

Clinical Study on Newly Detected Type II Diabetes Mellitus Patients with Special Reference to Serum Vitamin D Levels and Obesity

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ABSTRACT

Introduction: Diabetes mellitus (DM) is one of the major public health issues facing the world in the 21st century, WHO estimates >425 million people have DM worldwide, India having second highest, i.e., 72.9 million. The link of vitamin D with abnormal glucose metabolism gained more scientific attention in the last decade. Globally one in six adults is obese and nearly 2.8 million die each year due to obesity. Obesity and DM are chronic diseases harming human health. Studies demonstrate vitamin D deficiency is closely related to obesity and increased risk of DM.

Aims and objectives: To study the clinical profile of newly-detected-type-II-DM patients in relation to vitamin D levels. Correlation of vitamin D levels with BMI in newly-detected-type-II-DM patients.

Materials and methods: This is a cross-sectional observational study done over 1 year, among 150 newly-detected-type-II-DM patients, in RRMCH. Informed consent was taken and detailed history, physical examination was done. All patients were submitted for investigations like FBS, PPBS, HbA1c, and vitamin D levels.

Results: The mean age was 49.17 ± 12.72 . One hundred and eleven (74%) of them had vitamin D levels <30 ng/dL. Mean vitamin D levels were 24.24 ± 11.20 . Mean HbA1c was 10.96 ± 1.78 , 9.66 ± 1.37 , and 7.05 ± 0.65 , among patients having their vitamin D levels ranging <20, 20–30, and >30 ng/dL, respectively, showing p value < 0.001. Mean BMI was 29.90 ± 2.18 , of 111 of them who had vitamin D levels <30 ng/dL, 74 of them had BMI (18.5–22.9), 20 had BMI (23–24.9), and 17 of them had BMI >25.

Interpretation and conclusion: In our study, we found that the higher the HbA1c levels, the lower was the vitamin D levels suggesting a good correlation between poor glycemic control and low vitamin D levels. Also, BMI showed moderate correlation to vitamin D levels. Thus, we can conclude that vitamin D levels can be independent risk factors for the development of DM and obesity and hence must be treated promptly.

Keywords: BMI, Diabetes mellitus, HbA1c, Obesity, Vitamin D.

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INTRODUCTION

Diabetes mellitus (DM) is one of the major public health issues facing the world in the 21st century. Globally, an estimated 425 million people have diabetes in the world compared with 108 million in 1980, also there were over 72.9 million cases of diabetes in India by 2017 according to International Diabetes Federation statistics.¹

Diabetes mellitus is a chronic metabolic disease caused by inherited and/or acquired deficiency in the production of insulin, or by the ineffectiveness of the insulin produced by the pancreas.²

Type II diabetes may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance.³

Approximately 1 billion people in the world suffer from vitamin D deficiency, which possibly results from limited exposure to sunlight, long-term wearing of covering clothes, use of sunscreen, as well as low consumption of food containing ergocalciferol, and also malabsorption syndrome. The link of vitamin D with insulin insensitivity or abnormal glucose metabolism gained much more scientific attention in the last 10 years. While the exact mechanisms of how the underlying multiple effects of vitamin D on different tissues are not fully understood currently, one unique factor is the expression of vitamin D receptors (VDRs) in >30 tissues, including pancreatic islet cells. There is some evidence that polymorphisms in the VDR gene maybe associated with insulin resistance, insulin

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secretion, and fasting glucose concentrations suggesting that vitamin D is likely to contribute to glucose metabolism.⁴

According to the WHO World Health Statistics Report of 2012, worldwide one in six adults is said to be obese and nearly 2.8 million individuals die each year due to obesity or being overweight, due to increased risk of morbidity and mortality.⁵

Obesity and type II diabetes are chronic diseases harming human health. Although the association between obesity and type II diabetes is well established, the molecular mechanism is still unclear. Vitamin D deficiency has previously been considered only to influence bone metabolism but recent *in vivo* studies have revealed

that vitamin D deficiency reduces the insulin secretion capacity of islet beta cells in the pancreas. Moreover, epidemiological studies have also demonstrated that vitamin D deficiency is closely related to obesity and increased risk of developing type II DM.⁶

Accumulating evidence suggests that vitamin D plays an important role in the development of obesity and type II DM. In turn leads to the poor outcomes of diabetes management and cardiac complications, morbidity, and mortality. Keeping in mind above said views, we want to do this study in our hospital (tertiary care center).

