

## Research Article

## Frequency of Vitamin D Deficiency in Newly Diagnosed Type 2 Diabetes Mellitus Patients

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**Abstract: Objective:** To determine the frequency of vitamin D deficiency in newly diagnosed patients of type 2 diabetes mellitus.

**Study Design:** Prospective case control study.

**Place and Duration of Study:** Department of medicine, Pakistan Navy Ship (PNS) Shifa Hospital Karachi from January to December 2015.

**Materials and Methods:** A total of 302 study subjects were selected, out of which 151 healthy controls while 151 patients included in the study were newly diagnosed type-2 diabetes mellitus with non-probability, consecutive sampling at medical Out Patient Department (OPD) of PNS Shifa Karachi. All controls and newly diagnosed type-2 diabetics were tested for fasting plasma glucose, HbA1C and 25 hydroxycholecalciferol (25(OH) D<sub>3</sub>/ vitamin D) levels in pathology laboratory of PNS Shifa Hospital. Patients having serum level of 25(OH) D<sub>3</sub> < 25 nmol/L was considered as having vitamin D deficiency.

**Results:** Out of total 302 subjects, vitamin D levels of  $36 \pm 19$  nmol/L in newly diagnosed type 2 DM cases and of  $65 \pm 31$  nmol/L in controls of similar age groups and gender were found significantly lower in newly diagnosed type 2 DM. Vitamin D deficiency was found in 58 (38.4%) cases and 13 (8.6 %) in controls. In 151 newly diagnosed patients of type 2 Diabetes, 73 (48 %) were males and 78 (52 %) were females with mean age of  $53.7 \pm 8.7$  years in both gender. In cases, mean and SD of fasting plasma glucose was  $9.2 \pm 1.5$  mmol/L, HbA1C  $9.4 \pm 1.4$  % and serum 25(OH) D<sub>3</sub>  $36 \pm 19$  nmol/L. In cases, low vitamin D levels in different age groups and gender was found significant with advancing age predominantly in females. Significant correlation was found between hyperglycemia (HbA1C) and vitamin D deficiency (p-value < 0.001).

**Conclusion:** Higher frequency of vitamin D deficiency was found among patients newly diagnosed as diabetes mellitus type-2 with advancing age especially in females. Vitamin D levels were inversely related to hyperglycemia. Considering such high frequency, screening of diabetic patients for vitamin D deficiency would be beneficial.

**Keywords:** Type 2 diabetes mellitus, Vitamin D deficiency, Frequency, Hyperglycemia, Vitamin D receptor, Vitamin D binding protein.

### INTRODUCTION

Type 2 Diabetes Mellitus (DM) is considered as one of the major public health problem resulting in premature mortality and morbidity [1]. Similarly, low Vitamin D levels constitute a largely unrecognized problem in many populations and its global prevalence has been estimated from 30 to 87 % [2]. DM is a metabolic disease which can affect multiorgans in the body and recently vitamin D has aroused widespread interest in the pathogenesis of DM. Over the last five years, a number of large observational studies have suggested an association between DM type-2 and vitamin D deficiency [3, 4]. Vitamin D levels have been documented to have significant inverse relationship with hyperglycemia [5]. Data from various

studies on different populations regarding frequency of vitamin D deficiency in newly diagnosed cases of DM type-2 is showing a significant variation of 30% to 70% [6, 7].

Vitamin D has a well-known role in calcium homeostasis and bone metabolism. The suboptimal levels of vitamin D may contribute to many conditions including rickets, osteomalacia, osteoporosis, falls and fractures. In addition, epidemiologic observations have associated low vitamin D status with an increased risk of non-musculoskeletal diseases, such as cancer, multiple sclerosis and cardiovascular diseases apart from being a risk for developing DM and diabetic complications [8, 9].

Over many years, links between vitamin D status and diabetes mellitus have been identified. As early as the 1980s [10], it was shown that vitamin D deficiency in rodents and rabbits

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inhibits pancreatic insulin secretion, indicating that vitamin D is essential for the function of the endocrine pancreas. Later, the connection between vitamin D and diabetes was reinforced by the discovery of the VDR (Vitamin D Receptor) and DBP (Vitamin D Binding Protein) in pancreatic tissue (more specifically in the insulin-producing  $\beta$  cells) and also in various cell types of the immune system. Thus, vitamin D has been proposed as a possible therapeutic agent in the prevention and treatment of T1D and T2D [11].

