Original Article

ASSOCIATION OF VITAMIN D DEFICIENCY AND NEW ONSET TYPE-2 DIABETES MELLITUS

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ABSTRACT

Objective: To determine the association between vitamin D status in newly diagnosed patients with type-2 Diabetes mellitus.

Study Design: Comparative cross sectional study

Place & Period of Study: Department of Pathology and Department of Internal Medicine of Sheikh Zayed Hospital and Medical College, Rahim Yar Khan; from Januarary2015 to November 2015.

Method and Material: Ninety-seven newly diagnosed diabetics (subjects)and 93 non-diabetic persons (controls) were divided on the basis of their 25-hydroxyvitamin D_3 (25OHD) levels in three groups, normal (>31 ng/ml), insufficient (20-31ng/ml) and deficient (<20ng/ml). 25OHD was measured by electrochemiluminescence using - Cobas e 411. Their fresh Fasting Plasma Glucose (FPG) was also estimated by hexokinase method on Beckman coulter AU 480.

Results: Vitamin D levels were inversely correlated with frequency of diabetes mellitus ($r=-0.20$; $p<0.01$) with an Odd Ratio of 3.59 (95%confidence interval 1.29 to 8.70). Frequency of diabetes mellitus was significantly higher in vitamin D deficient patients as compared to patients with normal vitamin D status ($p<0.05$).

Conclusion: The chance of diabetes mellitus increases with worsening state of vitamin D.

Keywords: Vitamin D, Diabetes mellitus.

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INTRODUCTION

The so called sunshine “Vitamin D” plays an important role in the pathogenesis of skeletal disorders and calcium homeostasis, but its deficiency also results in the development of several chronic conditions [1,2]. The discovery of vitamin D receptors (VDR) in almost all the tissues has led to the identification of role of vitamin D in many systems of the body, instead of merely associated with bone disorders [3]. Like other steroid hormones, the mechanism of action of the active form of vitamin D is mediated by its binding to the specific vitamin D receptors (VDR) VDRs have been identified in various tissues, not just in those that participate in the classic actions of vitamin D such as bones, intestines and kidneys, and the enzyme responsible for converting 25 hydroxy Vitamin D [25 (OH)D] to 1,25 Dihydroxy Vitamin D [1,25(OH)2D] is also expressed in a variety of extra-renal sites, such as endothelial cells, beta cells, and immune cells [4].

Vitamin D deficiency and diabetes both share the same traits, as these two diseases are almost pandemic. The International Diabetes Federation has estimated the number of people with diabetes worldwide to be nearly 285 million, or 7% of the world's population and it is expected to exceed 435 million by 2030 [5]. In Pakistan, the prevalence of vitamin D deficiency has been reported upto 92% in ambulatory patients in various situations [6,7]. Low vitamin D not only impairs the secretion of insulin from pancreatic cells but also increases insulin resistance [8,9]. These two factors play major role in the development of type 2 diabetes mellitus [10]. Diabetes mellitus is becoming the world-wide epidemic as is shown by the incidence of type 2 diabetes mellitus (T2DM) which is increasing at an alarming rate both nationally and worldwide, with more than 1 million new cases per year diagnosed in the United States alone. Diabetes is the fifth leading cause of death in the United States, and it is also a

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major cause of significant morbidity [11]. According to the International Diabetic Federation (IDF) database on Diabetics, Pakistan currently stands at number seven in the list of countries with the highest number of Diabetic cases. The Diabetic population in Pakistan was estimated at 6.9 million in 2007 and it is projected to reach 11.5 million by the year 2025 with Pakistan ranking 5th in the IDF list [12].

There are only a few cross-sectional studies which have shown the epidemiological evidence of an association between vitamin D deficiency and type 2 diabetes [13-18]. The only prospective study demonstrating the effect of vitamin D deficiency on the incidence of T2DM was based on the intake of vitamin D [19]. Vitamin D intake is a weak proxy measure of vitamin D status while the tissue vitamin D gives a more reliable result [20]. The inverse association between vitamin D and dairy intake and the risk of T2DM may be due to the fact that dairy products are high in more readily absorbable calcium and are often fortified with vitamin D. Vitamin D deficiency is positively associated with insulin resistance and T2DM; however, more research is needed to understand this relationship [21].