MATERIALS AND METHODS

Source of Data

All newly detected type II diabetes patients >30 years of age, both the genders who are attending Medicine OPD, as well as admitted in all medical wards of RajaRajeswari Medical College and Hospital, Bengaluru.

Method of Collection of Data

All patients >30 years of age with newly-detected-type II DM patients who attended Medicine OPD and who were admitted in all medical wards of RajaRajeswari Medical College and Hospital.

Informed consent from the patients was taken. Detailed history and physical examination, detailed drug history was taken. Patient's anthropometric measurements were done, height, weight, BMI. Detailed clinical examination was done as per pre-designed proforma. Patients were categorized according to WHO and Asia-Pacific guidelines of BMI as <18.5 (underweight), 18.5–22.9 (normal), 23–24.9 (overweight), >25 (obese). All the patients were submitted for the following blood investigations: FBS PPBS HbA1c serum vitamin D levels CBC serum vitamin D levels were estimated by chemiluminescent immuno-assay. With the assistance of a statistician, the collected data were analyzed to find the correlation of serum vitamin-D levels with BMI in their respective group.

Sample size: 150 patients.

Type of study: Cross-sectional observational study duration: 1 year (February 2017 to January 2018)

Inclusion Criteria

All patients with newly-detected-type II DM (with FBS >126 mg/dL, HbA1c >6.5% or RBS >200 mg/dL with symptoms suggestive of DM polyuria, polydipsia, fatigue, weight loss). Both genders >30 years of age who are attending medicine OPD and admitted in all Medicine wards of RajaRajeswari Medical College and Hospital. Patients taken for this study had a duration of diabetes from the date of detection not >3 months.

Exclusion Criteria

Patients with type I DM, gestational DM knew case of type II DM patients who are on treatment as well as complicated DM patients, patients who are on vitamin D and calcium supplementation. Any chronic illness with general debility such as malignancy, infection chronic kidney disease, liver diseases and skin diseases malabsorption syndrome, IBD, cystic fibrosis patients who are on medications that affect vitamin D metabolism/absorption, phenytoin, rifampicin, etc.

RESULTS (TABLES 1 TO 6 AND FIGS 1 TO 6)

Study Design

An observational clinical correlation study.

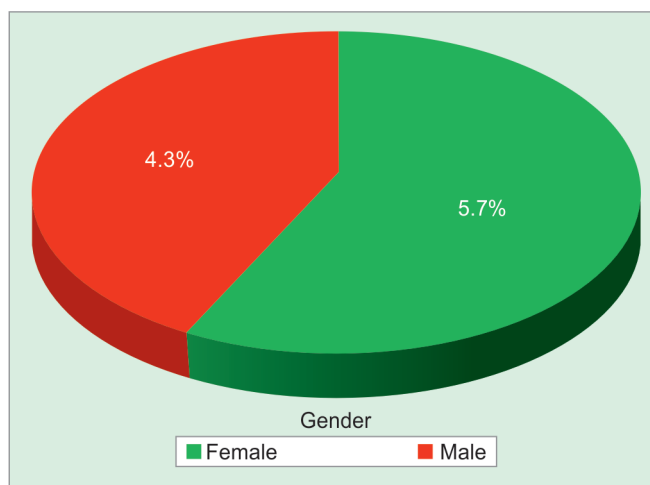


Fig. 1: Gender distribution of patients studied

Table 1: Gender distribution of patients studied

Gender	No. of patients	%
Female	86	57.3
Male	64	42.7
Total	150	100.0

Inference: In this study, out of 150 patients, there were 86 females (57.3%) and 64 males (42.7%)

