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Original Research Article

Study on Effect of Vitamin D Supplementation in Vitamin D Deficient Patients of Diabetes Mellitus with Poor Glycemic Control in a Tertiary Care Hospital of Andhra Pradesh

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Abstract

Background: Vitamin D_3 is fat soluble vitamin, known to affect glucose homeostasis and is inversely related to the glycosylated haemoglobin level in diabetes mellitus. Vitamin D_3 deficiency is associated with higher risk of insulin resistance and metabolic syndromes. This study was aimed to evaluate the relation of the levels of 25(OH)D_3 to HbA1C levels in diabetes mellitus cases and effect of supplementation of 25(OH)D_3 in cases with decreased Vit D levels in poor glycaemic control and changes in levels of Glycosylated haemoglobin post treatment.

Methods: This is a prospective interventional study of all patients with diabetes with less than normal Vit. D levels (above 33 years and less than 69 years) attending as outpatient in General Medicine Department, Tertiary Care Centre, Ananthapuramu. Parameters - FT_4, TSH, Calcium, Creatinine, Vitamin D_3 levels and HbA_1C level were analysed in serum and recorded prior to supplementation and after 3 month of supplementation with vitamin D_3. All patients were divided in to two groups - deficient and insufficient, according to the vitamin D_3 deficiency levels, the association between the levels of 25(OH)D_3 and HbA_1c was studied, pre supplementation and post supplementation.

Results: 176 patients had 25(OH)D_3 level <20 nanograms (Deficient Group) and 39 patients had 25(OH)D_3 levels of 20 -30 nanograms (Insufficient group). We observed lowering of HbA_1C after Vit D supplementation from 10.5± 2.5 in deficient group and 9.5 ± 2.4 in insufficient group to a mean of 8.5 ± 1.1 in deficient group, 7.5± 2.2 in insufficient group and 6.8 ± 1.2 in normal group. We found HbA_1C to be inversely related to Vitamin D3 levels in our study.

Conclusions: Patients with higher HbA1C had altered Vit D levels and supplementation of Vit D_3 improved HbA1C levels in poor glycemic control patients.

Keywords: Glycosylated Haemoglobin, HbA_1C, Vitamin D_3, Diabetes Mellitus

Introduction

Vitamin D_3, also called cholecalciferol is a fat-soluble vitamin,[1] which is essential for calcium metabolism and other physiological functions[2] and is also implicated in various metabolic disorders including Diabetes mellitus, Hypertension, Malignancies, immune system[3] etc. Its precursor is synthesized from cholesterol and activated at two levels –skin by the help of UV rays and kidneys.7- Dehydro cholesterol, an intermediate in cholesterol synthesis is present in malfigian layer of skin. It is converted to cholecalciferol or vitamin D3 by irradiation of skin with ultraviolet sunlight (290-350nm). It is further converted to calcitriol, active form of vitamin D_3 in kidney by a process called hydroxylation with the help of enzyme 1-alfa hydroxylase.[4]

The Main targets of action are intestine, kidney[5] and bones in relation to calcium and phosphate metabolism leads to increase in serum level of calcium and phosphate. This is achieved by inducing the synthesis of cal binding proteins and calcium transporters on mucosal cell of intestine, leading to increased transport of calcium from intestinal lumen to blood through mucosa.[6] It also increases reabsorption of calcium and phosphate from renal tubules thereby decreasing it's excretion.

It regulates the expression[7] of mRNA of bone matrix required for osteocalcin and osteopontin in osteoblasts. It is presently considered to be a immunomodulator which can effect wide range of functions with a role in diseases like diabetes mellitus, atherosclerosis, metabolic syndrome, coronary artery disease, Pre-eclampsia, toxaemia of Pregnancy, Cerebral stroke and diseases related to immunity.[8] It is known to have a role in maintaining metabolic parameters in women[9] also. It is recommended in management of covid 19.[10] Deficiency of vitamin D_3leads to rickets,[11] osteomalacia and hypocalcaemia directly and indirectly to hormonal disorders which are activated by calcium mediated action. Recent articles published in journals implicate vitamin D deficiency to many metabolic disorders, hormonal disorders, and Psychological disorders mostly due to defective vitamin D receptor.[12]

