Study of Vit D Supplementation in Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: Vitamin D deficiency is being evaluated as important risk factor in development of insulin resistance and Vitamin D supplementation may be beneficial in management of type 2 DM. A pre-post Intervention study in a tertiary care hospital was conducted to observe the effect of Vitamin D supplementation in glycemic control and insulin resistance in Type 2 Diabetes Mellitus.

Material and Methods: Estimation of Fasting and post prandial plasma sugar, 25 hydroxy Vitamin D, serum fasting insulin and Insulin resistance, calculated using Homeostatic model assessment of Insulin resistance (HOMA-IR) method, in 300 known cases of Type2 Diabetes Mellitus and 50 age and sex matched healthy controls was done. Oral supplementation of Vit D, 60,000IU/week for 4 weeks was given to the group of Diabetics with decreased vit D level <20 ng/ml. Fasting serum insulin and Vit D level was repeated after 7 days of 4th dose of vit D supplementation. The pre and post supplementation values of Fasting serum Insulin, vitamin D levels and Blood sugar levels were recorded and statistically analysed.

Results: The prevalence of vitamin D deficiency (< 20 ng/mL). in type II diabetics was 30%. Comparison of parameters after supplementation to the Vit D deficient Diabetic group, revealed a significant decrease in Fasting plasma glucose (p value 0.0028) with no significant change in the mean baseline 2 h plasma glucose or HbA1c. There is a statistically significant decrease in Fasting serum insulin levels (p <0.0031) and decrease in insulin resistance (p=<0.0001) after 4 weeks of Vit D supplementation.

Conclusion: Supplementation of Vit D results in decreasing the insulin levels and insulin resistance in the Vitamin D deficient type 2 diabetics in Indian population. Vitamin D supplementation in Diabetics could be beneficial in management of Type 2 DM.

Keyword: Type 2 Diabetes Mellitus, Vitamin D, Insulin Resistance, Insulin Levels, Glycemic Control

INTRODUCTION

Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease.[1] The problem of diabetes is not homogenous in India. Currently, 4.0-11.6 per cent of India's urban population and three per cent of the rural population above the age of 15 has diabetes. India has been called "the Diabetes capital of the world," and it is estimated that 41 million Indians have the disease and "every fifth diabetic in the world is an Indian.[2] Although there are now improved treatments available for treating the disease and its complications, prevention would always be preferable for this multisystem disorder which is one of the leading causes of mortality and morbidity. An interesting angle to the etiopathogenesis of Diabetes which is being studied, is the role of Vitamin D insufficiency as a risk factor, which may play a role in development of both type 1 and type 2 Diabetes Mellitus.[3,4]

Experimentally vit D is required for normal insulin secretion and glucose tolerance.[5] Inadequate calcium intake or vitamin D insufficiency may alter the balance between the extracellular and intracellular β -cell calcium pools, which may interfere with normal insulin release.[4] It is proposed that Vitamin D is an important risk factor in development of insulin resistance and the pathogenesis of type 2 DM by affecting either β-cell function, through the presence of vitamin D receptors on the beta cells or through the effect on calcium metabolism, or both.[6] Also, Vitamin D improves insulin sensitivity by its anti-inflammatory activity as it is proposed to attenuate the expression of pro-inflammatory cytokines involved in insulin resistance.[7,8]

There have been studies on establishing association between Vit D status and insulin secretion and insulin sensitivity with differing results in various ethnic populations.[9-13] Many have studied the effect of Vit D supplementation on T2DM again with differing results.[14-17]

With Vitamin D deficiency prevailing in epidemic proportions all over the Indian subcontinent and with a phenomenal prevalence of 70%–100% in the general population[18], we thought it was important to elucidate the status of vitamin D and its possible relation with insulin resistance in Type 2 DM. The study was designed as pre-post Intervention trial in which we observed the correlation of Vitamin D deficiency and insulin resistance in patients with Type 2 diabetes before and after supplementation with Vitamin D.

MATERIAL AND METHODS

The present study was conducted in the Department of Biochemistry of an urban tertiary care teaching hospital. Ethical clearance was obtained from the college ethical committee prior to starting the study. Written and informed consent was taken from all the patients.

