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VITAMIN D STATUS:A LINK BETWEEN BLOOD GLUCOSE AND RENAL FUNCTION INDICATORS

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ABSTRACT

Hypovitaminosis D is a widespread disorder targeting the current population across the world in general and developing countries in particular.Although UV radiation from sunlight is abundant in the tropical countries,malnutrition and skin pigmentation may be the principal cause for vitamin insufficiency in these regions.In addition to causing bone degeneration,vitamin D insufficiency is implicated in metabolic diseases like dyslipidemia,diabetes mellitus,endocrine dysfuntion like thyroid disorders and organ damage like liver and kidney disorders.One of the most common complications of diabetes mellitus is renal damage. This study focusses on the correlation of serum vitamin D levels with renal function in subjects with normal and elevated fasting blood glucose.Study group of 75 patients were categorized as Group1:Vitamin D sufficient(>30ng/ml); Group2:Vitamin D insufficient(20-30ng/ml) and Group3: Vitamin D deficient (<20ng/ml). Fasting glucose, serum creatinine and eGFR were estimated in serum of these subjects. Results indicated that elevated glucose was predominantly seen in Groups 2 & 3.A significant negative correlation of vitaminD levels with blood glucose in Groups 2&3 was observed which was more prominent in group3. A significant negative correlation between vitaminD and serum creatinine levels and a positive correlation between vitaminD and eGFRwere also observed in group 3.However age of the population did not appear to be a significant factor in this correlation study.Therefore this study establishes the fact that chronic complications of diabetes mellitus,particularly,renal damage may be aggravated with decreasing vitamin D levels.

KEY WORDS: **Vitamin D, e GFR, Impaired glucose tolerance, Creatinine**

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INTRODUCTION

Type 2 Diabetes mellitus is a metabolic disease that has established itself as a major cause of morbidity and mortality in the present day population mainly due to the inflammation associated with it.The link between vitamin D levels and Type 2 diabetes mellitus initiated with the identification of vitamin D receptor in the pancreas about 2 decades ago[1], following which the expression of 25 hydroxy vitaminD_3 1 alpha hydroxylase in pancreatic islets was reported[2].Vitamin D injections in animal studies decreased glycosylated haemoglobin[3] .Cross sectional study involving elderly population has also revealed the inverse association of HbA1c with vitamin D[4]. Vitamin D and calcium homeostasis appears to play a crucial role in glucose metabolism based on the following studies. Calcium is required for release of insulin from its storage granules[5].Changes in ionic calcium across the cell membrane may be the cause for cytokine induced apoptosis in beta cells.Calcium dependent phosphorylation of insulin receptor may result in impaired insulin signal transduction and therefore decreased GLUT-4 activity in skeletal muscle and adipose tissue [6].Chronic effects of type2 diabetes mellitus like nephropathy, neuropathy and retinopathy are well documented.This study focuses on the association of renal complications in impaired glucose tolerance subjects with vitamin D status based on the changes in serum levels of creatinine and eGFR, the indicators of renal damage.

MATERIALS AND METHODS

Inclusion criteria:Study population included 75 non hospitalized patients (42females & 33males) in the age group 24-79yrs who visited the OPD for routine health check up .Exclusion criteria: Patients who were t on vitamin D supplementsand who were diagnosed to have any type of kidney disorders or any other systemic illness. The study was approved by the institutional ethical committee.Informed consent was taken from all subjects.Vitamin D was estimated based on competitive principle by ECLIA[7].Blood glucose was estimated by glucose oxidase method and serum creatinine by Jaffe's method[8].eGFR values were obtained from the MDRD formula[9] as follows:eGFR(ml/min)= $1.86x(Pcr)^{-1.154}$ $x(age)^{-203}$.The study population was further categorized into 3 groups based on their vitamin D values.

Group 1: Vitamin D sufficient (>30ng/ml)
Group2:Vitamin D insufficient (20-29.9ng/ml)
Group 3:Vitamin D deficient (0-20ng/ml)

Serum creatinine, Blood glucose and eGFR were compared in the 3 groups using ANOVA followed by Post hoc Tukeys test. p value ≤ 0.05 was considered significant. Correlation of the various parameters between the groups was done by Pearson's correlation.

