ROLE OF VITAMIN D ON HbA1c LEVEL, AS AN ADJUVANT TO ORAL HYPOGLYCAEMIC DRUGS IN TYPE 2 DIABETIC PATIENTS

Shalini Gupta¹, Nilam Nigam², Sanjay Kumar Nigam³, Sunil Kumar⁴, Sugandha Garg⁵

¹Assistant Professor, Department of Pharmacology, Rama Medical College Hospital and Research Centre, Kanpur.

²Professor and HOD, Department of Pharmacology, Rama Medical College Hospital and Research Centre, Kanpur.

³Professor, Department of Pathology, Rama Medical College Hospital and Research Centre, Kanpur.

⁴MSc. Student (Medical), Department of Pharmacology, Rama Medical College Hospital and Research Centre, Kanpur.

⁵Postgraduate Student, Department of Pharmacology, Rama Medical College Hospital and Research Centre, Kanpur.

ABSTRACT

BACKGROUND

The incidence of type 2 diabetes mellitus is increasing at an alarming rate both nationally and internationally with more than 1 million new cases diagnosed every year. Diabetes warrants intense lifestyle adaptations, polypharmacy and insulin centred regimens. Conventional oral antidiabetic medications are associated with hypoglycaemias. Besides insulin, treatment has been linked to poor compliance, weight gain and possibly adverse cardiovascular outcomes.⁽³⁾ The role of vitamin D in the pathogenesis and prevention of diabetes has sparked widespread interest. Vitamin D receptors are present in both pancreatic beta-cells and immune cells. Beside its classical role as the major regulator for calcium absorption, vitamin D mediates the activity of β -cell calcium-dependent endopeptidases, promotes conversion of pro-insulin to insulin and increases insulin output.

Objective of this study is to see the effect of vit D on HbA1c level, as an adjuvant to oral hypoglycaemic drugs (of any class) in type 2 diabetic patients.

MATERIALS AND METHODS

Sixty patients (previously known cases of type 2 DM) aged above 18 years, attending Medicine OPD of Rama Medical College Hospital & Research Centre, Kanpur, over a period of one year were included in the study. The eligible patients (N=60) based on inclusion and exclusion criteria were divided in two groups of 30 patients in each group: group A (control group) on oral hypoglycaemic drugs without vit D supplementation & group B (study group) on oral hypoglycaemic drugs with vit D supplementation. The patients were randomly selected and the vit D supplementation was given on the basis of physician's direction and the dose of vit D (2000 IU orally) was fixed at the time of the inclusion in the study. Patients were then followed up for a period of 3 months.

RESULTS

On day 0, mean of fasting blood sugar levels in control group and in study group was 155.17 mg/dL $\pm$ 9.07 mg/dL and 152.13 mg/dL $\pm$ 3.45 mg/dL and mean of postprandial blood sugar levels in control group and in study group was 200.07 mg/dL $\pm$ 12.69 mg/dL and 197.37 mg/dL $\pm$ 5.40 mg/dL respectively (Table No. 1A) and on day 90, mean of fasting blood sugar levels in control group and in study group was 159.47 mg/dL $\pm$ 8.90 mg/dL and 120.10 mg/dL $\pm$ 21.99 mg/dL and mean of postprandial blood sugar levels in control group and in study group was 205.00 mg/dL $\pm$ 12.09 mg/dL and 160.17 mg/dL $\pm$ 22.43 mg/dL respectively (Table No. 1B) respectively. Mean HbA_{1c} in control group on day 0 was 6.457 mg/dL $\pm$ 0.778 mg/dL and on day 90 was 6.873 mg/dL $\pm$ 0.699 mg/dL and in study group on day 0 was 6.403 mg/dL $\pm$ 0.65 mg/dL and on day 90 was 5.61 mg/dL $\pm$ 0.533 mg/dL (Table No. 2). The difference in mean of HbA_{1c} level in both the groups was p < .001 which is highly significant, means that vitamin D therapy has had beneficial effect on the control of blood sugar in diabetic patients.

