

Prevalence of Hypovitaminosis D in Type 2 Diabetes Mellitus and its Relationship with Glycemic Control

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ABSTRACT

BACKGROUND: In addition to its effect on the bones, vitamin D has a myriad of extra skeletal roles. It has been implicated both in the development of type 1 and type 2 diabetes mellitus as well as glycemic control. There is widespread vitamin D deficiency in Pakistan. Incidence of diabetes mellitus is also increasing exponentially. There is a need to define the relationship between 25hydroxy vitamin D and type 2 diabetes.

OBJECTIVE: The purpose of this study was to determine the prevalence of hypovitaminosis D in type 2 diabetes and its association with the level of control of diabetes mellitus.

MATERIALS AND METHODS: This descriptive cross sectional study was conducted at the Department of Internal Medicine, Sir Syed College of Medical Sciences and Hospital Karachi from January to June 2015. Total 168 adult cases of Male and Females patients having type 2 Diabetes Mellitus were included. After taking the informed consent; demographic details, duration of diabetes, and modes of treatment for diabetes were recorded. The glycemic profile and levels of vitamin D were assessed. Glycemic control was categorized as satisfactory and unsatisfactory glycemic control while vitamin D levels were categorized as sufficient, insufficient and deficient. The data was analyzed on SPSS version 20.0. Mean \pm SD was computed for quantitative variables. Frequency and percentages was computed for categorical variables. Relationship of the glycemic control with vitamin D was computed through Chi-square test. P-value of <0.05 was considered significant.

RESULTS: Among 168 cases (45.2% males and 54.8% females), mean age was 46.7 ± 12 years and mean duration of diabetes 7 ± 4.4 years. Mean HbA1c was 8.3 ± 2.28 with 62% patients having unsatisfactory glycemic control. A large proportion of the patients had vitamin D deficiency (80.8%). Deficiency of vitamin D was significantly associated with both fasting and random blood glucose levels as well as HbA1c.

CONCLUSION: A large majority of patients with type 2 diabetes mellitus have vitamin D deficiency and the poorly controlled diabetes mellitus is significantly associated with vitamin D deficiency.

KEY WORDS: Hypovitaminosis D, Diabetes mellitus Type 2. Glycemic control.

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INTRODUCTION

Vitamin D (VD) is a basic fat soluble vitamin with multiple effects on human health and immunity. Along with its role in the absorption of calcium, phosphate and thus in bone mineralization, it is also known to play a role in the development of some chronic illnesses such as diabetes mellitus, cardiovascular diseases, autoimmune diseases, allergies, asthma and some malignancies.¹⁻⁴ The effect of VD on calcium metabolism is postulated to be the basis of the role it plays in a variety of systemic illnesses. VD receptors are found on more than 36 cell types including pancreatic beta cells, adipose tissue, hepatocytes and skeletal muscle cells.⁵ VD deficiency and insufficiency

is also associated with type 2 diabetes. Low level of VD are also seen in metabolic syndrome.⁶ Normal VD levels are related to low risk of development of type 2 diabetes and low VD levels have been found to be associated with a higher risk of developing type 2 diabetes mellitus.⁷ VD deficiency is a worldwide epidemic. According to WHO statistics, around one billion people are suffering from VD deficiency throughout the world. Although the main source of VD is sunlight, in most people vitamin D level has been found to be low in countries located in extremes of the hemispheres and also in tropical countries.⁸ Diabetes mellitus is one of the most common chronic illnesses in the world. Changing life styles and dietary habits has accelerated its occurrence. This increase is

very evident in South Asia where it has assumed epidemic proportions. The number of diabetic patients is expected to reach 370 million by the year 2030.⁹ Both environmental and genetic factors play a role in the development of diabetes mellitus. In most cases the presence of type 2 diabetes mellitus is related to some unhealthy form of lifestyle practices. Such factors can usually be modified. One of the most important of these modifiable factors is obesity. VD deficiency is also one such other modifiable factor which is being implicated in the development and control of diabetes.¹⁰ Studies have shown that VD deficiency is directly proportional to insulin resistance and cardiovascular risk in obese adolescents.¹¹

