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Evaluation of role of vitamin D supplementation on glycemic control in newly diagnosed cases of type 2 DM

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Abstract
Aims and Objective: Evidence provided by previous studies revealed that vitamin D may play a functional role in glucose tolerance through its effects on insulin secretion and insulin sensitivity. Some studies have shown that only vitamin D deficient individuals get the benefits of supplementation in regard to blood sugar regulation. This study evaluates the effects of vitamin D supplementation on glycemic control in T2DM independent of endogenous vitamin D levels, also presence of comorbid hypertension affecting the clinical outcomes.
Method: 150 cases of type 2 diabetes mellitus, aged 35–75 years, mean age 55.8 ± 1.1 years were recruited to either metformin only group or metformin with vitamin D group. Baseline FBS, PPBS, HbA1c were measured. Statistical evaluation of the results was performed using the statistical package SPSS16. Student's *t*-test was used to compare the patient group with the control group.
Results: Intergroup comparison highlighted, FBS reduction was statistically significant at the end of 3rd and 6th month in comparison to baseline, whereas PPBS reduction was significant only at the end of 6th month. Intra group comparison reflected that changes in mean HbA1c levels from baseline to 6th month was significant in both the groups but the difference in values of baseline to 6th month HbA1c among two groups were statistically significant, considering p values <0.01 to be highly significant with 99% distribution values.
Weight reduction was also statistically significant after 6 months of recruitment to study groups. There was no statistical significance in HbA1c changes between hypertensive and non-hypertensive individuals
Conclusions: Data analysis demonstrated that improvements in serum FBS, PPBS, HbA1c and weight reduction were statistically significant in metformin with vitamin D supplementation group, which could be attributed to reduced insulin resistance. Vitamin D may play a role in type 2 diabetes i.e glucose regulation, weight reduction and improvement in HbA1c.

Keywords: Diabetes, insulin resistance, vitamin d, metformin, glycemic variation

Introduction
T2 DM is the most prevalent disease in modern society affecting 340 million people in the world [1]. Approximately 60% of the world's population lives in Asia, which is undergoing rapid modernization accompanied by increased urbanization and mechanization. These transitions have led to major lifestyle changes and shift from communicable to non-communicable diseases resulting in explosions in the prevalence of obesity, metabolic syndrome, diabetes mellitus and co-morbidities [2, 4].
India has the notorious title of being the Diabetic capital of the world but it is on the declining side now. Still Indians are at higher risk with respect to diabetes mellitus, CVD and numbers are consistently on the rise in an alarming scale that remains an ongoing issue for diabetologists. Statistics report that by 2030, every fifth diabetic patient in the world is going to be an Indian. At present in India there are nearly 50 million Diabetics. Thus treating diabetes has become more important than ever before [5].
Many risk factors play a role in etiopathogenesis and in glycemic control. To prevent development, glycemic control, management of complications of DM, identification of environmental, easily modifiable risk factors (losing weight, physical activity) and use of simple natural remedies/supplements is the need of the hour in addition to existing therapy.
One such natural supplement is vitamin D, the so-called "sunshine vitamin," has recently raised the interest because it has been linked to everything from heart diseases to cancer [6]. There is increasing evidence suggesting that vitamin D may influence several non-skeletal medical conditions, including cardiovascular diseases, autoimmune disorders and type 2 diabetes [7].

It has been observed that people with prediabetes and established diabetes have lower blood 25[OH]D concentrations than patients with normal glucose tolerance, implicating that its supplementation might help in better sugar control [8, 9].

Insulin secreting pancreatic beta cells also found to have vitamin D receptors [Johnson *et al.* 1994] and active vitamin D can stimulate the expression of the insulin receptors in target cells. [Maestro *et al.* 2000]. This implicates that vitamin D might enhance insulin secretion and its action. [Bourlon *et al.* 1999; Zeitz *et al.* 2003]. Hence in diabetic individuals deficient vitamin D status might further interfere with insulin functions.