300 known cases of Type 2 Diabetes Mellitus (taking the prevalence of Type2 DM to be 26%, confidence interval 95% with error of margin 5%, sample size would be 296)

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and 50 age and sex matched healthy controls (taken only for biochemical reference) were chosen for the study. Cases of type 2 DM included both sexes in age group 18-75 years. Cases of Type 1 diabetes mellitus, age less than 18 years, impaired renal function, Gestational diabetes mellitus, parathyroid disorders and patients on drugs known to alter vitamin D metabolism (e.g seizure disorder) were excluded from the study. Cases of Controls who were found to be Vit D deficient were also excluded.

The study design was a Pre-post Intervention Trial. Fasting and postprandial venous blood samples were collected from the 300 known cases of Type 2 Diabetes mellitus and controls. Fasting and post prandial plasma sugar, serum urea, creatinine, 25 hydroxy Vitamin D and fasting serum insulin was estimated in all the samples. Vitamin D and Insulin was estimated by solid phase enzyme-linked immunoassay (ELISA). Insulin resistance was calculated using Homeostatic model assessment of Insulin resistance (HOMA-IR) method using the following formula

The subjects were divided into two groups based on Vit. D levels. In Group I (subjects with normal vit D level >20ng/ml), no vit. D supplementation was given, whereas Gp II (with decreased vit D level <20 ng/ml), oral supplementation of vit D, 60,000IU/week for 4 weeks was given. Fasting serum insulin and Vit. D level was repeated after 7 days of 4th dose of vit D supplementation. The Fasting serum Insulin, vitamin D levels and Blood sugar levels were estimated in Vit.D deficient group II (pre, post supplementation). The values were recorded and association of vit. D deficiency, glucose intolerance, serum insulin level and insulin resistance in pre and post vit. D supplementation group was compared using unpaired t test.

Age-wise distribution	T2 DM (n=300)
30-40	011(3.66%)
41-50	095 (31.66%)
51-60	104 (34.66%)
61-70	075 (25%)
71-80	015 (5%)
Total	300

Table-1: Age wise distribution of the type II Diabetic patients

RESULTS

A total of 300 Type 2 Diabetes Mellitus (T2DM) subjects and 50 age- and sex-matched healthy controls were enrolled in the study (Table 1). The mean age of the patients in the type 2 DM group was 55.08 ± 9.21 years and that of healthy controls was 55.78 ± 7.9 years. Using unpaired t- test it was found that the age difference between two groups is statistically not significant (p=0.5323). The details of age wise distribution of 300 subjects are given Table 1. There were 230/300 (76.67%) males and 70 (23.33%) females in the T2 DM group and 40/50 (80%) males and 10 (20%) females in the healthy control groups.

Table 2 shows the baseline levels of all parameters in the 300 Type II DM subjects and controls. The mean serum Vitamin D level in the T2DM group was 33.39 ± 19.83 ng/mL and in the healthy control was group 33.42 ± 11.36ng/mL (table-2). Using the unpaired t-test it was found that Vitamin D levels

Characteristics	T2DM (Mean ± SD) (n=300)	Healthy controls (Mean ± SD) (n=50)	P value*
Fasting plasma glucose (mg/dL)	142.78 ± 48.26	84.24 ± 7.66	<0.0001
2 h plasma glucose (Post glucose load) (mg/dL)	221.59 ± 65.05	116.3 ± 12.91	<0.0001
HbA1C%	7.24 ± 0.97	5.20 ± 0.29	<0.0001
Vitamin D (ng/mL) Mean ± SD	33.39 ± 19.83	33.42 ± 11.36	0.9337
Fasting Serum Insulin (µIU/mL)	20.72 ± 23.59	6.30 ± 3.85	<0.0001
Insulin resistance	7.36 ± 8.52	1.30 ± 0.79	<0.0001
*Using unpaired t test, p<0.05 is considered significant			
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71-80		015 (5%)	
Total		300	

Table-2: Baseline parameters in both study groups (pre-supplementation) (n=300)

Characteristics	GP I Normal Vit D T2DM (Mean ± SD) (n=210)	Gp II Vit D deficient T2DM (Mean ± SD) (n=90)	P value*
Fasting plasma glucose (mg/dL)	142.40 ± 48.43	143.67 ± 48.07	0.8367
2 h plasma glucose (post glucose load) (mg/dL)	223.32 ± 64.07	217.39 ± 67.52	0.4733
HbA1C%	7.21 ± 0.87	7.29 ± 1.18	1.000
Vitamin D (ng/mL) Mean ± SD	41.67 ± 17.76	13.44 ± 4.03	0.0472
Fasting Serum Insulin (µIU/mL)	19.05 ± 26.17	24.73 ± 15.10	0.4468
Insulin resistance (IU)	6.70 ± 9.16	8.98 ± 6.50	0.0346
*Using unpaired t test, p<0.05 is considered significant			