Diabetes mellitus is endocrine disorder related to insulin synthesis and insulin action. There are four broad categories of diabetes includes type 1 diabetes ,type 2 diabetes ,other forms of diabetes and gestational diabetes.[13] Type 1 diabetes accounts for 5-10% of diabetes and results from autoimmune destruction of beta cells of islet leading to total or near insulin deficiency.[14] Pathogenesis of type 2 diabetes mellitus is complex and it is heterogeneous syndrome of dysregulated glucose homeostasis associated with impaired insulin secretion and insulin action. Impaired beta cell function, insulin resistance and dysregulated hepatic glucose metabolism leading to noncardiogenic atherosclerotic vascular diseases.[15]

Lifestyle and natural diet of low vitamin D consumption may cause poor glucose control in diabetic patients. Vitamin D deficiency is related to onset of diabetes mellitus. Vitamin D maintains the normal release of insulin by pancreatic beta cells. Type 2 diabetes mellitus occurs by insulin resistance. Beta cells overcome resistance by releasing more insulin to prevent hyperglycaemia. Thus, hyperactivity of beta cells experiences excessive ca^{2+} and reactive oxygen species (ROS) signalling that leads to cell death and onset of diabetes. Vitamin D deficiency leads to initial insulin resistance and subsequent onset of diabetes by beta cell death. Vitamin D mainly reduce inflammation, which is major process in inducing insulin resistance. Vitamin D also maintains normal resting levels of ca+ and ROS that are elevated in beta –cells. Vitamin D also has a role in maintaining the epigenome. Epigenetic alterations usually occur in diabetes. Hypermethylation is prevented by vitamin D level by increasing the expression of DNA demethylases that prevent hypermethylation of multiple gene promoter regions of many diabetes related genes. So, vitamin D deficiency leads to many cellular processes begin to decline and sets to onset of various diseases such as diabetes. Prognosis of Diabetes mellitus and Gestational diabetes mellitus is also related to vitamin D deficiency. Vitamin D deficiency is associated with metabolic syndrome[16]. Polymorphism of vitamin D receptor gene found to be related to components of the metabolic syndrome. Vitamin D levels found to be inversely related to glycosylated haemoglobin levels and has important role in prognosis of diabetes mellitus.[17]

In this area there are no publications or studies on vitamin D levels in diabetic cases. This area is of tropical climate with a very good opportunity for sun exposure. So, the Vitamin D levels in diabetic cases were studied to see if any deficiency exists and the effects of oral supplementation in correcting the deficiency and changes in HbA1c values.

Aim & Objective of the study

To study the status of vit. D levels in diabetic patients on regular treatment and effect of supplementation of Vit. D on Glycemic status in diabetics with decreased vit. D levels

METHODS

This Prospective interventional study comprised of total 336 patients of diabetes mellitus on regular treatment from medical O.P of Government General Hospital, Anantapuramu in association with department of Biochemistry and Pharmacology, Government medical college, Anantapuramu, Andhra Pradesh from January to September 2020 after obtaining clearance from institutional ethical committee. Sample size was calculated online[18] by Andrew Fisher's Formula with a standard deviation of 0.5 and confidence level of 98%. Study subjects included 336 diabetes mellitus patients on regular treatment with good follow up history and diabetes mellitus with decreased vit D levels were further studied for the effect of supplementation of Vit. D on HbA1C, and calcium. Prior consent was obtained from subjects for willingness to participate in study, for giving blood samples and analysing the values prior to enrolment. Subjects not willing were excluded from the study.

Inclusion Criteria

- Age limit between 33 – 69years
- Both sexes
- Diabetes mellitus cases with Vitamin D level < 30ng/ml
- Diabetes mellitus 1 & 2 patients on regular treatment and follow-up

Fasting blood samples were collected under aseptic standard precautions and serum was analysed for HbA_1C, free Thyroxine (FT_4), TSH, serum creatinine and serum calcium

levels, Pre and post –supplementation of Vitamin D using standard kits in immunoassay and auto-analyser.

All the cases were screened by Ultrasonography for liver, pancreas, and kidneys to rule out any pathology, as certain disorders of liver, kidney or intestine could have an effect on Vit D levels.

Exclusion Criteria

- Age <33 years and> 69 years.
- Cases having co morbidities like pancreatic disorders, hepatic disorders, renal failure, colitis, Thyroid disorders, CVS disorders and CNS disorders
- On vitamin D or calcium supplementation
- Pregnancy – gestational diabetes mellitus
- Lactating mothers.

HbA1C, Vit D, FT3, FT4, TSH, Calcium and creatinine levels were studied pre and post supplementation to assess the effect of supplementation

Grouping of Patients

All patients were divided into four groups[19] according to their vitamin D level as per international guidelines as follows; Deficiency (<20ng/ml) and insufficiency (20-30ng/ml), sufficient (30-50ng/l) and high (>50ng/ml). Association between $25(OH)D_3$ and HbA_1C was tested. Only deficient and insufficient groups were further studied.

