

**Original research article****Effect of Metformin therapy on the levels of Vitamin D in patients of Type 2 Diabetes Mellitus****<sup>1</sup>Dr.S Mahaboob Fayaz, <sup>2</sup>Dr.Pradeep N, <sup>3</sup>Dr.Narendran A**<sup>1,2,3</sup>Associate Professor, Department of General Medicine, East Point College of Medical Sciences and Research Centre, Bangalore, Karnataka, India**Corresponding Author:**

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**Abstract****Introduction**

Type 2 Diabetes Mellitus currently affects 10.5% of world's population. The first drug of choice for the management of Type 2 DM is Metformin. Most common side effects of Metformin therapy is gastro intestinal intolerance which can lead to malabsorption of certain vitamins. There is recent evidence that decrease in vitamin D levels can cause increased insulin resistance.

**Objective/Aim:** To know the effect of metformin therapy on the levels of vitamin D in patients of Type 2 Diabetes Mellitus.

**Methods and Materials**

The study was designated as a case control study. 30 patients were on Metformin (CASES) and the other 30 were on other anti-diabetic drugs (Sulfonylurea, Acarbose and Pioglitazone ) (CONTROLS) with age and sex matched, fulfilling the inclusion and exclusion criteria. Vitamin D levels were measured by radio-immunoassay method in both groups and the values were assessed.

**Results:** In this study, the mean vitamin-D levels among the cases were  $15.14 \pm 4.73$  (SD) ng/ml, whereas among the controls was  $17.8 \pm 7.05$  (SD) ng/ml. When we compared the severity of the vitamin D levels in between cases and controls, we found that there is no significant difference between the two groups.

**Conclusion:** This study suggests that vitamin D deficiency is not a clinical concern among Metformin-treated patients with Type 2 Diabetes, as the difference between the two groups was not statistically significant.

**Keywords:**Metformin Therapy, Vitamin D, Type 2 Diabetes Mellitus

**Introduction**

Type 2 Diabetes Mellitus currently affects 10.5% of the world's population. This disease has substantial associated morbidity and mortality, with the potential to affect adversely the cardiovascular, renal, and neurologic systems of each person with the disease <sup>[1]</sup>. Treatment of Type 2 Diabetes includes many options such as diet modification, lifestyle changes, a variety of oral medications, and insulin. One medication that has proved effective in treatment of Type 2 Diabetes and is considered as the first choice, as recommended by the American Diabetes Association is Metformin. Metformin acts through multiple mechanisms including decreasing hepatic glucose output, increasing insulin-mediated glucose use in peripheral tissues, and increasing intestinal glucose utilization.

Most common side effects of Metformin are mild and can include gastrointestinal distress, soft stools, and diarrhea <sup>[2]</sup>. It is well documented that these gastrointestinal side effects can lead to malabsorption of vitamins in a dose and time dependent manner <sup>[3,4]</sup>. Metformin increases the bile acid pool within the intestine predominantly through reduced ileal absorption <sup>[5]</sup>. This disruption of the enterohepatic circulation of bile salts has potential consequences of cholesterol homeostasis, entero-endocrine function and glucose homeostasis. It may also contribute to Metformin intolerance through alterations in the micro biome and stool consistency. As discussed previously the alteration in bile acid absorption may result in increased GLP-1 secretion, in a similar way to that observed with bile acid sequestrants such as colestevlam <sup>[5]</sup>. Since Vitamin-D is a fat soluble vitamin, it is worthwhile investigating the effect of Metformin therapy on vitamin D level in patients with Type 2 Diabetes Mellitus.

Vitamin D has a small but important role in diabetes. Investigators have suggested that an association exists between decreased vitamin D and increased insulin resistance in Type 2 Diabetes <sup>[6,7]</sup>. Vitamin D is produced endogenously when ultraviolet rays initiate its synthesis in the skin, but vitamin D is also absorbed in the intestine from various natural and fortified food sources <sup>[8]</sup>. If gastrointestinal symptoms from Metformin use can lead to malabsorption of vitamin B12, it is probable that vitamin D could also be malabsorbed. Hence, this study focuses on the effect of Metformin therapy on Vitamin D levels in patients of Type 2 Diabetes Mellitus.