RESULTS

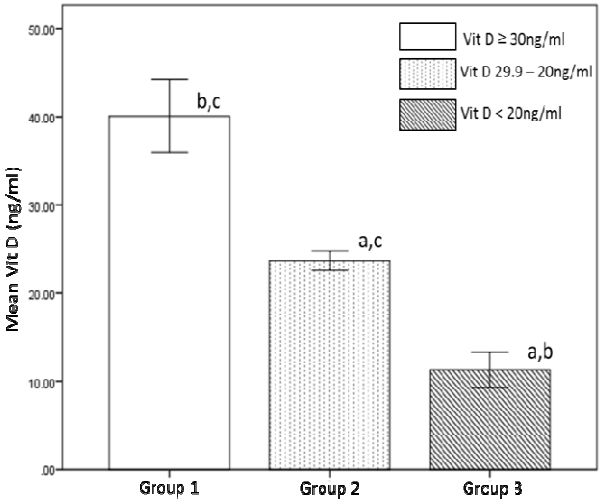
Mean values ofblood glucose was found to be highest in group 3, the vitaminD deficient group. Mean values for serum creatinine was higher in group 2 & 3 and mean eGFR was found to be higher in group1 compared to other groups,although the values were statistically nonsignificant (Table1).Further, correlation studies between thegroups, indicated that there was a negative correlation between vitamin D and blood glucose, vitaminD and serum creatinine and a positive correlation between vitamin D and eGFR, of which the correlation was significant with respect to blood glucose. This correlation was stronger in group2($p<0.05$)and strongest in group3($p<0.02$).A significant negative correlation between vitamin D and serum creatinine($p=0.013$) and a positive correlation between vitamin D and e GFR($p=0.029$) were observed in group 3(Table 2). Number of patients with prediabetes was higher in group 3(n=11), compared to group 2(n=7); although mean glucose levels appear to be in the diabetic range in Group 3(Fig 2).

Table 1

	Group 1 (n=25)	Group 2 (n=25)	Group 3 (n=25) Vit D(0-20ng/ml)
Age (years)	48.5±14	49.2±18.3	47.2±16.4
Vit D (ng/ml)	$40±10^{b,c}$	$23.6±2.6^{a,c}$	$11.3±4.8^{a,b}$
Glucose(mg/dl)	109±26	119.7±40.7	125.5±65.2
Serum Creatinine (mg/dl)	0.86±0.17	0.96±0.34	0.93±0.5
eGFR (mL/min/1.73 m^2)	96.3±22.8	90.9±49.1	94.2±43

a (p<0.05) comparison with group 1, b (p<0.05) with group 2 and c (p<0.05) with group 3. p-Values by ANOVA followed by Post Hoc Tukeys test

Figure 1
Error bar showing comparison of Vit D in different groups.



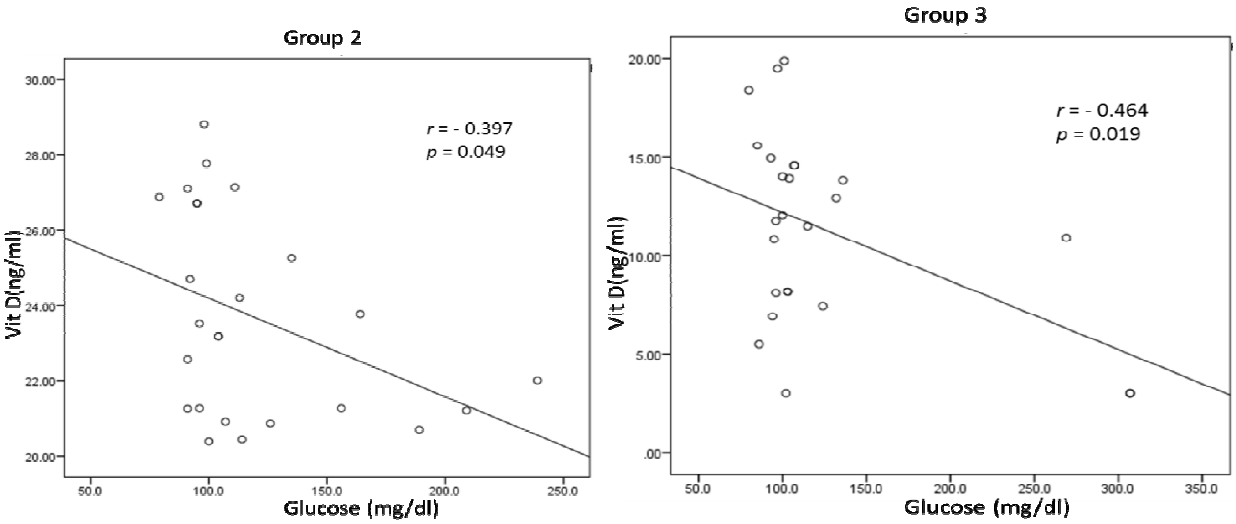
a (p<0.05) comparison with group 1, b (p<0.05) with group 2 and c (p<0.05) with group 3. p-Values by ANOVA followed by Post Hoc Tukeys test

