tube, lithium heparin tube, sodium fluoride tube and ethylenediamine tetra acetic acid (EDTA) tube. Potassium EDTA tubes were used for sampling of plasma iPTH levels, and the samples were transported to the laboratory in icepacks. Refrigerated centrifugation was carried out and the blood samples were analysed within 20-30 minutes of collection. HbA1c sample was also collected in separate Potassium EDTA tube. Sodium Fluoride tube was used for collection of glucose sample. Serum calcium, phosphorus, ALP, albuminand creatinine were analysed on fully automated random-access discrete chemistry analyser (ADVIA 1800, Siemens Healthcare Diagnostics Inc. New York, United States [USA]). Plasma iPTH was carried out by fully automated random access two-site chemiluminescent enzyme labelled immunoassay (Immulite 2000, Siemens Healthcare Diagnostics Inc. New York, USA) with an intra-assay precision of 4.2-5.7% and inter-assay precision of 6.3-8.8%, linearity of 263 pmol/l and detection limit of 0.3pmo/l (kit lot number 327 and 328). Total Vitamin D quantification was performed by competitive chemiluminescence immunoassay (Advia Centaur, Siemens Healthcare Diagnostics Inc. New York, USA), with an inter-assay precision of 3.0-5.3% and intra-assay precision of 4.2-11.9%, linearity of 374 nmol/l and detection limit of 8.0 nmol/l. Manufacturer-provided controls were run for all analytes in each batch of analysis for internal quality control. Plasma glucose was analysed by photometry on chemistry analyser ADVIA 1800. HbA1c was analysed by Capillary Electrophoresis onSebia CAPILLARYS-2 FLEX-PIERCING.Serum corrected calcium was used instead of serum total calcium in case of low albumin levels (<40g/L) by using the formula measured calcium±0.02 (40-albumin). Data were analysed using SPSS 24 and Microsoft Excel 365.For statistical analysis of data, patients were divided into three groups of normoglycemic, prediabetics, and diabetics based on their FPG and HbA1c levels according to the ADA criteria. Subjects were further divided into subgroups based on their Vitamin D levels and PTH. Based on Vitamin D levels they were grouped as: those with Vitamin D level <25 nmol/l labelled as deficient; insufficiency was between 25-75 nmol/l and sufficiency was 75-250 nmol/l. Similarly, subjects were divided into three categories based on PTH levels: low with PTH <0.8 pmol/l, normal with PTH 0.8-6.0 pmol/l and high when PTH was >6.0pmol/l.The effects of gender and age on PTH and Vitamin D levels were evaluated through independent sample T test and spearmen correlation.Kruskal Wallis test was used to compare the levels of Vitamin D and PTH among three groups. Independent sample t-test was applied to compare age and gender with the variables.

RESULTS

The result was comparable in terms of their Vitamin D and PTH status. All groups were deficient in Vitamin D irrespective of their diabetic status. Of the 319 subjects, 208(65%) were male and 111(35%) were female. Overall mean age was 51±20 years. Among these subjects 181(57%) individuals were from rural areas and 137(43%) were from urban areas.We did not find any significant effect of age and gender on PTH and Vitamin D levels..Outof these 319 participants included in the study 111(34.8%) were normoglycemic, 110(34.4%) were prediabetics and 97(30.8%) were diabetics. Among the prediabetic group, 27% of participants were insufficient in Vitamin D and 81% were deficient in Vitamin D, while 29% had normal PTH and 80% had raised PTH levels. In the diabetic group 24% were insufficient while 73% were deficient in Vitamin D, while 93% of subjects had raised PTH levels.

Table-I: Association of Age and Gender with Vit D & PTH (n=319)

Variable	Vitamin D (*p*-value)	PTH (*p*-value)
Age	0.947	0.842
Gender	0.574	0.153

Healthy subjects with Vitamin D deficiency or insufficiency had normal PTH levels. Participants with Vitamin D deficiency and raised PTH have increased fasting plasma glucose. Among diabetics 90% had Vitamin D deficiency and raised PTH with HbA1c >7% while 10% were with Vitamin D insufficiency and normal PTH level with good glycaemic control (HbA1c<7%). Result of mean values of fasting plasma glucose iPTH and Vitamin D levels showedsignificant association (p<0.001) among the three groups.

N is normal of subjects, FPG Fasting Plasma Glucose, HbA1c Glycosylated haemoglobin, PTH Parathyroid Hormone.

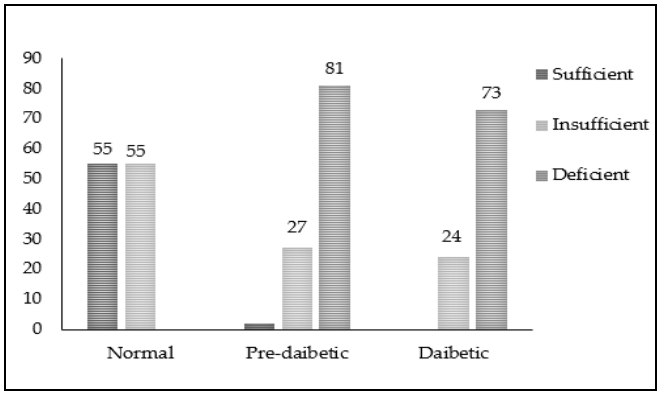

Figure-1: Level of Vitamin D in Patients with Diabetes, Prediabetes and Normoglycemia (n=319)