A negative correlation between serum glucose and insulin levels with 25OHD and a positive correlation with insulin sensitivity has been observed in several human and animal model studies [22]. It has also been observed that vitamin D supplementation can improve insulin secretion and reduce insulin resistance in T2DM and non-diabetic subjects [23]. Thus, accumulating the evidence from several studies, vitamin D is likely to have a role in T2DM and haemoglobin glycation [24].

There are only a few studies in our country to document the association between these two common metabolic disorders. This study, therefore, will focus on the role of vitamin D as an environmental factor in T2DM. It will help future researchers to suggest a protective role and the possible mechanisms by which this protection may occur.

MATERIAL AND METHODS

In our study, there were 97 patients with new onset T2DM as study population and 93 non-diabetic persons as controls. The subjects were selected by non-probability convenience sampling out of the patients referred for vitamin D estimation. The sample population consisted of patients with normoglycaemia (NG) i.e. control group, and DM. NG was defined as Fasting Plasma Glucose (FPG) <100 mg/dl, IFG: 100-126 mg/dl and DM >126 mg/dl (Position Statement-American Diabetic Association-2009) (25). Similarly, on the basis of their 25OHDlevels in blood the subjects were clustered in three groups, normal (>31 ng/ml), Vitamin D Insufficient (VDI) (20-31ng/ml) and Vitamin D Deficient(VDD) (<20ng/ml) (26). 25OHD was measured by using electro chemiluminescence technique on cobas e 411 while glucose were estimated by glucose Hexokinase G6PD-DH method on Beckman coulter AU 480.Both of these parameters were estimated after ensuring the quality control on each instrument by a qualified and well trained technologist.

Statistical analyses: The data was recorded in SPSS 16 and frequencies of various groups of subjects according to Vitamin D status were determined. Comparison of frequencies was carried out using Chi Square test and continuous data was compared by students` t test i.e. comparison of frequency of DM in various groups of Vitamin D status. Then correlation studies were carried out between FPG and 25OHD levels using Pearson`s Correlation Coefficient. VDD and VDI of vitamin D status groups were combined and IFG and DM of glucose categories were combined and then 2x2 table was constructed for comparison and calculation of Odd Ratio (OR) using chi-square test.

RESULTS

There was a slight male preponderance in the study population (67% male vs 33% females). On the other hand, in healthy control group 46% were male and 54% were females. Majority of the subjects and control groups belonged to the age bracket of 31 to 70 years. Ethnicity analysis of the study population as shown in Table-1 indicated vast majority of subjects and controls were Urdu speaking. Other study parameters of the subjects and controls like dwelling and education are also given in Table-1.

Vitamin D inadequacy and vitamin D deficiency (VDI and VDD) were found among 78% of the cases in study population while 22 % had normal vitamin D level; while 29% of the controls had vitamin D deficiency and 71% had normal vitamin D level ($p<0.005$) (Table 2). Similarly, more patients with DM were found in VDD (87%) and VDI (67%) groups as compared to subjects with normoglycaemia (13% and 33%), respectively (Table-2). This difference was found statistically significant ($p<0.001$). A gradual worsening of glycaemic condition was found on progressing from normal vitamin D status to VDI and VDD (Figure-1). Vitamin D levels were inversely correlated with frequency of DM ($r=-0.20$; $p < 0.01$) (Table-3). Table 3 shows that Vitamin D inadequacy was far more likely in the DM category with OR: 3.59 (95% confidence interval 1.29-8.70).

Table-1: Study parameters of the subjects and controls.