Diabetic patients from our region frequently suffer complications because of lack of awareness, socio-economic constraints and delayed referral to specialized centers, also due to multiple co-morbid conditions poly-pharmacy and dietary constraints generalized health of diabetics deteriorates further.¹²

Keeping in view the growing epidemic of diabetes mellitus in South Asia and high prevalence of VD deficiency, the relationship between them should be clarified in our part of the world. The determinates of this relationship if found, may lead to preventive measures and therapeutic interventions for this target population.^{13,14}

This study aimed to investigate the prevalence of VD deficiency among patients with type 2 diabetes mellitus and to ascertain the relationship between VD deficiency and the level of glycemic control.

MATERIALS AND METHODS

Study design:

This study was carried out in the Medical outpatient Department of Sir Syed College of Medical Sciences and Hospital, Karachi from January 2015 to July 2015. It is a descriptive cross-sectional study. The patients were collected using non-probability convenient sampling.

Inclusion criteria:

Adult (>18 years age) patients with type 2 diabetes mellitus coming to the Medical outpatient Department. Diabetes was diagnosed according to OGTT criteria, HbA1c criteria, a known history of diabetes and use of diabetes medication. Patients were labeled type 2 diabetes when diagnosed beyond 35 years of age irrespective of treatment and also if treated with diet or oral hypoglycemic drugs irrespective of age at diagnosis.

Exclusion Criteria:

Patients with acute illnesses, taking medications that altered VD metabolism, pregnant females and those

patients with history of chronic liver disease and chronic kidney disease were excluded.

The study was approved by the ethical committee of the institution. Informed consent was obtained from all participants.

All the demographic data was entered on structured proforma. Duration of diabetes, complications of diabetes and the anti-diabetic drugs being taken were recorded. Blood glucose was measured in both fasting and random states. HbA1c levels were recorded for glycemic control. Hemoglobin A1c was measured by automated high-performance liquid chromatography analyzer (Bio-Rad Diamat, Milan, Italy); The upper limit of normal for our laboratory was 5.8%. Glycemic control was categorized as satisfactory if HbA1c was below 7 and unsatisfactory if the level of HbA1c was above 7%.

VD levels were measured as serum 25(OH) vitamin D by high-performance liquid chromatography. Deficiency was defined as below 20ng/ml, insufficiency 21-30 ng/ml and sufficiency >30ng/ml. A cut off point of <30 ng/ml of 25(OH) D was used to classify patients as with low vitamin D status.^{1,15} The glycemic control and vitamin D levels, variables of interest for this study, were categorized as categorical variables.

The data was entered and analyzed on SPSS version 20.0. Mean \pm SD was computed for quantitative variables like age, duration of diabetes, fasting and random blood sugar levels, HbA1c levels and 25-hydroxy vitamin D3 levels. Frequency and percentages was computed for categorical variables like gender, the level of glycemic control and grade of vitamin D deficiency. Relationship of the glycemic control with vitamin D was computed through Chi-square test. P-value of <0.05 was considered significant.

RESULTS

There were a total of 168 patients with type 2 diabetes mellitus, whose mean age \pm SD was 46.7 \pm 12 years. There were 45.2% male subjects and 54.8% female subjects. The mean duration of diabetes was 7 \pm 4.4 years (mean \pm SD). Mean fasting blood sugar in these patients was 170 \pm 64.6mg/dl and the mean random blood glucose level was 261 \pm 87mg/dl. Glycemic control, assessed by HbA1c, in these patients was 8.3 \pm 2.28, around 38% (n=64) of the subjects had satisfactory glycemic control with a HbA1c of 7 and below, while the majority (n=104) subjects had unsatisfactory glycemic control (62%). Around 70% of the patients population had one or more of diabetic complications. With regard to the therapeutic agent being used 82.7% of the patients were on oral hypoglycemic only, 14.9% were taking both oral hypoglycemic and insulin while 2.4% of the subjects were taking only insulin for