Vitamin D status is defined by measuring the level of 25 hydroxy-cholecalciferol [ $25(\text{OH})\text{D}_3$ ] in the blood owing to its longer half-life in plasma. There are different views regarding recommended levels of  $25(\text{OH})\text{D}_3$ , however in latest reviews it has been suggested that a serum concentration of less than 25 nmol/L must be considered as vitamin D deficiency, having varied musculoskeletal and systemic effects. The aim of our study is to find out frequency of vitamin D deficiency in newly diagnosed patients of type 2 DM in our setup in comparison with healthy age and gender matched controls. This study will clarify the variations in our targeted population and also record its frequency in newly diagnosed type 2 DM cases and its correlation with hyperglycemia. This study will further be helpful in timely management of vitamin D deficiency associated morbidity.

## MATERIALS AND METHODS

This prospective case control study was conducted in the department of medicine, Pakistan Navy Ship (PNS) Shifa Hospital Karachi from January to December 2015. A total of 302 study subjects were selected after approval of the institutional ethical committee. Out of which 151 newly diagnosed type 2 diabetes cases [on the basis of American Diabetic Association (ADA) criteria] from Medical Out Patient Department (OPD) of the Hospital were selected through non probability consecutive sampling. Age and gender matched 151 healthy subjects from general population were identified and selected as controls randomly. Newly diagnosed type 2 DM patients and controls of both genders, between 35 to 65 years of age were included in the study. Already diagnosed old cases of DM and vitamin D deficiency on the basis of history and medical record or those under treatment for vitamin D deficiency were excluded from the study. Informed consent of included patients was taken after explaining the study protocol. All the patients were investigated for serum  $25(\text{OH})\text{D}_3$  measured by electrochemiluminescence immunoassay using Roche Elecsys® Systems while plasma glucose and HbA1c were estimated by routine methods on Roche Hitachi® in pathology laboratory of PNS Shifa Hospital. Vitamin D deficiency was defined as serum level of  $25(\text{OH})\text{D}_3$  less than 25 nmol/L while insufficiency from 25 to 50 nmol/L and sufficiency more than 50 nmol/L. The patients were declared as newly diagnosed type 2 DM with HbA1c more than 6.5 % and fasting plasma

glucose of more than 7 mmol/L on more than two occasions, one week apart [12].

Statistical analysis of all the data was done in statistical package for social sciences version 22 (SPSS Inc. Chicago, IL, USA). Mean and standard deviation were calculated for quantitative variables like age, plasma glucose fasting, HbA1c and serum  $25(\text{OH})\text{D}_3$  levels. Frequencies and percentages were calculated for qualitative variables like gender, different age groups (35 to 50, 51 to 65) and vitamin D deficiency. Independent sample T test was applied to see vitamin D deficiency between cases of newly diagnosed type 2 DM and controls of similar age groups and gender. Independent sample T test was applied to see significance of different age groups and gender with regard to vitamin D levels in cases of newly diagnosed type 2 DM and healthy controls separately. Pearson correlation and linear regression curve estimation between vitamin D levels and HbA1c was also analyzed [P value of < 0.05 was considered as significant (2 tailed)].

## RESULTS

Out of total 302 study subjects, Vitamin D levels of  $36 \pm 19$  in 151 newly diagnosed type 2 DM cases and of  $65 \pm 31$  in 151 controls of similar age groups and gender were compared. Vitamin D levels were found significantly lower in newly diagnosed type 2 DM having p value < 0.001. Frequency of vitamin D deficiency in newly diagnosed type 2 DM cases was recorded in 58 (38.4 %), insufficiency in 61 (40.4 %) and 32 (21.2 %) were having normal levels while in healthy controls vitamin D deficiency was found in 13 (8.6 %), insufficiency in 53 (35 %) while 85 (56 %) were having normal levels showing p value of < 0.05 (Table 1).