CONCLUSION

HbA_{1c} level in patients included in the study was significantly better on day 90 as compared to day 0 & the blood sugar levels (both fasting and postprandial) were improved in the study group significantly.

KEYWORDS

Type 2 diabetes mellitus, Vitamin D.

HOW TO CITE THIS ARTICLE: Gupta S, Nigam N, Nigam SK, et al. Role of vitamin D on HbA_{1c} level, as an adjuvant to oral hypoglycaemic drugs in type 2 diabetic patients. J. Evolution Med. Dent. Sci. 2017;6(53):4017-4020, DOI: 10.14260/Jemds/2017/868

Financial or Other, Competing Interest: None.

Submission 26-05-2017, Peer Review 22-06-2017,

Acceptance 27-06-2017, Published 03-07-2017.

Corresponding Author:

Dr. Nilam Nigam,

Professor and HOD,

Department of Pharmacology,

Rama Medical College Hospital

& Research Centre, Kanpur.

E-mail: drnilamnigam@gmail.com

DOI: 10.14260/Jemds/2017/868

BACKGROUND

The incidence of type 2 diabetes mellitus is increasing at an alarming rate both nationally and internationally with more than 1 million new cases diagnosed every year.⁽¹⁾ Despite the advancements in the diagnosis and management of diabetes, achieving normoglycaemia or optimal glycaemic control is still considered challenging.⁽²⁾ This is because care of type 2 diabetes warrants intense lifestyle adaptations, polypharmacy and insulin centred regimens. Conventional oral antidiabetic medications are associated with hypoglycaemias. Besides insulin, treatment has been linked

to poor compliance, weight gain and possibly adverse cardiovascular outcomes.⁽³⁾ The role of vitamin D in the pathogenesis and prevention of diabetes has sparked widespread interest. Vitamin D receptors are present in both pancreatic beta-cells and immune cells. Beside its classical role as the major regulator for calcium absorption, vitamin D mediates the activity of β -cell calcium-dependent endopeptidases, promotes conversion of proinsulin to insulin and increases insulin output. In peripheral insulin target tissues, vitamin D enhances insulin action via regulation of the calcium pool. The effect of vitamin D on insulin secretion may be mediated by changes in intracellular calcium concentration in β -cells.^(4,5)

Vitamin D is not only essential for maintaining bone health, but it also plays a role in several other biochemical mechanisms within the human body. The mechanism of action of the active form of vitamin D is similar to that of other steroid hormones and is mediated by its binding to vitamin D receptor (VDR). VDRs are found in most tissues, not just in those that participate in the classic actions of vitamin D such as bones, intestines and kidneys. The enzyme responsible for converting 25 (OH) D to 1, 25 (OH) 2D is also expressed in a variety of extrarenal sites, such as endothelial cells, beta cells and immune cells.⁽⁶⁾

Studies suggest an inverse association between vitamin D status and glucose intolerance/type 2 diabetes.^(7,8) Accumulating evidences suggest that vitamin D deficiency is associated with increased risk for diabetes. Hypovitaminosis D is a risk factor for glucose intolerance and diabetes.^(9, 10) Vitamin D deficiency appears to be related to the development of type 2 diabetes mellitus. Mild-to-moderate vitamin D insufficiency has been proposed as a risk factor for type 2 diabetes. Higher plasma vitamin D has been shown to be related with a lower risk for the development of diabetes mellitus in high risk patients.

So, with this background the present study is being undertaken to see the effect of vitamin D in glycaemic control in type 2 diabetic patients on oral hypoglycaemic drugs.

MATERIAL AND METHODS

Study Setting

This study was conducted in the Department of Pharmacology and General Medicine, Rama Medical College Hospital and Research centre – Mandhana, Kanpur.

Study Design

Descriptive Study

This study is a prospective, open label, randomised control trial done in the Department of Pharmacology and General Medicine, Rama Medical College Hospital and Research Centre Kanpur, over a period of twelve months. 60 subjects of type 2 diabetes mellitus were recruited from Medicine OPD after taking informed consent.

Study Population

Study was conducted over a period of twelve months. 60 subjects of type 2 diabetes mellitus were recruited from the Department of Medicine OPD at Rama Medical College Hospital.