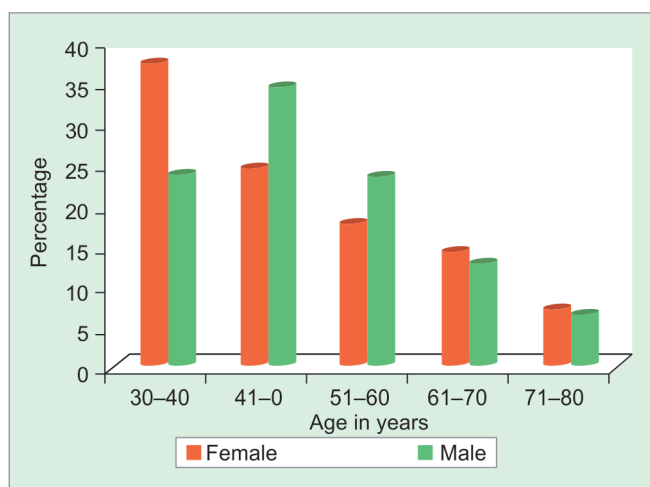


Fig. 2: Age distribution of patients studied

DISCUSSION

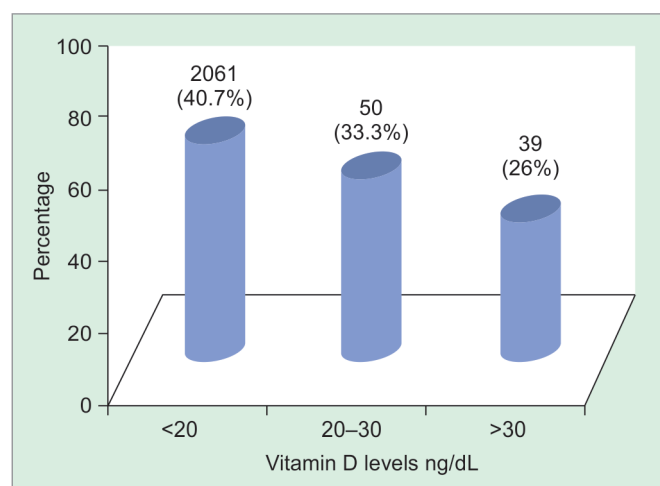
Diabetes mellitus is one of the most significant chronic health problems in the world. The world prevalence and incidence of DM vary considerably in different regions. The difference in ethnicity

Table 2: Age distribution of patients studied

Age in years	Gender		Total
	Female	Male	
30–40	32 (37.2)	15 (23.4)	47 (31.3)
41–50	21 (24.4)	22 (34.4)	43 (28.7)
51–60	15 (17.4)	15 (23.4)	30 (20)
61–70	12 (14)	8 (12.5)	19 (12.7)
71–80	6 (7)	4 (6.3)	10 (6.7)
Total	86 (100)	64 (100)	150 (100)
Mean \pm SD	48.60 \pm 13.56	49.94 \pm 11.55	49.17 \pm 12.7