In both groups, baseline HbA_1C, FT_4, TSH, Serum calcium, serum creatinine and Vit D levels were recorded prior to supplementation.

Out of 336 patients, 215 patients, in categories of deficient and insufficient group according to their Vit D level were included and studied with regular follow up. All participants had received their regular treatment with either insulin or oral hypoglycaemic agents or both. Subjects who are deficient or insufficient were treated with capsules of vitamin D 60,000 IU orally as per the guidelines of endocrine society clinical practice guidelines[20] weekly once for 12 weeks and continued for those who were deficient or insufficient for another 12 weeks. The effects caused by confounding variables was manged by restriction.

Statistical Methods

Continuous variables were tabulated in Microsoft Excel and various statistical methods were used. They are represented as mean ± SD and percentages. The data obtained were statistically analysed using SPSS version 2..

Results

A total of 215 patients with deficiency or insufficiency status of vitamin D and poor glycemic status were studied. In addition, TSH, Free T_4, Serum calcium, serum creatinine parameters were analysed. The distribution of age and sex was studied. The mean age group of cases studied was 48±8 in deficient group and 54 ± 13 in insufficient group. Out of the 215 cases studied, males are a total of 166 and females are 49 and among which deficient group had 135 males and 41 females and insufficient group had 31 males and 08 females.

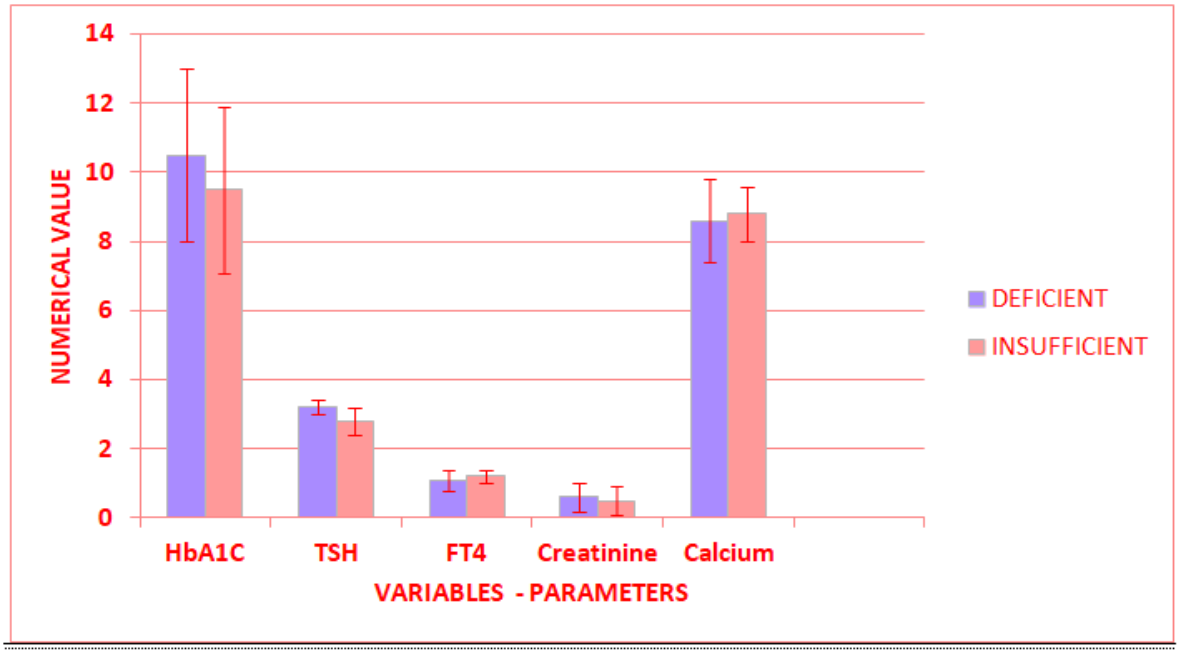
The values obtained are depicted in Table no.1 below**.**

Table 1. Baseline Characteristics of study participants – Pre supplementation

Baseline Characteristics	Vit D deficient<20ng/ml	Vit D insufficient20-30ng/ml
Total no. of patients	176	39
Male patients	135	31
Female patients	41	8
Agein years (mean ±SD)	48±8	54±13
HbA_1C(%)	10.5 ±2.5	9.5± 2.4
TSH(mIU/L)	3.2±0.2	2.8± 0.4
FT4(ng/dl)	1.1± 0.3	1.2±0.2
Serum calcium (mg/dl)	8.6±1.2	8.8± 0.8
Serum creatinine(mg/dl)	0.6±0.4	0.5± 0.4

In176 Vitamin D deficient patients, 135 were males and 41 were females. The mean age was48±8 years. The values of basal parameters obtained are HbA_1C pre supplementation (%) value of 10.5±2.5, TSH (mIU/L) of 3.2±0.2,FT4 (ng/dl) of 1.1±0.3,serum calcium (mg/dl) of 8.6±1.2 and serum creatinine (mg/dl) of 0.6±0.4.