Since insulin secretion is a calcium dependent process, vitamin D may indirectly regulate extracellular calcium [10]. Therefore it is established that inadequate calcium intake or vitamin D insufficiency may alter the balance in calcium pools, which leads to interference with normal insulin release, especially in response to a glucose load [9].

Though not proven, based on this hypothesis, it would be physiologically correct to recommend vitamin D supplementation to improve glucose control in type 2 diabetes mellitus patients [Osei, 2010]. Accordingly, it has been tried on diabetic patients in multiple studies [Borissova *et al.* 2008; Al-Daghri *et al.* 2012; Heshmat *et al.* 2012; Breslavsky *et al.* 2013]. However, these studies have not shown consistent results; could be due to heterogeneous study populations, different doses of vitamin D used, different endogenous 25 OH vitamin D levels and environmental factors.

Recent systematic reviews of RCTs concluded that there was insufficient evidence to recommend the use of vitamin D for improving glycemic control and preventing diabetes [8, 11, 12].

But in a meta-analysis of observational studies a relatively consistent association between low vitamin D status and the prevalence of T2DM or metabolic syndrome was reported [9]. However, due to confounding and selection bias in epidemiological studies, a causal link cannot be established. To determine whether the relation between vitamin D deficiency and glycaemic control is causal in nature, randomised controlled trials with vitamin D supplementation are needed. Till date, only few clinical trials examining this relation with glycaemic control as primary outcome in T2DM have been performed [13, 19].

Another meta-analysis done by George *et al* [11] demonstrated a small effect of vitamin D supplementation on fasting glucose and insulin resistance, with no effect on HbA1c. However most of these reviewed studies did not include diabetic patients nor had insulin resistance as primary outcome [20, 24].

This study evaluates the effects of vitamin D supplementation on glycemic control in T2DM independent of endogenous vitamin D levels. Furthermore, we set out to examine whether vitamin D supplementation is effective in preventing progression of diabetes in those with and without hypertension.

We performed this study with the following objectives:

1. To investigate the effect of vitamin D supplementation on glycaemic control in patients with T2DM
2. To analyze the effect of Vitamin D among hypertensive diabetics on HbA1c after 6 months.

Methodology

This study was conducted over a period of one year, where newly diagnosed consecutive cases of diabetes mellitus with or without hypertension between 35-75 years of age were recruited and allocated to two groups on alternate basis. After seeking the informed consent, baseline FBS, PPBS, weight, h/o hypertension with duration and other demographic details were recorded. We assigned hundred patients into 1:1 ratio to receive either metformin alone or metformin with vitamin D 60,000 IU at weekly intervals for 4 weeks. The follow-up duration is six months. The cohorts of 150 diabetes mellitus type 2 patients included in the study were on dietary and lifestyle changes.

Inclusion criteria

- Age 35- 75 years.
- Residents of Shimoga district
- Willing for regular follow up.
- Agreed to follow dietary modifications.

Exclusion criteria

- Non hypertensive comorbidities-anaemia, hypothyroidism
- Allergic to vitamin preparations.
- Cases lost to follow up
- Uncontrolled cases that required addition of other OHAs.
- Prior exposure to vitamin D.

Statistical evaluation of the results was performed using the statistical package SPSS19. Student's *t*-test was used to compare the patient group with the control group. Regression analysis was performed to analyse the relationship between HbA1c.

Drugs and chemicals: Metformin 500 mg SR. OD - Group 1
Metformin 500mg SR OD +vitamin D3 weekly – Group 2

Results

Table 1: Demographic details

No. of cases		Group A 68	Group B 62
AGE	Mean ± SD Range	52.3±9.3	58.2±12.2
Gender	Male	20(29%)	26(42%)
	Female	48(71%)	36(58%)
Hypertension	Yes	34(50%)	26(42%)
	No	34(50%)	36(58%)