$p = 0.530$, Student's t -test

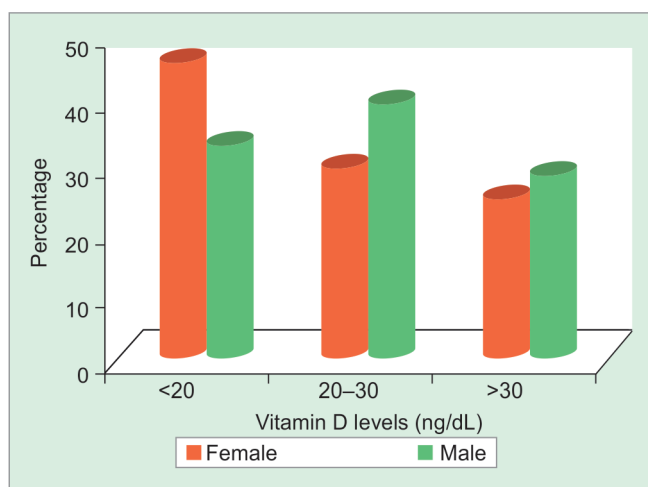
Inference: Maximum number of patients, i.e., 90 patients of both genders were in the age group between 30 and 50 years, 50 of them were from 50 to 70 years, and only 10 patients were in the age group of 70 to 80 years. The mean age group among females was 48.60 \pm 13.56, and among males was 49.9 \pm 11.55

**Fig. 3:** Distribution of vitamin D levels among study patients (ng/dL)**Table 3:** Distribution of vitamin D levels among study patients (ng/dL)

Vitamin D levels	No. of patients	%
<20	61	40.7
21–29	50	33.3
≥ 30	39	26.0
Total	150	100.0

Inference: Out of 150 patients, 111 patients (74%) had vitamin D levels <30 ng/dL, and only 39 of them had >30 ng/dL.

and race plays an important role in this variation.⁷ It is known for a long time that vitamin D deficiency constitutes a risk factor for impaired glucose tolerance. Vitamin D levels are reported to be lower in T1DM patients than in non-diabetics. Researches also have shown that there is a positive correlation between vitamin D level and insulin sensitivity in normal-weight individuals with normal glucose tolerance; a low level of vitamin D constitutes an independent risk factor for metabolic syndrome in a great part of the population.⁸ Vitamin D levels were comparatively lower in patients with the risk of DM than in patients without risk of DM. Vitamin D deficiency is associated with impaired insulin secretion, which is a high-risk factor for diabetes.⁹ Increasing evidence from animal and

**Fig. 4:** Vitamin D levels (ng/dL) distribution of patients studied**Table 4A:** Vitamin D levels (ng/dL) distribution of patients studied

Vitamin D levels (ng/dL)	Female
<20	40 (46.5)
20–30	25 (29.1)
>30	21 (24.4)
Total	86 (100)

$p = 0.105$, Fisher's exact test

Table 4B: Vitamin D levels (ng/dL) distribution of patients studied

Vitamin D levels (ng/dL)	Male
<20	21 (32.8)
20–30	25 (39.1)
>30	18 (28.1)
Total	64 (100)

$p = 0.185$, Fisher's exact test

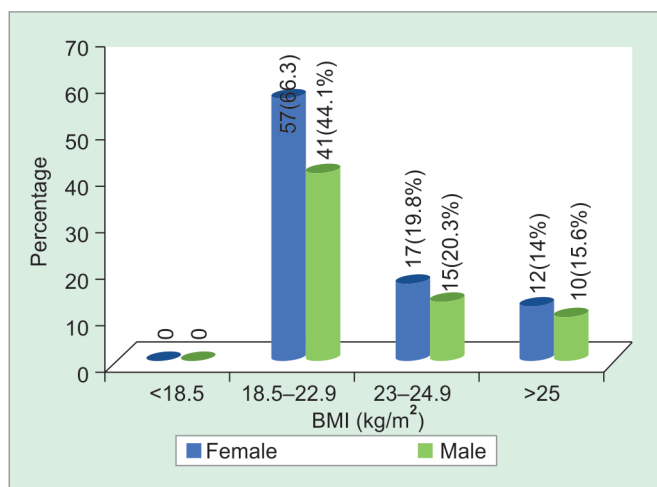
Table 4C: Vitamin D levels (ng/dL) distribution of patients studied

Vitamin D levels (ng/dL)	Gender		Total
	Female	Male	
<20	40 (46.5)	21 (32.8)	61 (40.7)
20–30	25 (29.1)	25 (39.1)	50 (33.3)
>30	21 (24.4)	18 (28.1)	39 (26)
Total	86 (100)	64 (100)	150 (100)