TABLE I: CHARACTERISTICS OF SUBJECTS ACCORDING TO GLYCEMIC CONTROL

Variable		Good Glycemic Control	Poor Glycemic Control	P-value
Age		42±12	49±11	-
Gender	Male	36%(23)	51%(53)	0.07
	Female	64%(41)	49%(51)	
Duration of diabetes		6.4±0.5	7.5±4.6	-
Fasting blood sugar		124.5±20	198±67	-
Random blood sugar		217±53.6	289±92	-
HbA1c		6.4±0.5	9.5±2.1	-
Vitamin D level		17.2±7.8	11.7±7	-
Vitamin D3 levels	Deficient	71.4%(45)	86.5%(90)	0.04
	Insufficient	19%(12)	10.5%(11)	
	Sufficient	9.5%(6)	3%(3)	
Presence of Complications	Yes	64%(41)	74%(77)	0.22
	No	36%(23)	26%(27)	
Type of Therapeutic Agent	Oral only	89.1%(57)	78.8%(82)	0.23
	Oral + insulin	9.45%(6)	18.3%(19)	
	Insulin only	1.6%(1)	2.9%(3)	

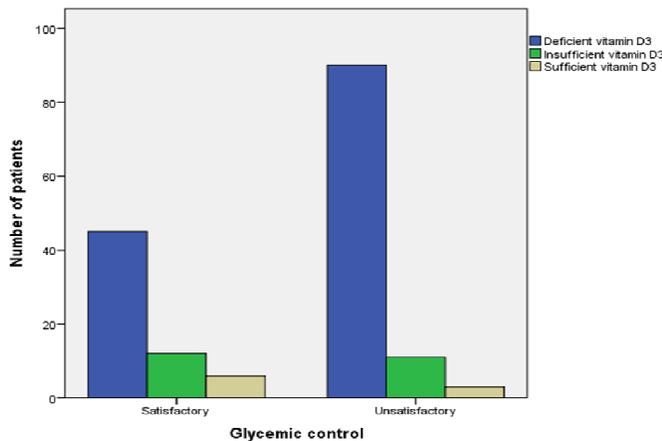
TABLE II: RELATIONSHIP OF VITAMIN D STATUS WITH GLYCEMIC INDICES

Diabetic indices		Vitamin D Status			P-value
		Deficient	Insufficient	Sufficient	
Fasting blood sugar	<120mg%	52.2%	30.4%	17.4%	0.001
	>120mg%	85.2%	11.3%	3.5%	
Random blood sugar	<140mg%	60%	30%	10%	0.003
	>140mg%	83.2%	12.9%	3.9%	
HbA1c	<7%	71.4%	19%	9.6%	0.042
	>7%	86.5%	10.5%	3%	

control of diabetes mellitus.

Regarding VD status, the mean 25 hydroxy vitamin D3 value was 15.9 ±9.9SD. Most of the patients were deficient in vitamin D3 (80.8%), 13.8% were insufficient while 5.4% of the subjects had sufficient vitamin D levels. The characteristics of the subjects according to level of glycemic control are enumerated in (Table I). Out of the variables assessed only vitamin D status was significantly associated with the degree of glycemic control. The objective of the study was to determine the relationship of glycemic control with vitamin

D status. Keeping in view fasting blood glucose levels 52.2% of the patients in the group with fasting blood glucose levels below 120 mg% had deficient VD, while 85.2% of the patients with blood glucose above this level were deficient for VD. (p-value<0.01). (Table II). Also random blood glucose and HbA1c were also significantly associated with VD status of the subjects (Table II). This relationship is made clear with the graph (Figure I) which shows deficiency of VD more prevalent in patients with unsatisfactory glycemic control.