Inclusion Criteria

1. Patients of both sexes aged between 30 years to 60 years.
2. Established diagnosis of Type 2 DM, without complications.
3. Patients without any concurrent illness.

Exclusion Criteria

1. Patients diagnosed as Type 1 DM.
2. Patients on vitamin D supplementation for last 12 weeks.
3. Patients with any acute or long term comorbidity.
4. Pregnant or lactating women.

Collections

Blood sample was collected from the patients followed for both fasting and postprandial blood sugar levels every fortnightly.

Study Duration

Study was conducted over a period of twelve months.

Sampling and Sample size

Statistical Analysis- The treatment groups were compared and the results were analysed by using Unpaired t test on SPSS 21 trial version.

$$n \geq \frac{(s.d_1^2 + s.d_2^2) (z\alpha + z\beta)^2}{(S.E \text{ of difference})^2}$$

$$= \frac{(.4^2 + 2.1^2) (2.8)^2}{(1.1)^2}$$

$$n = 29.58 \sim 30 \text{ for each group}$$

n = no. of sample use in study for each group
 $z\alpha = .84$
 $z\beta = 1.9$
 $d = 1.1$

(SD1 & SD2 taken from this reference) → "Serdar Olt Relationship between vitamin D and glycaemic control in patients with type 2 diabetes mellitus, Int J Clin Exp Med 2015;8(10):19180-19183^[11]

Sampling and Sample Size

60 type 2 diabetic patients attending medicine OPD were randomly divided into two groups by card system and 30 cards per group.

- **Group A-** (Control group)- 30 Type 2 diabetic patients on oral hypoglycaemic drugs without vitamin D supplementation.
- **Group B-** (Study group)- 30 Type 2 diabetic patients on oral hypoglycaemic drugs with vitamin D supplementation.

Estimation of HbA_{1c}

Various methods for detection of glycosylated Hb:

1. Starch block electrophoresis (Schroeder et al, 1960).
2. Column chromatography technique. This method is very slow.

3. High performance liquid chromatography method (HPLC) for Hb ----> this method has been used in this study.

Method of Collection of Data

All the eligible patients underwent both routine and specific investigations (HbA_{1c} level) on the first visit. The study group (group B) were prescribed Vitamin D 2000 IU orally daily for twelve weeks (as prescribed by the physician). Patients were followed for both Fasting and postprandial blood sugar levels every fort nightly. At the end of the therapy (After 12 weeks) again patients underwent both routine and specific investigations and were compared from the baseline (day 0). The cases were followed for compliance with the therapy and adverse drug reactions if any on each follow up visit.

Ethical Issues

The study was started after approval from the institutional medical ethical committee.

RESULTS

On day 0, mean of fasting blood sugar levels in control group and in study group was 155.17 mg/dL $\pm$ 9.07 mg/dL and 152.13 mg/dL $\pm$ 3.45 mg/dL and mean of postprandial blood sugar levels in control group and in study group was 200.07 mg/dL $\pm$ 12.69 mg/dL and 197.37 mg/dL $\pm$ 5.40 mg/dL respectively (Table No. 1A) and on day 90, mean of fasting blood sugar levels in control group and in study group was 159.47 mg/dL $\pm$ 8.90 mg/dL and 120.10 mg/dL $\pm$ 21.99 mg/dL and mean of postprandial blood sugar levels in control group and in study group was 205.00 mg/dL $\pm$ 12.09 mg/dL and 160.17 mg/dL $\pm$ 22.43 mg/dL respectively (Table No. 1B).

Mean HbA_{1c} in control group on day 0 was 6.457 mg/dL $\pm$ 0.778 mg/dL and on day 90 was 6.873 mg/dL $\pm$ 0.699 mg/dL and in study group on day 0 was 6.403 mg/dL $\pm$ 0.65 mg/dL and on day 90 was 5.61 mg/dL $\pm$ 0.533 mg/dL (Table No. 2).