$p = 0.185$, Fisher's exact test

Inference: Out of 150 patients, 111 patients (74%), i.e., 65 females and 46 males had vitamin D levels <30 ng/dL and only 39 of them had vitamin D levels >30 ng/dL. "p" value is more significant in females compared with males

human studies shows that vitamin D may play an important role in modifying the risk of type II diabetes. Vitamin D has both direct effects (through activation of the VDR) and indirect (via regulation of calcium homeostasis) effects on various mechanisms related to the pathophysiology of type II DM and, including the pancreatic beta-cell dysfunction, impaired insulin action, systemic inflammation, and alterations in the renin–angiotensin–aldosterone system. The bulk of the evidence from human studies comes from many observational studies, most of which show an inverse association

Fig. 5: BMI (kg/m²) distribution of patients studiedTable 5: BMI (kg/m²) distribution of patients studied

BMI (kg/m ²)	Gender		Total
	Female	Male	
<18.5	0 (0)	0 (0)	0 (0)
18.5–22.9	57 (66.3)	41 (64.1)	98 (65.3)
23–24.9	17 (19.8)	13 (20.3)	30 (20)
>25	12 (14)	10 (15.6)	22 (14.7)
Total	86 (100)	64 (100)	150 (100)
Mean ± SD	22.92 ± 2.20	22.87 ± 2.18	22.90 ± 2.18

$p = 1.000$, Fisher's exact test

Inference: Out of 150 patients, 98 (65.3%) of them had BMI within the range of 18.5–22.9, 30 (20%) had BMI in the overweight range, i.e., 23–24.9, and 22 (14.7%) had BMI >25 (obese)

between vitamin D status and prevalence or incidence of type II diabetes. Results from underpowered clinical trials that have specifically examined the effect of vitamin D supplementation in the prevention or treatment of type II diabetes are inconclusive. Therefore, the causal link between vitamin D and type II diabetes remains to be determined. The prevalence of vitamin D deficiency in type II diabetics is almost double that in non-diabetic subjects.^{10,11} The risk factors for vitamin D deficiency and type II diabetes are often shared and include greater BMI, increasing age, and lack of physical activity.¹² Seasonal fluctuations in glucose and insulin concentrations have also been demonstrated (Desouza and Meier, 1987). This may, at least in part, be due to variations in 25(OH)D concentrations resulting from shorter durations of sun exposure in cold seasons.¹³ Furthermore, research has demonstrated that when accompanied by vitamin D deficiency, type II diabetes is associated with a greater risk of cardiovascular mortality (Joergensen et al., 2010).¹⁴ These observations have led to a need for randomized clinical trials to investigate the actual effects of vitamin D intake on the glycemic status of type II diabetics. From such studies, several theories for the mechanisms of action of vitamin D in diabetes have been established. Firstly, vitamin D has been shown to improve markers of glycemia via increased insulin secretion and reduced peripheral insulin resistance.^{15–17} Secondly, an improvement in the lipid profiles of type II diabetics have been demonstrated when supplemented with dietary vitamin D.^{15,18,19} Finally, vitamin D has been shown to upregulate endogenous antioxidants and