**Table 1.** Difference of Vitamin D Levels between Newly Diagnosed Type 2 DM Cases and Healthy Controls (n = 302).

Parameter	DM (Cases) Mean + SD (n=151)	No DM (Controls) Mean + SD (n=151)	P- Value
Age in Years	53.7 $\pm$ 8.7	53.2 $\pm$ 8.8	0.633
Plasma Glucose Fasting	9.2 $\pm$ 1.5	5.1 $\pm$ 0.7	0.000
HbA1c	9.4 $\pm$ 1.4	5.7 $\pm$ 0.6	0.000
Vitamin D Level	36 $\pm$ 19	65 $\pm$ 31	0.000
Vitamin D Sufficiency	64 $\pm$ 16	86 $\pm$ 25	0.000
Vitamin D Insufficiency	37 $\pm$ 7	43 $\pm$ 10	0.001
Vitamin D Deficiency	19 $\pm$ 4	22 $\pm$ 1.6	0.012

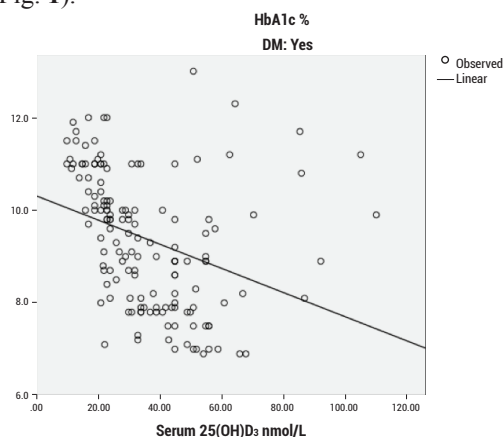
Out of 302 subjects, in 151 newly diagnosed type 2 diabetes patients, 73 (48 %) were male and 78 (52 %) female while 56 (37 %) were between 35-50 years of age and 95 (63 %) were

between 51 - 65 years, with mean age of  $53.7 \pm 8.7$  years. Vitamin D deficiency with regards to age showed that out of 58 vitamin D deficient cases, 12 were between 35 - 50 years and 46 between 51 - 65 years of age, revealing more deficient cases with advancing age. Significant difference was found in low vitamin D levels in different age groups both for cases and controls separately ( $p$  value  $< 0.05$ ). With regard to gender, out of 58 cases of vitamin D deficiency 22 were male and 36 were females in newly diagnosed type 2 DM patients. Significant difference was found in vitamin D levels with regard to gender in cases ( $p$  value  $< 0.05$ ) but was found insignificant in healthy controls ( $p$  value  $> 0.05$ ) (Table 2).

**Table 2.** Comparison of Vitamin D Levels with Regards to Gender and Age Groups Separately in Controls and Cases of Newly Diagnosed type 2 DM in PNS Shifa Hospital, Karachi (n = 302).

Parameter	n (%)	25 (OH) D <sub>3</sub> Mean $\pm$ SD	P- Value
<b>CASES</b>			
Gender			0.001
Male	73 (48%)	$41 \pm 21$	
Female	78 (52%)	$31 \pm 14$	
Age Groups			0.001
35-50 years	56 (37%)	$42 \pm 17$	
51-65 years	95 (63%)	$32 \pm 19$	
<b>CONTROLS</b>			
Gender			0.734
Male	73 (48%)	$64 \pm 29$	
Female	78 (52%)	$66 \pm 33$	
Age Groups			0.000
35-50 years	61 (40%)	$77 \pm 30$	
51-65 years	90 (60%)	$57 \pm 30$	

Correlation between vitamin D deficiency and HbA1C was found to have inverse relationship with significant  $p$  value  $< 0.001$  (Fig. 1).



**Fig. (1).** Correlation between Vitamin D Deficiency and HbA1c in Newly Diagnosed Type 2 DM Patients Showing  $p$  value 0.000. (n = 151).

## DISCUSSION

Pakistani population has high prevalence of type 2 DM [13]. Among the normal healthy individuals of different ages the prevalence of vitamin D deficiency is high [14]. The association of Vitamin D and DM has been described for more than twenty-five years now [15]. Many studies have revealed that vitamin D is related to various aspects of glucose metabolism e.g. improving beta-cell function of pancreas, insulin secretion and insulin sensitivity and its deficiency is one of the important environmental factors leading to hyperglycemia [16, 17].