In 39 insufficient patients, 31 were males and 8 were females with a mean age of 54±13 years. The values detected are HbA_1C pre supplementation (%) of 9.5 ± 2.4, TSH mIU/L) of 2.8±0.4, FT_4(ng/dl) of 1.2±0.2, serum calcium (mg/dl) of 8.8± 0.8 and serum creatinine (mg/dl) of0.5±0.4. The values are graphically represented in Figure 1.



All the patients were supplemented with Vit. D - 60000 units, orally once in a week for 03 months. The analytes were checked after supplementation, the values of analytes obtained are in Table.2 and Figure 2.

Table 2. Baseline characteristics after 12 weeks of supplementation

Baseline Characteristics	Vit D deficient<20ng/ml	Vit D insufficient20-30ng/ml	Normal >30ng/ml
Total no. of patients	16	9	190
Male patients	3	4	159
Female patients	13	5	31
Age (years) (mean±SD)	48±8	54±13	52 ± 08
HbA1c -(%)	8.5 ±1.1	7.5± 2.2	6.8±1.2
TSH (mIU/L)	3.2±0.2	2.8± 0.4	2.7 ± 0.4
FT4 (ng/dl)	1.1± 0.3	1.2±0.2	1.1 ±0.1
Serum calcium (mg/dl)	9.1±1.2	9.2± 0.8	9.3± 0.4
Serum creatinine(mg/dl)	0.6±0.4	0.5± 0.4	0.6 ±0.2

After Vit D supplementation for 12 weeks, all the cases in insufficient group showed normal values of Vit D. Out of 176 in deficient group, only 16 patients remained in deficiency group and 9 in insufficient group. HbA_1Cimproved to 8.5±1.1% for cases remaining in deficient group, 7.5 ± 2.2 remaining in insufficient group and 6.8 ± 1.2 for normal group. Serum calcium improved to 9.1±1.2 mg/dl in deficient group, 9.2 ± 0.8 in insufficient group and 9.3 ± 0.4in normal group and the values of remaining analytes were within normal range as shown in table.

In 39 insufficient patients, HbA1 C (%) improved to 6.8 ± 1.2, and serum calcium improved to 9.3± 0.4. the remaining values obtained were within normal range as shown in table

.