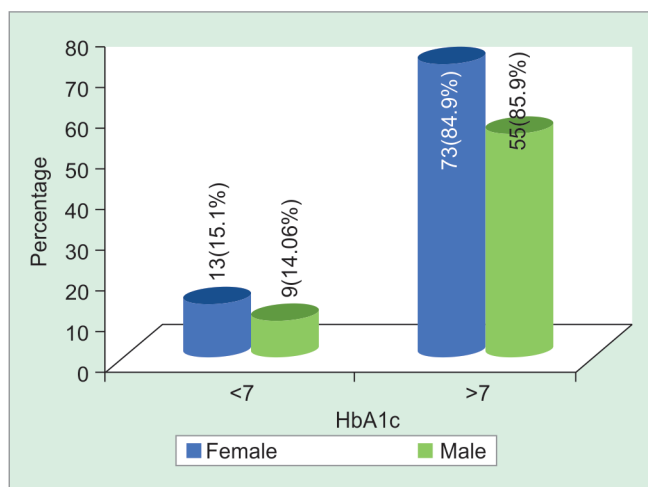


Fig. 6: HbA1c% distribution of patients studied

Table 6: HbA1c% distribution of patients studied

HbA1c%	Gender		Total
	Female	Male	
<7	13 (15.1)	9 (14.06)	22 (14.1)
>7	73 (84.9)	55 (85.9)	128 (85.9)
Total	86 (100)	64 (100)	150 (100)
Mean ± SD	9.67 ± 2.06	9.30 ± 2.20	9.51 ± 2.12

$p = 0.306$, Fisher's exact test

Inference: Out of 150 newly-detected-type II diabetic patients, 22 (14.1%) of them had HbA1c <7, and 128 (85.9%) of them had HbA1c >7. Out of 22 patients who had HbA1c <7, 13 (15.1%) were females and 9 (14.06%) were males. Out of 128 patients who had HbA1c >7, 73 (84.9%) were females and 55 (85.9%) were males

Student's t-test two-tailed, independent

Inference: In comparison of variables, the mean age was 49.17 ± 12.72 , mean vitamin D levels were 24.24 ± 11.20 , mean BMI was 22.90 ± 2.18 , and mean HbA1c was 9.51 ± 2.12

therefore may have the potential to attenuate oxidative stress in diabetic individuals.²⁰

In 2008, it was estimated one billion people were diagnosed with vitamin D deficiency.²¹ One recent study concluded that serum vitamin D concentrations were below satisfactory (30 ng/mL) in every region of the world; however, severe deficiency (concentration below 10 ng/mL) was found to be most prevalent in South Asia and the 22 Middle East.²² Lower concentrations of circulating 25(OH)D have been associated with increasing age, gender, dietary customs, latitude, exposure to sunlight, and skin pigmentation.²³ India is facing concurrent epidemics of type II DM and hypovitaminosis D due to urbanization and industrialization. Despite adequate sunshine throughout the year in our country, hypovitaminosis D is commonly seen among Indians across all age groups in urban as well as rural regions. It is associated with IR which progresses toward type II DM and its subsequent complications. Indian researchers investigated the association of vitamin D deficiency with insulin resistance, type II DM, glycemic control, and progression of complications among diabetics. After extensive literature and researches, Indian studies evaluating the association of vitamin D with TIIDM were selected in the present review. Vitamin D deficiency has been identified as an independent adjunctive risk factor for TIIDM. Following papers were studied to evaluate the relation of vitamin D status with TIIDM among Indians.