**Materials and Methods**

**Source of data**

The study was carried out in a Medical College affiliated to a Tertiary care centre for a period of 2 years. The study was designated as a case control study. 30 patients were on Metformin (CASES) and the other 30 were on other anti-diabetic drugs (Sulfonylureas, Acarbose and Pioglitazone) (CONTROLS) with age and sex matched, fulfilling the inclusion and exclusion criteria.

**Inclusion Criteria**

1. AGE > 30 years
2. Type2 DM patients who are on Metformin therapy for more than 6 months (cases)
3. Type 2 DM patients who are on anti diabetic drugs for more than six months (other than Metformin) - (controls)

**Exclusion criteria**

1. AGE < 30 years
2. Type1 DM patients
3. Patients who are on vitamin D supplementation
4. Patients who are on steroid therapy, oral contraceptive pills and diuretics
5. Pregnancy
6. Critically ill patients
7. Patients with tuberculosis
8. Patients with renal impairment

**Method of collection of data**

A detailed proforma was filled up for each patient, which included age, sex, IP and OP number, relevant present, past, personal history, diet history and clinical examination was done.

Anthropometric measurements like height and weight were measured and BMI was calculated for each patient in the study group. Venous plasma glucose was measured both fasting and post prandial (120 min after a 75 g glucose load). HbA1C was measured by high performance liquid chromatography method.

**Measurement of serum 25-(OH) vitamin D**

Serum 25-Hydroxy vitamin D levels were measured and stored at -20°C collected from both cases and controls. Serum 25-(OH) vitamin D was measured by Radioimmuno assay method.

**Statistical methods applied**

The results were analysed by appropriate statistical methods. All the statistical methods were carried out through SPSS for windows (version 16.0).

**Table 1:** Age distribution among cases and controls \*number in bracket indicates (PERCENTAGE)

Age groups (Years)	Cases	Controls	Total
<65	20(33.3)	20(33.3)	40(66.6)
≥65	10(16.6)	10(16.6)	20(33.3)
Total	30	30	60

In this study, the study group constituted cases between the ages 32-90 years. Majority of the cases and controls were less than 65 years of age which constituted to 66.6% of the total group.

**Table 2:** Sex wise distribution of cases and controls

Sex	group		Total
	Case	Ctrl	
Male	16	16	32
			53.3%
Female	14	14	28
			46.7%
Total	30	30	60
			100.0%

In this study, 53.3% were males and 46.7% were females in both the groups.

**Table3:** HbA<sub>1</sub>C among cases and controls

	Group	N	Mean	Std. Deviation	Std. Error Mean
HbA <sub>1</sub> C	Case	30	6.7633	1.30503	.23826
	Control	30	7.1517	1.32811	.24248

In this study, the mean HbA1C among the cases was 6.76±1.3 (SD)%, whereas among the controls was 7.15±1.32 (SD)%.

**Table4:** BMI among cases and controls

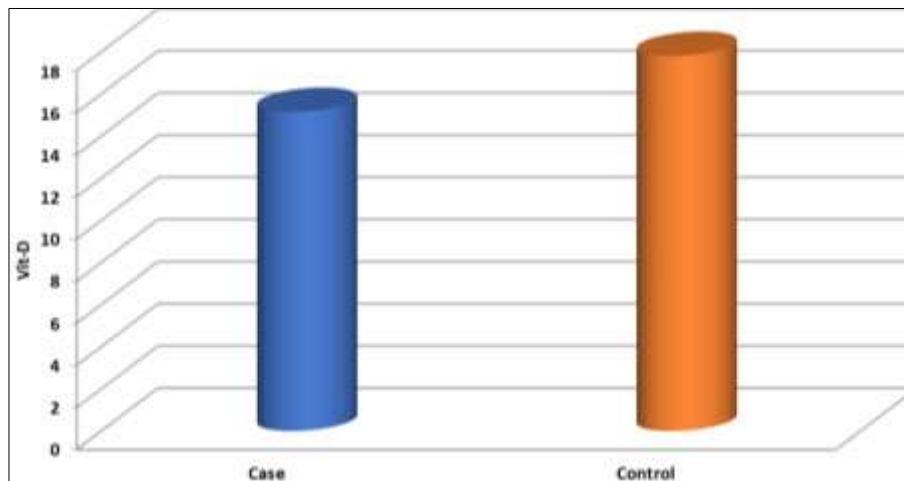
		GROUP			Total
		Case	Ctrl		
BMI	<25	Count	15	12	27
		% of GROUP	50.0%	40.0%	45.0%
	>25	Count	15	18	33
		% of GROUP	50.0%	60.0%	55.0%
Total	Count	30	30	60	
	% of GROUP	100.0%	100.0%	100.0%	