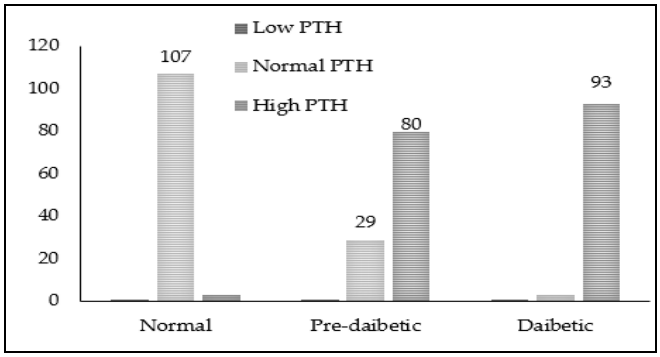

Figure-2: Level of Parathyroid Hormone in Patients with Diabetes, Prediabetes and Normoglycemia (n=319)

DISCUSSION

It has been observed in our study that Vitamin D is deficient in all groups, irrespective of their diabetic status suggesting the importance of Vitamin D supplementation in our general population. About half of Pakistani population is deficient in Vitamin D, as has been reported in many local studies.[12] Prevalence of Vitamin D deficiency has been increased in our population irrespective of age. Local studies suggest that 90 percent of our population between age 18-23 are deficient in Vitamin D.[13]

Table-II: Median and range of Variables in Patients with Diabetes, Prediabetes and Normoglycemia (n=319)

Variables	Normoglycemic N=111				Pre-diabetics N=110				Diabetics N=97				*p*-value
	Median	Inter Quartile Range (Percentile)			Median	Inter Quartile Range			Median	Inter Quartile Range			
		25	50	75		25	50	75		25	50	75	
Vitamin D nmol/l	69.5	35	69	131	20	15	20	35	19	14	19	20	<0.001
PTH pmol/l	4.0	1.5	4	5.9	17	5	17	29	21	15	21	32	<0.001
Calcium mmol/l	2.39	2.3	2.3	2.5	2.3	2.2	2.3	2.3	2.2	2.3	2.3	2.5	0.250
Phosphorous mmol/l	1.3	0.9	1.2	1.2	1.2	0.9	1.2	1.3	1.2	1.0	1.2	1.2	0.87

In our study, Patients with Prediabeteswith Vitamin D deficiency had raised PTH levels but patients with Vitamin D insufficiency had normal PTH levels.Amongpatients with diabetesthose with Vitamin D deficiency had raised PTH levels while patients with Vitamin D insufficiency had normal PTH levels. Healthy subjects with Vitamin D deficiency or insufficiency had normal PTH Hormone levels. These result shows that PTH has a role in glucose homeostasis in patients with diabetes and prediabetes. In our data no significant change was observed in calcium and phosphorous suggesting there might be some mecha-nism or role of hyperglycaemia in counteracting the effect of PTH and it needs to be evaluated further.

Similar to our study Karras *et al*. performed a cross-sectional study in old prediabetic patients and signified that Prediabetics with vitamin D deficiency and raised PTH also had raised HOMA-IR suggesting insulin resistance in such patients, which suggests that PTH has a role in effecting the glycaemic control in old patients with Prediabetes especially when it is combined with vitamin D deficiency and assessment of both markers 25(OH)D and PTH.[14] And these concentrations have more significance in showing the glucose homeostasis in prediabetic individuals than either marker alone.

A pilot study by Karras *et al*. wasconducted to see the effect of high PTH and prediabetics on glycaemic control and compared with prediabetics with normal PTH.[15] Resultsrevealed that high PTH in prediabetics result in high fasting plasma glucose level suggesting the role of PTH in causing deranged plasma glucose level. Similarly, Nachankar *et al*. conducted a study in pregnant women and suggestedthat raised level of PTH was associated with gestational diabetes and insulin insensitivity, butthe effect of Vitamin D in gestational diabetes was insignificant, suggesting that PTH has a role in effecting glycemia independent of Vitamin D status.[16]

Hussain *et al*. studied the response of Parathyroid gland to Vitamin D deficiency in patients with diabetes.[17] Results showed that not all participants with Vitamin D deficiency had raised PTH levels, and raised level of PTH was found in severe Vitamin D deficient groups in both diabetics and normoglycemic,a finding that suggests that there should be a new criterion for diagnosis and treatment of diabetic patients with low Vitamin D levels, and signifies the role of PTH testing in such patients.

In contrast to our study, Bora *et al*. conducteda study in India which showed no relationship of Vitamin D or Parathyroid Hormone in effecting glucose level in known diabetic patients.[18] This suggested that there were other factors which affected glucose homeostasis in known diabetics. Non-parametric data and cross-sectional nature of our study which did not help to establish a cause and effect relationship was a limitation of our study.

CONCLUSION

In conclusion, our population is generally deficient in Vitamin D and there is a need of supplementing the diet with VitaminD in our general population. There is a relationship between the levels of Vitamin D, PTH and diabetic status, suggesting the importance of measuring VitaminD and PTH inpatients with diabetes and Prediabetes.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

AK & NA & TAK: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

AK & MY & QUA: Data acquisition, data analysis, concept, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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