Author and reference	Study design	Number and characteristics	Main outcome
1. Kotwal et al. ¹⁹ Indian Journal of Endocrinology and Metabolism 18:726–730.	Case-control	102 newly detected and similar controls. North Indian subjects	81% of cases and 67% of controls had a deficiency. 16.2% diabetics and 2.5% controls had severe deficiency. Mean vitamin D in cases 18.81 ± 15.18 vs 28.26 ± 18.89 in controls ($p < 0.0001$)
2. Daga et al. ²⁰ High prevalence of vitamin D deficiency among newly diagnosed youth-onset diabetes mellitus in north India	Case-control	72 newly diagnosed youth onset (<25 years), type I DM (13) and type II DM (58) and healthy controls	Severe deficiency in T1DM than T2DM. Mean vitamin D cases— 7.8 ± 1.2 ng/mL, controls— 16.64 ng/mL (p value 0.26) 91.1% of cases and 58.5% of normal individuals were deficient
3. Doddamani ²¹ S. N. Medical College and HSK Hospital, Navanagar, Bagalkot, India	Cross-sectional	Newly diagnosed cases of T2DM ($n = 50$)	70% of patients had vitamin D <20 ng/dL ($p < 0.001$), inverse correlation with HbA1c and fasting plasma glucose ($p = 0.006, 0.001$), respectively
4. Modi et al. Journal of Diabetes and Metabolic Disorders 2015 ²²	Cross-sectional, observational study	Type II DM (group I; $n = 274$), pre-diabetics (group II; $n = 62$)	A total of 85% of patients in this study had vitamin D deficiency, i.e., serum vitamin D levels <30 ng/dL
5. Rolim et al. Diabetology and Metabolic Syndrome (2016) 8:77 ²³	Cross-sectional study	108 patients with a mean duration of T2DM of 14.34 ± 8.05 years and HbA1c of $9.2 \pm 2.1\%$	The prevalence of hypovitaminosis D was 62%
6. Antara Sen et al., Spectrum of vitamin D in type II DM: Journal of evidence-based medicine and Healthcare, Silchar Medical College and Hospital, Assam. March 2018 volume 5, issue 12 ¹¹	Prospective case-control study	100 type II DM patients and 100 non-diabetic patients (controls)	71% were vitamin D deficient, i.e., (<20 ng/mL) whereas in the control group 45% were found to be vitamin D deficient
7. Our study at Raja Rajeswari Medical College and Hospital, Bengaluru 2016–2017	Cross-sectional observational study	150 newly-detected type II diabetes mellitus patients, with mean age 49.17 ± 12.72 years, and mean HbA1c 9.51 ± 2.11	A total of 74% of patients in our study had vitamin D deficiency, i.e., serum vitamin D levels <30 ng/dL. Significant inverse correlation was found with HbA1c (p value < 0.001)

Vitamin D Deficiency, Obesity, and Insulin Resistance

Association of obesity with low levels of serum vitamin D has been reported in various studies. Physical inactivity including reduced outdoor activities may lead to diminished exposure to sunlight/ultraviolet light. This may partly be responsible for the low level of serum vitamin D in overweight and obese participants, who are more likely to be sedentary in their lifestyle. In the prevalence of the vitamin D deficiency among the study population who had increased outdoor physical activities in the previous month before data collection. In addition to this, the lipid solubility of vitamin D also modifies its bioavailability due to sequestration in the adipose tissue and may contribute to the low serum levels of vitamin D in overweight and obese persons. There are some observational and case-control studies suggesting that hypovitaminosis D is associated with decreased insulin secretion and that vitamin D supplementation reduces the concentrations of free fatty acids in diabetics, thereby improving insulin sensitivity.

Scragg et al. reported hypovitaminosis D is associated with higher insulin resistance and increased risk of diabetes.¹¹ Pittas et al. prospectively evaluated the effect of vitamin D supplementation (400 IU/day) on fasting glucose which improved after 3 years of therapy when compared with subjects on placebo.²⁴ In a Framingham Offspring study done in 2010 involving non-diabetic individuals, a strong inverse correlation between serum vitamin D concentrations and fasting plasma glucose as well as fasting insulin

levels were found, after adjustment for age, gender, BMI, waist circumference, and smoking.²⁵

Resnick and his colleagues exposed an “ionic”-based theory for the onset and development of hypertension, type II diabetes, obesity, and other manifestations of the metabolic syndrome that is characterized by elevated intracellular calcium, reduced intracellular magnesium, and reduced intracellular pH. Intracellular calcium is said to have a biphasic effect on the differentiation of preadipocytes to adipocytes. Low serum calcium resulting from low dietary intake or vitamin D deficiency leads to secondary elevation of PTH which, in turn, causes increased intracellular calcium that leads to increased differentiation of preadipocytes to adipocytes.²⁶

It is a well-known fact that one of the two major sources of vitamin D is cutaneous synthesis by solar ultraviolet B radiation and the other is dietary intake. The cutaneous synthesis of vitamin D is affected by many factors, such as season, latitude, time of day, skin pigmentation, the amount of skin exposed, and whether makeup with sunscreen lotion is used, so serum 25-hydroxyvitamin D levels vary between areas and persons. Hence, dietary supplementation of vitamin D and physical activity might be a feasible way for patients with diabetes to maintain sufficient 25-hydroxyvitamin D levels. Physical activity may increase serum 25-hydroxyvitamin D concentrations as a consequence of an associated increase in sunlight exposure.