	Control		Study	
	FBS (mg/dL)	PP (mg/dL)	FBS (mg/dL)	PP (mg/dL)
Mean	155.17	200.07	152.13	197.37
SD	$\pm$ 9.07	$\pm$ 12.96	$\pm$ 3.45	$\pm$ 5.40

Table -1A. Relationship between Fasting and Postprandial Levels in Control and Study Group (day-0)

Graph Representing Table 1-A

	Control		Study	
	FBS (mg/dL)	PP (mg/dL)	FBS (mg/dL)	PP (mg/dL)
Mean	159.47	205.00	120.10	160.17
SD	$\pm$ 8.90	$\pm$ 12.09	$\pm$ 21.99	$\pm$ 22.43

Table 1B. Postprandial Levels In Control and Study Group (Day-90)

Graph Representing Table 1-B

	Control (Baseline)	Study (Baseline)	Control	Study	P Value
	Day 0	Day 0	Day 90	Day 90	
Mean + SD	6.457 $\pm$ 0.778	6.403 $\pm$ 0.65	6.873 $\pm$ 0.699	5.61 $\pm$ 0.533	.001

Table 2. Relationship between Mean HbA_{1c} in Control and Study Group

Graph Representing Table 2

The difference in mean HbA_{1c} level was $p < 0.001$ which is highly significant.

DISCUSSION

Hypovitaminosis D is a risk factor for glucose intolerance and diabetes.^(9,10) Mild-to-moderate vitamin D insufficiency has been proposed as a risk factor for type 2 diabetes. Higher plasma vitamin D level has been shown to be related with a lower risk for the development of diabetes mellitus in high risk patients. Vitamin D improves insulin sensitivity by its anti-inflammatory activity. Currently vitamin D is called as "Sunshine Hormone". Major amount of vitamin D is synthesised by the skin on exposure to UVB rays.⁽¹²⁾ There is

a growing global concern about the deficiency of vitamin D.⁽¹³⁾ The best marker for vitamin D status is 25 hydroxyvitamin D [25 (OH)D].⁽¹⁴⁾ Vitamin D receptors are present in both pancreatic beta-cells and immune cells.^(4,5) From a biological perspective, the presence of the vitamin D receptor in many cell types and organs, and the local production of 1, 25 (OH)₂D in several extrarenal organs, including β -pancreatic cells, supports potential broad-ranging effects of vitamin D outside of skeletal health, including type 2 diabetes. Vitamin D is thought to have both direct (by the activation of the vitamin D receptor) and indirect (by the regulation of calcium homeostasis) effects on various mechanisms related to the pathophysiology of type 2 diabetes, including impaired pancreatic- β cell function and insulin resistance.^(4,5) found an inverse relation between 25 (OH) vitamin D concentration and FPG, but a direct relation with insulin sensitivity.⁽¹⁵⁾ As to these studies, our study shows that mean FPG and mean HbA_{1c} was significantly reduced after increased vitamin D intake.⁽¹⁶⁾ The main purpose of this study was to investigate the effects of vitamin D supplementation on glucose homeostasis. The results showed that vitamin D supplementation significantly decreased serum FPG, insulin in patients with T2DM. Thus, showing an inverse relation between final FPG and basal 25 (OH) D concentration. In other words, higher serum basal 25 (OH) D led to lower final FPG. This showed that patients who had a higher serum basal 25 (OH) D concentration benefited more of vitamin D intake to lowering final FPG. This may be because of non-skeletal effects of vitamin D which appears in higher vitamin D concentration and the effects of lower vitamin D concentration are limited to the bone and muscles.⁽¹⁷⁾ The rationale of addition of vit D in the present study was based on inadequate glycaemic control with oral hypoglycaemic drugs. The dose of vit D was fixed (2000 IU/Day) throughout the study period after the selection of patients as per their clinical presentation at the time of start of study.