In this study, 50% of the cases were with BMI>25 and 50% were with BMI<25, whereas in controls, 60% of them had BMI>25 and 40% had BMI <25%.

**Table5:** Vitamin-D levels among cases and controls

	Group	N	Mean	Std. Deviation	Std. Error Mean
Vit-D	Case	30	15.1497	4.73958	.86533
	Control	30	17.8077	7.05819	1.28864

p-value 0.092



**Fig 1:** Vitamin-D levels among cases and controls

In this study, the mean vitamin-D levels among the cases was 15.14±4.73 (SD) ng/ml, whereas among the controls was 17.8±7.05 (SD) ng/ml.

**Table6:** Classification of cases and controls in terms of Vit-D levels \*number in bracket indicates%

Vitamin-D (ng/ml)	Cases	Controls	Total
<20 (deficient)	25(41.66)	20(33.33)	45(75)
20-29.9 (Insufficient)	5(8.33)	8(13.3)	13(21.66)
>30 (Sufficient)	0(0)	2(3.33)	2(3.33)
Total	30	30	60

In this study, among the cases 83.32% were Vitamin-D deficient, 16.66% were insufficient and 0% were sufficient. Among the controls 66.66% were deficient, 26.6% were insufficient and 6.66% were sufficient.

Also, as a whole, 75% were Vitamin-D deficient, 21.66% were insufficient and 3.33% were sufficient

**Discussion**

In the present study, serum 25(OH)-Vitamin D were estimated in Type 2 Diabetic patients of which 30 patients were on Metformin (CASES) and the other 30 were on other anti-diabetic drugs(Sulfonylureas, Acarbose and Pioglitazone)(CONTROLS) with age and sex matched, fulfilling the inclusion and exclusion criteria.

**Age distribution of cases and controls:** In this study,the study group constituted cases between the ages

32-90 years. Majority of the cases and controls were less than 65 years of age which constituted to 66.6% of the total group. The mean age of the cases was  $57.8 \pm 16.15$  (SD) years and of the controls was  $58.7 \pm 10.47$  (SD) years. This was similar to the findings of R Anil Kumar *et al*<sup>[9]</sup>.

**Sex wise distribution of the cases and controls:** In this study, 53.3% were males and 46.7% were females in both the groups. The males and females were almost equally distributed with a male to female ratio of 1.14:1. This was corroborating with the findings of R Anil Kumar *et al*<sup>[9]</sup> and Elizabeth Kos *et al*<sup>[10]</sup>.

**Vitamin-D levels among cases and controls:** In this study, among the cases 83.32% were Vitamin-D deficient, 16.66% were insufficient and 0% were sufficient. Among the controls, 66.66% were deficient, 26.6% were insufficient and 6.66% were sufficient.

Also, as a whole 75% were Vitamin-D deficient, 21.66% were insufficient and 3.33% were sufficient. According to a South Indian study, Vitamin D deficiency was present in 83% of type 2 diabetes individuals and 82% of normal individuals. So both Type 2 Diabetes and normal individuals are equally deficient in vitamin D<sup>[9]</sup>.

However in a study by Elizabeth Kos *et al*, vitamin D deficiency was not a clinical concern among Metformin treated patients with Type 2 Diabetes and that Metformin does not negatively affect treatment of vitamin D deficiency in these patients<sup>[10]</sup>.

Additionally in a study by S S Zharghaniet *al*<sup>[11]</sup>, they found that combining vitamin D with Metformin can help combat insulin resistance and Diabetes Mellitus in the obese Diabetic patients.

### Conclusion

This study suggests that vitamin D deficiency is not a clinical concern among Type 2 Diabetes patients treated with Metformin. Also, Vitamin D deficiency is common among Indian Type 2 Diabetics and general population.

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