Parameter	Subjects (DM) (n =97)	Controls (NG) (n = 93)	P Value
Gender	Male: 64 Females: 33	Male: 46 Females: 47	P < 0.01*
Age	Median: 50 years IQR: 15	Median: 53 years IQR: 16	P =0.25**
Ethnicity	Punjabi: 9 Siraki: 7 Pushto: 1 Urdu: 80	Punjabi: 40 Siraki: 0 Pushto: 0 Urdu: 53	P < 0.01*
Dwelling	Rural: 11 Urban: 86	Rural: 0 Urban: 93	P < 0.01*
Education	Illiterate: 12 Literate: 85	Illiterate: 90 Literate: 3	P < 0.01*

*By applying chi-square test, **By applying independent sample median test

Table 2: Distribution of various glycaemic groups in subjects with different vitamin D status.

Vitamin D Status	No of subjects (n=190)	Controls (Normoglycaemia) (FPG < 5.6 mmol/L)	DM (FPG > 7.0 mmol/L)	Significance levels (Chi Square Test)
Normal (>30ng/ml)	n=88	66 (76%)	22 (24%)	Normal and insufficiency group (p= <0.001)
Insufficiency (20-30 ng/ml)	n=66	22 (33%)	44 (67%)	Insufficiency and deficiency group (p= <0.001)
Deficiency (<20 ng/ml)	n= 36	5 (13%)	31 (87%)	Normal and deficiency group (p<0.001)

FPG: Fasting Plasma Glucose, **DM:** Diabetes Mellitus

DISCUSSION

Vitamin D is now described as a hormone as it exerts its effect on almost all the tissues of the body because of the universal presence of vitamin D Receptors (VDR) in the body. Various aspects of glucose metabolism are adversely affected by VDD e.g. improving beta-cell function of pancreas, insulin

secretion and insulin sensitivity and is one of the most important environmental factors causing T2DM [27,28]. Similarly, the association of Vitamin D and DM has also been widely studied [29]. Our data has shown two significant findings i.e. higher prevalence of IFG and frank DM in patients with VDI and VDD, and a significance correlation of FPG and vitamin D levels. Many cross-sectional studies carried out in Western populations have generally reported an inverse association between vitamin D status and prevalent hyperglycemia [30]. Similar associations between higher fasting plasma glucose levels and vitamin D status were observed in a community-based study of older adults without known diabetes [31]. Expressing this association in another manner, Tahrani *et al* (2010) has shown that a low serum 25OHD(< 20 ng/ml) was more common in diabetics as compared to controls (83% vs. 70%; $p < 0.07$) (32). In another study from US, mean 25OHD levels among T2DM patients were found significantly lower than in individuals without T2DM (OR 1.85; 95% CI 1.03 – 3.32; P = 0.038) [23]. Conversely, in an Indonesian study 81% diabetic were found to be having VDD as compared to 75% non-diabetic (OR: 0.8; 95% CI 0.42 – 1.21; P = 0.46) (34) whereas our study showed an OR of 3.35 (95% CI: 1.29-8.70). This discrepancy is difficult to explain but is probably due to difference in age of the selected population.

The close association between vitamin status and DM has been further emphasized by the finding that inadequate vitamin D level is an important risk factor for the development of type 2 DM [35,36]. The intervention studies to improve glycaemic control with certain doses of vitamin D, however, have shown variable results [37,38]. Beneficial effect of vitamin D on T2DM is needed to be confirmed in large trials specifically designed to test the hypothesis that vitamin D status is a direct contributor to the pathogenesis of T2DM. If such an intervention is clearly shown to be effective then this could have substantial public health implications [30].

The present study did have some limitations e.g. impaired glucose tolerance which is a category of hyperglycaemia based on oral glucose tolerance test could not be studied. Similarly, data regarding glycosylated hemoglobin could not be recorded.

CONCLUSION

Present study has documented a close association between frequency of diabetes mellitus and vitamin D inadequacy in newly diagnosed diabetics with a clue towards adverse effects of vitamin deficiency on hyperglycaemia. So, it seems that vitamin D deficiency or insufficiency is undesirable in patients with any form of hyperglycaemia.

AUTHORS CONTRIBUTIONS

Sabahat Tariq: Conceived the idea, carried out the laboratory tests and drafted the manuscript.

Zafar Majeed and Muhammad Tariq Ghafoor: Selected the patient from their clinics, carried out clinical work and sent them to laboratory for analyses.

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