Mean HbA_{1c} in control group on day 0 was 6.457 mg/dL $\pm$ 0.778 mg/dL and on day 90 was 6.873 mg/dL $\pm$ 0.699 mg/dL and in study group on day 0 was 6.403 mg/dL $\pm$ 0.65 mg/dL and on day 90 was 5.61 mg/dL $\pm$ 0.533 mg/dL (Table No. 2). The difference in mean HbA_{1c} level was $p < .001$ which is highly significant. The findings of this study indicate that the metabolic profile of T2DM subjects is significantly improved after the onset of vitamin D supplementation. To conclude, the add on therapy was seen to be effective in lowering the blood glucose level (both fasting and postprandial) along with reduction in HbA_{1c} when used in combination therapy with vitamin D over a period of three months in type 2 diabetic subjects. The benefit seen in blood glucose control was highly significant in both the groups. In view of the positive effects seen in all parameters with the use of combination therapy, it can be assumed that if the therapy had been continued for a longer duration, even better results would have been seen. Moreover, this combination therapy was safe and no serious adverse events were reported in the study.

CONCLUSION

HbA_{1c} level in patients included in the study was significantly better on day 90 as compared to day 0 and the blood sugar levels (both fasting & postprandial) were also improved

significantly in the study group. There was no intergroup difference in the level of HbA_{1c}. No serious adverse events were reported in the study. This indicates the potential of this supplementation in the treatment of type 2 diabetes and may halt the progression of disease-related complication because of controlling the blood glucose levels at optimal levels.

REFERENCES

- [1] Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA* 2003;289(1):76-9.
- [2] Wallace TM, Matthews DR. Poor glycaemic control in type 2 diabetes: a conspiracy of disease, suboptimal therapy and attitude. *QJM* 2000;93(6):369-74.
- [3] Montane J, Cadavez L, Novials A. Stress and the inflammatory process; a major cause of pancreatic cell death in type 2 diabetes. *Diabetes Metab Syndr Obes* 2014;7:25-34.
- [4] Bournon PM, Billaudel B, Faure-Dussert A. Influence of Vitamin D3 deficiency and 1,25 dihydroxyvitamin D3 on de novo insulin biosynthesis in islets of the rat endocrine pancreas. *J Endocrinol* 1999;160(1):87-95.
- [5] Danescu LG, Levy S, Levy J. Vitamin D and diabetes mellitus. *Endocrine* 2009;35(1):11-7.
- [6] Bikle D. Nonclassic actions of vitamin D. *J Clin Endocrinol Metab* 2009;94(1):26-34.
- [7] Scragg R, Sowers M, Bell C. Serum 25-hydroxyvitamin D, diabetes and ethnicity in the Third National Health and Nutrition Examination Survey. *Diabetes Care* 2004;27(12):2813-8.
- [8] Ford ES, Ajani UA, McGuire LC, et al. Concentrations of serum vitamin D and the metabolic syndrome among US adults. *Diabetes Care* 2005;28(5):1228-30.
- [9] Chiu KC, Chu A, Go VLW, et al. Hypovitaminosis D is associated with insulin resistance and β cell dysfunction. *Am J Clin Nutr* 2004;79(5):820-5.
- [10] Pittas AG, Lau J, Hu FB, et al. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. *J Clin Endocrinol Metab* 2007;92(6):2017-29.
- [11] Olt S. Relationship between vitamin D and glycemic control in patients with type 2 diabetes mellitus. *Int J Clin Exp Med* 2015;8(10):19180-3.
- [12] Kochupillai N. The physiology of vitamin D: current concepts. *Indian J Med Res* 2008;127(3):256-62.
- [13] Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357(3):266-81.
- [14] Takiishi T, Gysemans C, Bouillon R, et al. Vitamin D and diabetes. *Rheum Dis Clin North Am* 2012;38(1):179-206.
- [15] Chiu KC, Chu A, Go VL, et al. Hypovitaminosis D is associated with insulin resistance and Beta cell dysfunction. *Am J Clin Nutr* 2004;79(5):820-5.
- [16] Pittas AG, Harris SS, Stark PC, et al. The effects of calcium and vitamin D supplementation on blood glucose and markers of inflammation in non-diabetic adults. *Diabetes Care* 2007;30(4):980-6.
- [17] Inzucchi SE, Maggs DG, Spollett GR, et al. Efficacy and metabolic effect of metformin and troglitazone in type 2 Diabetes mellitus. *N Engl J Med* 1998;338(13):867-73.