Table 2: Comparison of changes in FBS in 2 groups

Groups	Particulars	Baseline (BL)	1st month	3rd month	6th month	BL- 1st month	BL- 3rd month	BL- 6th month
Group A	Mean ± SD	156.8 ± 21.9	149.3± 24.2	114. 2 ± 19.7	107.9± 17.3	7.5±12.2	42.6±18.1	48.9±22.2
	t[a]	-	-	-	-	3.59	13.71	12.84
	P	-	-	-	-	0.001**	0.00**	0.00**
Group B	Mean ± SD	150.7± 27.0	145.4±23.7	132.1±24.4	129.8±26.9	5.3±10.8	18.5±29.6	20.9±26.6
	t[a]	-	-	-	-	2.72	3.49	4.37
	P	-	-	-	-	0.44	0.002**	0.00**
Group A vs B	t[b]	1.00	0.66	3.24	3.86	0.78	3.92	4.58
	P	0.32	0.51	0.002*	0.00**	0.44	0.00**	0.00**

a- Paired t- test: intragroup * $p < 0.05$- significant
b- Unpaired t- test: intergroup ** $p < 0.001$- highly significant

Table 3: comparison of changes in PPBS in two groups

Groups	Particulars	Baseline (BL)	1st month	3rd month	6th month	BL- 1st month	BL- 3rd month	BL- 6th month
Group A	Mean ± SD	215.9 ± 29.1	208.8± 32.3	175.0 ± 27.9	164.3± 24.6	7.0±18.1	40.9 ±24.1	51.6 ±27.9
	t[a]	-	-	-	-	2.27	9.87	10.79
	P	-	-	-	-	0.03*	0.00**	0.00**
Group B	Mean ± SD	223.1± 29.5	218.8 ±28.2	192.0 ±31.8	196.2 ±35.9	4.3± 7.3	31.1 ± 26.2	26.9± 29.4
	t[a]	-	-	-	-	3.30	6.61	5.09
	P	-	-	-	-	0.003**	0.00**	0.00**
Group A vs B	t[b]	1.00	1.33	2.29	4.14	0.80	1.56	3.46
	P	0.32	0.19	0.03*	0.00**	0.43	0.13	0.001**

Table 4: Comparison of changes in HBa1 C between 2 groups

Groups	Particulars	Baseline	6th month	Difference BL- 6th month
Group A	Mean ± SD	7.59 ±0.35	7.02± 0.30	0.56 ±0.27
	t[a]	-	-	12.32
	P	-	-	0.00**
Group B	Mean ± SD	7.42± 0.31	7.23 ±0.28	0.19± 0.29
	t[a]	-	-	3.56
	P	-	-	0.001**
Group A vs B	t[b]	2.09	2.87	5.41
	P	0.04*	0.006**	0.00**

Table 5: Comparison of changes in weight in two groups

Groups	Particulars	Baseline (BL)	1st month	3rd month	6th month	BL- 1st month	BL- 3rd month	BL- 6th month
Group A	Mean ± SD	68.50 ± 8.49	67.35± 7.82	65.79 ± 7.49	64.94± 6.86	1.15±1.92	2.71 ±1.73	3.56 ± 2.31
	t[a]	-	-	-	-	2.27	9.87	10.79
	P	-	-	-	-	0.03*	0.00**	0.00**
Group B	Mean ± SD	223.1± 29.5	218.8 ±28.2	192.0 ±31.8	196.2 ±35.9	4.3± 7.3	31.1 ± 26.2	26.9± 29.4
	t[a]	-	-	-	-	3.30	6.61	5.09
	P	-	-	-	-	0.003*	0.00*	0.00**
Group A vs B	t[b]	1.00	1.33	2.29	4.14	0.80	1.56	3.46
	P	0.32	0.19	0.03*	0.00*	0.43	0.13	0.001**

Table 6: HbA1c changes in 6 months

	Groups	Mean	SD	N	Sig.
Group A	Diabetic	0.600	0.2828	17	0.30
	Diab + HTN	0.506	0.2358	17	NS
Group B	Diabetic	0.183	0.2383	18	0.95
	Diab + HTN	0.177	0.3244	13	NS

Discussion: The main purpose of this study is to measure the effect of vitamin D supplementation on glycaemic control and also analyze the outcomes in hypertensive diabetics (T2DM). There is widespread interest in the potential causal role of vitamin D on the pathogenesis and progression of T2DM. We hope this study will give new insight into this causality. To measure a difference in HbA1c level it is hypothesized that, the maximal effect will be seen at least at six months as red blood cells circulate about 100 days in the blood and HbA1c levels takes around six weeks to change.