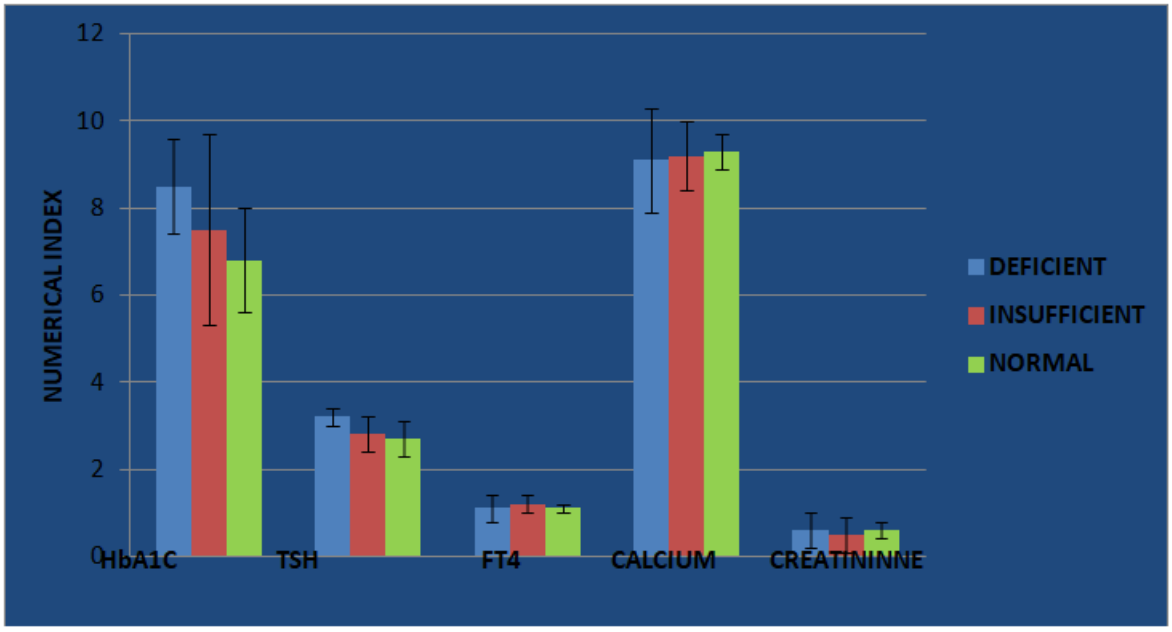


Figure 2: Post supplementation values of variables

Discussion

Vitamin D has a very important role in skeletal [21] functions through calcium homeostasis and has several extra skeletal functions including a very important role Diabetes Mellitus[22] by altering insulin sensitivity and insulin production by direct and indirect effect.

Type 2 DM occurs by insulin resistance lead to beta cells over production of insulin to prevent hyperglycaemia. These hyperactivity of beta cells experience excess $ca^{+2}$and reactive oxygen species signalling that leads to cell death and diabetes. Vitamin D deficiency[23] leads to initial insulin resistance and subsequent onset of diabetes. Vit D mainly reduce inflammation which is major process in inducing insulin resistance.[24,25]

Serum levels of 25(OH)D3 in the case of our study was less than 20ng/ml in 176 patients and between 20-30ng/ml in 39 patients. Vitamin D levels was found to be decreased in cases of Diabetes Mellitus. Our study findings are in similar to study conducted by Anitha subramanyam etal,[26] Martin etal.[27]

The association between HbA1 C and Vitamin D levels in our study was inversely proportional. The Vit D deficient group (<20ng/ml),had a mean HbA1Clevels of 10.5 +2.5 and vitamin D insufficient group (20-30ng/ml) and a HbA1Cof 9.5 +2.4 our findings are similar to the findings of a study conducted by padala Ravi kumar PS et al[28] and Talaat, I.Metal.[29]

There serum calcium levels in our study were 8.6 +1.2 mg/dl and 8.8+0.8mg/dl in deficient and insufficient groups respectively. Calcium levels were near to normal range in majority of patients in both groups. Similar findings were obtained in a study conducted by Husel et al.[30] Serum levels of FT4 was 1.1+3.0 and 1.2 +0.2 in deficient and insufficient groups. This is within normal range. The TSH levels 3.2 +0.2 and 2.8+0.4 in respective groups. There were no abnormal values obtained in the patients studied in this group. Similar findings were obtained in a study conducted by Arun Acharya et al.[31]

Supplementation of Vitamin D has showed improved glycemic control in patients with type -2 Diabetes mellitus in our study. This is also supported by studies of Peterson etal,[31] Hurst, P. Vet al,[32] and Scott, D et al.[33]

Another study of Buhary et al[34] showed lowering of HbA_1C after vitamin D supplementation (HbA1c 10.55to 7.7) and they found inverse relation between serum vitamin D levels with HbA1C before and after supplementation.

Vitamin D has shown to be related to glucose metabolism and development of diabetes mellitus and metabolic syndrome in studies of pitas et al,[35] Mezza et al.[36]

In our present study, in spite of tropical climate in this area, where there is a significant sun exposure even in winters it is surprising to find vitamin D deficiency levels among population. We observed lower $25(OH)D_3$ levels in this cohort of diabetes mellitus people and decrease in glycosylated haemoglobin levels in diabetes mellitus patients after treatment with vitamin D. It appears vitamin D may be related to glucose control in diabetes mellitus. As vitamin D is related to bone metabolism, it is a secosteroid synthesized in the skin by the action of ultraviolet irradiation from sun. Extraskeletal effects of vitamin D mainly need to be investigated more to find out the actions of Vit D.

Conclusions

Our study, on Vitamin D deficient or insufficient case of diabetes mellitus shows that glycemic status improves with supplementation of Vit D. Authors

recommend screening of all individuals for Vit D levels now and then.

Further scope of the study

However further studies of larger size and multicentric trials are required to confirm the same, identify the cause for deficiency in hot climate areas and evolve strategies to correct the deficiency and there by better glycemic status and prevent complications.

Limitations

As the study is of population attending a hospital the findings need to be confirmed by multicentric studies and on a larger population.

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