FIGURE I: RELATIONSHIP OF VITAMIN D STATUS WITH GLYCEMIC CONTROL

DISCUSSION

Diabetes mellitus is currently the most prevalent chronic illness in the world having a prevalence of around 9% in the adult population.¹⁶ While at this point in time it affects 240 million people in the world. The projection of its incidence reveals that by 2030 it will be affecting around 370 million⁹ people globally. Thus data shows that diabetes mellitus is increasing in prevalence. This disease entails both great morbidity and mortality. The management of diabetes mellitus and its complications places a huge economic burden especially in the developing countries where it is assuming epidemic proportions. More than a million deaths were reported to be directly cause of diabetes mellitus with more than 80% of these deaths occurring in developing countries including Pakistan.¹⁷ Pakistan has a high prevalence of diabetes, recent data showing that around 7 million people are suffering from this disease country wide. If the current trend continues we will be seeing doubling of the affected population by the year 2025 and the disease will be affecting 11.5 million people approximately by that time.¹⁸

Because of its relationship with many chronic illnesses VD has gained much attention in the recent years. Chronic inflammatory diseases like tuberculosis, cardiovascular disease, many cancers and diabetes mellitus have all been found to be associated with low levels of VD. Vitamin D deficiency (VDD) is a global public health issue and is on the rise in Pakistani population. VD has been found to be deficient in areas which receive less sunlight and also in tropical areas where sunlight hours are prolonged and sufficient. Dietary deficiency has been implicated as a cause of hypovitaminosis D in such areas. Pakistan is one such country which has a very high prevalence of hypovitaminosis D in the general population.

VDD has been observed in a many studies conducted throughout Pakistan. VDD was observed in a very

large proportion of our study population. This finding is similar to other studies conducted in the region. In our study around 81% of the subjects were vitamin D deficient with a mean vitamin D3 level of 15.5ng/dl. The female population had a greater deficiency and insufficiency of vitamin D compared to the male patients in our sample. This finding is corroborated by other studies in the region.¹⁹⁻²³

The studies conducted in the country have shown that vitamin D deficiency in the various parts of the country is rampant. A study from Islamabad Pakistan showed that deficiency was more prevalent in females (56.2%) as compared to males (15.3%), while insufficiency have been reported as 11.3%, and only 17.2% of the subjects had normal levels.¹⁹

The causes of vitamin D deficiency could be due to changing life style with people adopting a more sedentary life, little exposure to sunlight, reduced outdoor activity, changes in dietary habits with the focus shifting from dairy foods towards high caloric, carbohydrate and saturated fat enhanced diet. These factors also contribute to both development of type 2 diabetes mellitus and poor control of diabetes.

Vitamin D deficiency has received special attention lately because of its high incidence and its implication in the genesis of multiple chronic illnesses. The high prevalence of vitamin D deficiency in our study population underlines the fact that vitamin D deficiency is more common in chronic diseases like diabetes mellitus. Our study showed that vitamin D was inadequate in a large population of patients with type 2 diabetes. Lower vitamin D levels were associated with a poor glycemic control. This was more strongly associated with fasting and random blood glucose levels (p -value<0.01) than with HbA1c (p -value<0.05). The study indicates a poor glycemic control in a majority (62%) of patients compared to 38% patients with good glycemic control. In patients having HbA1c greater than 7.0 vitamin D deficiency was significantly greater (86.5%) compared to 71% patients with good glycemic control (HbA1c <7) p -value< 0.05. There was a stronger co-relation between fasting blood sugar levels and serum vitamin D3 levels. Among patients who had fasting blood sugars below 120mg/dl only, 52% were vitamin D deficient while 30% were vitamin D insufficient and 17 % had vitamin D within normal limits with markedly deficient vitamin D levels in subjects who had uncontrolled fasting blood sugar levels (p -value<0.01). Random blood sugar also showed a stronger inverse relationship with vitamin D levels. Random blood sugars of less than 140mg/dl demonstrated 56% deficiency of vitamin D3 compared to 85% in patients who had uncontrolled random blood sugar levels (p -value<0.01). These findings are supported by a number of international studies. Some

studies show significant association with high fasting and random blood glucose levels with deficiency of vitamin D and no association of a low vitamin D with HbA1c levels.²⁴ But inverse correlation between the level of vitamin D and glucose level is well known.^{25, 26} In many studies vitamin D levels were low in subjects having higher HbA1c values both in patients with or without diabetes mellitus indicating that they are inversely related.²⁷⁻³⁰