Patients were randomly allocated to 2 groups on alternate basis. Among total 150 patients only 68 in group A and 62 in group B who met inclusion criteria and could complete 6 months of follow up were included in final statistical analysis.

In both groups female subjects were more and 50% in group A and 45% in group B had comorbid hypertension; mean age being 52.3 ± 9.3 in group A and 58.2 ±12.2 in group B.

Changes in FBS in 2 groups showed statistical significance at the end of 3rd and 6th month in comparison to baseline.

On comparing changes in PPBS and HbA1c in two groups, values were statistically significant at the end of 6th month. P value was less than 0.001* for changes in difference between 6th month to baseline weight, indicating the weight reduction was also statistically significant.

In both groups, there was no statistical significance in HbA1c changes between hypertensive and non-hypertensive individuals indicating that blood glucose regulation has not been affected by presence of comorbid hypertension. This could be attributed to short duration of follow up or due to newly diagnosed cases of DM wherein setting in of metabolic syndrome is unlikely.

After conducting a meta-analysis and review of the impact of vitamin D and calcium on glycemic control in patients with type 2 diabetes, Pittas *et al*. concluded that insufficient vitamin D and calcium appears to hinder glycemic control and that supplementing both nutrients may be necessary to optimize glucose metabolism [9].

It is possible that optimal levels of serum vitamin D may be different for people at risk for developing diabetes, those with diabetes and those without diabetes. There may be even ethnic and cultural determinants for vitamin D status. Hence in this study, we tried evaluating antihyperglycemic action of vitamin D. We could derive at a conclusion that in our cultural and ethnic setup, residents of Shimoga district could be benefited with vitamin D supplementation in terms of better glycemic control.

In the past according to some RCTs, vitamin D supplements showed beneficial effects in terms of glycemic control only in vitamin deficient individuals and some studies reflected that there were no beneficial effects of supplementation on glycemic measures among persons with normal glucose tolerance in contrast to patients with glucose intolerance.

In our study patients were recruited independent of their 25 OH vitamin D levels. Results showed that there was a significant difference in vitamin D supplemented group in terms of FBS, PPBS, HbA1c and weight reduction.

Limitations: It is a short duration study with small sample size, therefore no conclusion can be made as far as any cause and effect relationship is concerned between vitamin D deficiency and diabetes mellitus type 2. Many studies in the past reflected that only vitamin deficient individuals respond better to supplements. Since serum 25 OH vitamin D was not taken into consideration status of individual cannot be assured.

However, to better define the role of vitamin D in the development and progression of type 2 diabetes, high-quality observational studies and RCTs that measure blood 25-hydroxyvitamin D concentration and clinically relevant glycemic outcomes are needed.