Among type II diabetes patients with normal renal function, the relationship between serum 25(OH)D and glycemic control yielded

inconsistent results. In a prospective study of >5,000 healthy Danish individuals aged 30–65 years, hypovitaminosis D was associated with worsened insulin resistance and subsequent hyperglycemia.²⁷ In addition, every 25-nmol/L elevation in serum 25(OH)D resulted in a 17% reduced risk of incident type II diabetes in a prospective cohort of non-diabetes and obesity.²⁸ Type II diabetes is one of the most costly and burdensome chronic diseases of our time and is a condition that is increasing in epidemic proportions throughout the world. Over the last 10 years, a large number of observational studies have suggested an association between the onset of type II diabetes, vitamin D deficiency, and obesity. Type II DM, obesity, and vitamin D deficiency have one major trait in common: they are all pandemic. The International Diabetes Federation estimates the number of people with diabetes worldwide to be nearly 425 million, or 8% of the world's population. The estimated prevalence of vitamin D deficiency/insufficiency in India ranges between 50 and 90%²⁹ with similar trends found worldwide.^{30,31} Various previous studies showed that individuals with type II DM are at higher risk for developing vitamin D deficiency compared with non-diseased controls. Also, a study done in Command Hospital, Bengaluru in 2012 proved that the metabolic profile of type II DM patients, significantly improved over a period of 6 months after the onset of vitamin D3 supplementation, suggesting that vitamin D is a promising anti-diabetic and cardioprotective intervention in vitamin D-deficient populations.³² Vitamin D supplementation is a cheap, safe, and simple intervention. If it can be demonstrated that vitamin D supplementation can reduce the risk of type II DM, it may have significant implications for people at risk for the development of this potentially devastating long-term condition.

LIMITATIONS OF OUR STUDY

- Our study has not included control subjects, so correlation could not be studied.
- Since our study is a cross-sectional observational study, we have not given any vitamin D supplementation in patients with poor glycemic control, so follow-up with subjects was not done.

CONCLUSION

In this study of 150 newly-detected-type II diabetes patients, most of the patients studied were females (i.e., 57.3%) and the average BMI was found to be higher in females compared with males.

A total of 111 patients had vitamin D deficiency, i.e., serum vitamin D levels <30 ng/dL, among which 65 were females and 46 were males.

In this study, a significant correlation between HbA1c and vitamin D levels, i.e., vitamin D deficiency was seen with poor glycemic control status (HbA1c >7), compared patients with good glycemic control (HbA1c <7), it can be concluded that vitamin D plays an important role in glycemic control and can be an independent risk factor for the development of diabetes.

Also, vitamin D levels showed moderate correlation with BMI of patients, i.e., greater the BMI, more severe was the vitamin D deficiency. It can be concluded that vitamin D deficiency can be an independent risk factor for the development of obesity.

Treatment of vitamin D deficiency is simple, cost-effective, and safe, and supplementing vitamin D in oral/parenteral form can reduce the risk of developing type II DM in pre-diabetics, and also prevents further chronic complications in diabetics and greater risk of cardiovascular mortality. Hence, good glycemic control

with the maintenance of optimum serum vitamin D levels is to be followed in all diabetic patients. Since type II DM, obesity, and vitamin D deficiency are pandemic, easy to diagnose and treat, large multicenter studies are to be done in this regard.

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