Thus a poor glycemic control was associated with low vitamin D levels, showing an flipped relationship between serum vitamin D levels and type 2 diabetes as well as markers of adverse glucose hemostasis in many studies.^{7,30}

In addition to the effect of vitamin D on calcium metabolism and insulin secretion another interesting theory has been hypothesized for the inverse relationship of vitamin D and glycemic control, which reverses the cause and effect relationship between the two. According to these studies a higher blood glucose level can reduce vitamin D levels. Blood sugar levels can influence the level of vitamin D through different processes. One of the first would be the unhealthy lifestyle choices of a poorly controlled diabetic patient. Such subjects would have unhealthy dietary habits and low physical activity and inadequate time in the open for sufficient vitamin D synthesis. Poor glycemic control, duration of diabetes, increased BMI, increased waist circumference are all negatively related to vitamin D levels. Among the diabetic patients, the ones with good control had higher levels of vitamin D as compared to those patients with unsatisfactory control. The improvement of blood sugar levels increased serum 25 hydroxyvitamin D levels supports the theory that vitamin D metabolism is affected by poorly controlled diabetes mellitus. Interventional studies designed to address this issue can have clinical implications. The fact demonstrated in some studies that the administration of vitamin D to poorly controlled diabetics does not improve glycemic control may be due to the reduced 25 hydroxylase activity in the liver.³¹ Another factor which may contribute to hypovitaminosis D in diabetic patients is the hydroxylation of vitamin D in the kidney. In patients with diabetes mellitus diabetic nephropathy develops which affects the metabolic pathway of vitamin D through one-alpha hydroxylation. Multiple studies have underlined the observation that vitamin D levels are lower in patients with diabetes mellitus and impaired glucose levels. In our study the deficiency of vitamin D was found to be related to worsening of glycemic control and thus mean fasting and random blood glucose levels were inversely related to serum vitamin D levels.

This relationship has been duplicated in many studies with hypovitaminosis D found in patients with unsatis-

factory glycemic indices and increased weight.³¹

Although it is well documented that there is an inverse relationship between vitamin D levels and type 2 diabetes. Obesity is a common factor with both low vitamin D levels and type 2 diabetes. BMI can be the main confounding variable in these studies. Some studies that have adjusted for obesity still demonstrate the association of low vitamin D levels with the probability of a patient's lifetime risk of type 2 diabetes.³²

Another study has shown evidence that 25 hydroxyvitamin D is independently associated with development of type 2 diabetes while discounting for the effect of obesity and HOMA-IR etc which specifically test for insulin resistance and beta cell function.³³

But the contribution that addition of vitamin D can have in improving glycemic status has not been proven as the data regarding this is not extensive. A few case studies have shown the efficacy of vitamin D supplementation in improving the glycemic status. Different parameter of insulin resistance improved by 60% with induction of vitamin D sufficiency.^{34,35}

Our study provides basis for trial of vitamin D supplementation to improve glycemic control in diabetic patients. This study also emphasizes the need for investigating that addition of vitamin D to the patients prescription can effectively reduce the risk of development of diabetes mellitus in people with presence of other risk factors.

CONCLUSION

Vitamin D is deficient in a large proportion of patients with type 2 diabetes mellitus. The status of vitamin D is inversely related to glycemic control. Additional studies investigating the effect of supplementation of vitamin D on the incidence of type 2 diabetes mellitus and on glycemic control can significantly help in management of type 2 diabetes mellitus.

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