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References

1. Danaei G *et al*. National, regional and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic examination of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. Lancet, 2011; 378:31-49.
2. Chan JC *et al*. Diabetes in Asia: Epidemiology, risk factors, and pathophysiology. JAMA, 2009; 301:2129-2140.
3. Misra A, Khurana L. Obesity and the metabolic syndrome in developing countries. J. Clin. Endocrinol. Metab. 2008; 93(1):S9-S30.
4. Ramchandran A, Snehalatha C. Diabetes in Asia. Lancet, 2010; 375:408- 418.
5. Diabetes. Nature Clinical Collections. 2014.
6. Teresa Martin, Keith Campbell R. Vitamin D and Diabetes **(**Pharmacy and Therapeutics). Diabetes Spectrum, 2011; 24:113-118.
7. European Journal of Clinical Nutrition, 2011; 65:1005-1015. doi:10.1038/ejcn.2011.118
8. Mitri J, Muraru MD, Pittas AG. Vitamin D and type 2 diabetes: a systematic review. Eur J Clin Nutr. 2011; 65(9):1005-1015. [PMCID: PMC4066381][PubMed: 21731035]
9. Pittas AG, Lau J, Hu FB, Dawson-Hughes B. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. J Clin Endocrinol Metab. 2007; 92(6):2017-2029.
   [PMCID: PMC2085234] [PubMed: 17389701]
10. Milner RD, Hales CN. The role of calcium and magnesium in insulin secretion from rabbit pancreas studied *in vitro*. Diabetologia.1967; 3:47-49.
11. George PS, Pearson ER, Witham MD. Effect of vitamin D supplementation on glycaemic control and insulin resistance: a systematic review and meta-analysis. Diabet Med. 2012; 29(8):e142-e150. [PubMed: 22486204]
12. Autier P, Boniol M, Pizot C, Mullie P. Vitamin D status and ill health: a systematic review. Lancet Diabetes Endocrinol. 2014; 2(1):76-89. [PubMed: 24622671]
13. Borissova AM, Tankova T, Kirilov G, Dakovska L, Kovacheva R. The effect of vitamin D3 on insulin secretion and peripheral insulin sensitivity in type 2 diabetic patients. Int J Clin Pract. 2003; 57:258-261.
14. Heshmat R, Tabatabaei-Malazy O, Abbaszadeh-Ahranjani S, Shahbazi S, Khooshehchin G, Bandarian F *et al*. Effect of vitamin D on insulin resistance and anthropometric parameters in Type 2 diabetes; a randomized double-blind clinical trial. Daru, 2012, 20:10.
15. Inomata S, Kadowaki S, Yamatani T, Fukase M, Fujita T. Effect of 1 alpha (OH)-vitamin D3 on insulin secretion in diabetes mellitus. Bone Miner. 1986; 1:187-192.
16. Jorde R, Figenschau Y. Supplementation with cholecalciferol does not improve glycaemic control in diabetic subjects with normal serum 25-hydroxyvitamin D levels. Eur J Nutr. 2009; 48:349-354.
17. Orwoll E, Riddle M, Prince M. Effects of vitamin D on insulin and glucagon secretion in non-insulin-dependent diabetes mellitus. Am J Clin Nutr. 1994; 59:1083-1087.
18. Soric MM, Renner ET, Smith SR. Effect of daily vitamin D supplementation on HbA1c in patients with uncontrolled type 2 diabetes mellitus: a pilot study. J Diabetes. 2012; 4:104-105.
19. Talaei A, Mohamadi M, Adgi Z. The effect of vitamin D on insulin resistance in patients with type 2 diabetes. Diabetol Metab Syndr, 2013, 5-8.
20. de Boer IH, Tinker LF, Connelly S, Curb JD, Howard BV, Kestenbaum B, *et al*. Calcium plus vitamin D supplementation and the risk of incident diabetes in the Women's Health Initiative. Diabetes Care 2008; 31:701–707.
21. De Zeeuw D, Agarwal R, Amdahl M, Audhya P, Coyne D, Garimella T *et al*: Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): a randomised controlled trial. Lancet, 2010; 376:1543-1551.
22. Ljunghall S, Lind L, Lithell H, Skarfors E, Selinus I, Sorensen OH *et al*. Treatment with one-alpha-hydroxycholecalciferol in middle-aged men with impaired glucose tolerance–a prospective randomized double-blind study. Acta Med Scand, 1987; 222:361-367.
23. Nagpal J, Pande JN, Bhartia A. A double-blind, randomized, placebo-controlled trial of the short-term effect of vitamin D3 supplementation on insulin sensitivity in apparently healthy, middle-aged, centrally obese men. Diabet Med, 2009; 26:19-27.
24. Pittas AG, Harris SS, Stark PC, Dawson-Hughes B. The effects of calcium and vitamin D supplementation on blood glucose and markers of inflammation in non-diabetic adults. Diabetes Care. 2007; 30:980-986.