In our study, using serum vitamin D levels of less than 25 nmol/L, vitamin D deficiency was found in 38.4 % patients of newly diagnosed DM as compared to 8.6 % in controls. Similarly, insufficiency (25 - 50 nmol/L) of vitamin D was 40.4 % in cases as compared to 35 % in controls. During literature search, no such case control study was found in Pakistan but results from a similar study conducted by Riyaz Ahmad Daga, *et al.* [18] in northern India in 2012 on newly diagnosed patients of both type 1 and type 2 DM, recorded a deficiency of 91.1 % in cases as compared to 58.5 % in healthy controls. Another study by Dr. G. B. Doddamani *et al.* in 2013 at Bagalkot town of India [19] on vitamin D status found that 70 % of the newly detected type 2 DM patients were vitamin D deficient ( $< 50$  nmol/L). This difference is because their cut off level for vitamin D deficiency was 50 nmol/L while as per latest guidelines our lower cut off level was at 25 nmol/L. Further splitting the results with regards to age and gender it was found that the frequency of vitamin D deficiency escalated considerably with advancing age and was more prevalent in females in cases, also found more deficiency in advancing age but similar vitamin D levels for gender in healthy controls. Possible reasons for this female preponderance can be predominantly home bound females, not seeking early medical care. Similarly, poor nutritional status, limited sun exposure and age-related decrease in cutaneous synthesis may be the cause of increased deficiency with advancing age. These findings are similarly supported by a case control study performed by Bayani MA, *et al.* in 2014 at a teaching hospital of northern Iran in which they recorded a deficiency of 64.2 % with a cut off value of 50 nmol/L with a mean concentration of vitamin D being lower in women and with advancing age [20].

Another significant finding in this study was inverse relationship between vitamin D level and HbA1c and our study results are consistent with observations from a recent cross sectional study performed by Khalida Iqbal, *et al.* in 2016, in Karachi [21] study by Harish Kumar, *et al.* in 2015, by Kant, *et al.* in 2010 [22], another large study performed by Kositsawat J, *et al.* on US population in 2010 [23] and a number of observational studies carried out in European countries [24, 25]. The inverse relationships between Vitamin

D level and glycemic control support an active role of vitamin D in pathogenesis of type 2 DM. The postulated mechanisms by which vitamin D could be influencing glucose metabolism in diabetic patients include: improvement in insulin sensitivity and  $\beta$  cell survival, increased insulin secretion from pancreatic  $\beta$  cells and regulation of calcium flux for normalization of glucose tolerance and protection of beta cells against cytokine induced apoptosis [26].

### LIMITATION OF THE STUDY

Our study does not clarify exactly whether vitamin D deficiency is due to type 2 DM or vitamin D deficiency has a role in causing hyperglycemia. To better understand the role of vitamin D in the development and progression of type 2 DM, high quality randomized control trials (RCTs) are needed that may find out the exact pathogenesis of vitamin D deficiency in type 2 DM patients.

### CONCLUSION

We concluded that the frequency of vitamin D deficiency is high among patients with newly diagnosed type 2 DM with advancing age and more common in females. The association of vitamin D deficiency with poor glycaemic control in Pakistani patients with type 2 DM points towards the possible role of vitamin D supplementation in regulation of glycemic control in these patients. So, it is recommended that every patient who is newly diagnosed with type 2 DM should be screened for vitamin D deficiency and vitamin D supplementation must be given where necessary.

### AUTHORS' CONTRIBUTION

- **Zara-tul-ain Bashir** and **Huma Amjad** designed the study.
- **Syed Tanveer Abbas Gilani**, and **Amjad Khan** collected the data.
- **Amjad Khan** and **Syeda Urooj Riaz** performed literature analysis.
- **Huma Amjad** performed statistical analyses.
- **Zara-tul-ain Bashir** performed critical revision of the manuscript.

### CONFLICT OF INTEREST

Declared none.

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