Table 2
Pearson's Correlation between groups

			Age (years)	Glucose (mg/dl)	Creatinine (mg/dl)	eGFR (mL/min/1.73 m^2)
Vit D (ng/ml)	Group1	*r*	0.358	-0.243	0.039	-0.221
		p	0.08	0.241	0.85	0.287
	Group2	*r*	0.022	-0.397*	-0.101	0.147
		p	0.917	0.049	0.631	0.48
	Group3	*r*	-0.339	-0.464*	-0.49*	0.437*
		p	0.09	0.019	0.013	0.029

***p<0.05;significant**

Figure 2
Scatter Plot between Vit D and blood glucose



DISCUSSION

The results of our study throws light on the fact that prediabetes and diabetes is more prevalent in vitamin D insufficient and deficient groups.Similarly, markers of kidney disease namely eGFRshowed a significant positive correlation and serum creatinine a significant negative correlation in vitamin D deficient groups as compared to vitamin D sufficient group,although the values were in the normal range. A higher mean GFR in group 3 in relation to group 2,may be attributed to the lower mean age in group 3 which was higher than group 2.Since vitaminD has several important mechanisms that are linked to insulin secretion[5,6],it is evident through our results that vitamin D deficiency could be involved in the development of prediabetes and diabetes thereafter. Our findings are in agreement with the reports of Kayaniyil etal[10] who have stated a positive correlation between 25(OH) D and Insulin sensitivity index for

OGTT, a significant negative association between 25(OH)D and HOMA-IR, as well as significant positive association between 25(OH)D and ß cell dysfunction calculated by dividing Insulinogenic index and insulin secretion sensitivity index . In support to this observation, certain animal studies indicate that 25(OH)D_3activated the invitro production of insulin by rat pancreatic beta cell as well as activated conversion of proinsulin to insulin [11]. On the contrary,insulin sensitivity did not improve with oral vitamin D supplementation in prediabetic patients [12].Similar paradoxical findings have also been reported with respect to diabetes. A very recent systematic review of interventional studies by NigilHaroonetal[13]suggested that supplementation of vitamin did not improve glycemic control, insulin resistance and beta cell dysfunction.These findings point to the fact that the impaired glucose metabolism observed in vitamin D deficiency cannot be reverted by supplementation of vitamin D[14].Diabetes mellitus triggers events that lead to inflammatory damage to the kidneys culminating in diabetic nephropathy[15] .Recent study reports state that incidence of CKD in prediabetics is also quite high[16]. The molecular mechanisms underlying diabetic nephropathy include activation of TGF-ß, NF-kß and MAPK signaling pathways which along with advanced glycation end products is responsible for activation of renin–angiotensin system and vascular endothelial growth factors resulting in modification of extracellular matrix proteins leading to hypertrophy of the kidney tissue and apoptosis of the kidney,particularly glomerulus resulting in decreased GFR[17] . Low levels of vitamin D was associated with macro albuminuria while supplementation of vitamin D decreased microalbuminuria in Chinese type2 diabetic patients with nephropathy [18].However,the results of meta analysis conducted by Hoda[19]showed that although there is an inverse relation between vitamin D status and diabetic nephropathy in cross sectional studies , clinical trials indicated that there is no improvement in diabetic nephropathy after supplementation with vitamin D .It is also true that there is impaired glucose metabolism in chronic kidney disease. VitaminD is found to improve insulin secretion and sensitivity in hemodialysis patients [20]. Insulin resistance is present in early stages of kidney diseases and has an inverse relation with 25(OH) D levels as stated by Chonchol and Scragg[21].Therefore vitamin D seems to play a crucial role in maintaining a delicate balance between glucose homeostasis and maintaining the normal function of the kidneys.A positive association of eGFR and a negative association of serum creatinine levels in vitamin D deficient group in our work are in accordance with the above findings. Current research on vitamin D considers it to be an immune molecule. Mechanisms that support this finding are inhibition of lipopolysaccharide induced p38 activation and production of inflammatory cytokines like IL6 and TNF-α[22] by vitaminD,reduction of inflammation by inhibition of TGF-ß signaling,inhibition of NF-kß and p38 MAPK pathways[23].Since vitamin D has an inhibitory effect on these pathways, Vitamin D deficiency may be one of the factors causing the precipitation of the multifactorial inflammatory damages to organs, due to poor control of blood glucose levels.

CONCLUSION

Outcome of the study suggests that vitamin D deficiency may impair fasting glucose levels leading to the development of prediabetes and diabetes thereafter and may also have a role to play in the pathogenesis/progression of kidney damage in these patients.However,since the study was conducted on a small group of patients, further studies are needed to establish the link between hypovitaminosis D and complicationsl of diabetes mellitus.

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