Table-3: Comparison between normal vit D level patients of T2DM Gp I (n=210) and Vit D deficient patients, Gp II (n=90)

Characteristics (n=90)	Pre supplementation	Post supplementation	P value*
Fasting plasma glucose (mg/dL)	142.92 ± 47.79	125.06 ± 28.12	0.0028
2 h plasma glucose (Post-glucose load) (mg/dL)	216.71 ± 66.94	210.92 ± 42.73	0.4935
HbA1C%	7.29 ± 1.17	7.31 ± 1.16	0.9182
Vitamin D (ng/mL)	13.32 ± 4.07	32.26 ± 7.02	<0.0001
Fasting Serum Insulin (µIU/mL)	24.67 ± 14.95	18.76 ± 11.00	0.0031
Insulin resistance in units	8.98 ± 6.50	5.82 ± 3.70	<0.0001
*Using paired t-test, p value<0.05 is considered significant			

Table-4: Comparison of parameters in Gp II (vitamin D deficient T2DM Subjects, n=90) pre-supplementation and post-supplementation of vitamin D.

between T2DM and healthy controls was comparable (p=0.9337). However 90 T2DM subjects were found to have Vitamin D deficiency (< 20 ng/mL). The prevalence of vitamin D deficiency in T2DM group was 30% (90/300).

The Fasting serum insulin level in the T2DM group was 20.72 ± 23.59 µIU/mL and that in the healthy control group was 6.30 ± 3.85µIU/mL (table-2). Using unpaired t-test it was noted that the fasting serum insulin levels in T2DM were increased and statistically significant than in healthy controls (p<0.0001).The insulin resistance in both subjects and controls was calculated using HOMA IR method**.** The serum insulin resistance levels in T2DM were high as compared to healthy control (Table-2). The difference between the two groups is statistically significant.

The type 2 DM cases were divided into two gps based on Vit D levels. The results of the various parameters in Gp I (Type 2 DM cases with normal Vit D levels) and Gp II (Vit D deficient Type II DM cases) are shown in table 3.

Gp II (with decreased vit D level <20 ng/ml) was given oral supplementation of vit D, 60,000IU/week for 4 weeks. Fasting serum insulin and Vit. D level was repeated after 7 days of 4th dose of vit. D supplementation(Table 2).

Comparison of parameters in Gp 2 pre-supplementation and post-supplementation of vitamin D is given in table 4. The mean FPG decreased significantly from 142.92 ± 47.79 mg/dl to 125.06 ± 28.12 mg/dL however there was not a significant change in the mean baseline 2 h plasma glucose (Post-glucose load) level in the pre and post supplement group of Vit D deficient diabetics(Table 3).

There was a statistically significant decrease in Fasting serum insulin levels (from 24.67 ± 14.95 µIU/ml to 18.76 ± 11.00 µIU/ml) (p <0.0031) and a statistically significant decrease in insulin resistance (from 8.98 ± 6.50 to 5.82 ± 3.70) (p=<0.0001) post supplementation of 4 weeks of Vit D (Table 4).

DISCUSSION

Vitamin D plays a pivotal role in calcium metabolism, and vitamin D deficiency may be associated with a range of serious diseases, including cancer, cardiovascular disease, and type 2 diabetes.[19] Vitamin D deficiency has been shown to alter insulin synthesis and secretion in both humans and animal models. There is evidence to suggest that altered vitamin D homeostasis may play a role in the development of type 2 diabetes. The role of vitamin D deficiency in type 2 diabetes is suggested by cross-sectional studies showing that low serum concentrations of 25- hydroxyl vitamin D [25(OH)D] are associated with impaired glucose tolerance, altered insulin secretion and diabetes.[20,21]

With this back ground, a pre-post interventional study was carried out by us. The prevalence of Vitamin D deficiency in our study was 30% (90/300) in the T2DM group. There have been many Indian studies which have reported a prevalence of 66%% in type 2 diabetes with pulmonary tuberculosis[22], 53% in Indian post menopausal diabetics[23] to almost 91.1% in north India.[24] The Gp 1 patients (T2DM subjects with normal vitamin D level > 20ng/ml), were not included in further study of project, and Gp II patients, who were deficient (< 20ng/ml), were evaluated after oral vitamin D supplementation of 60,000 IU/week for four weeks.

The mean baseline serum Vitamin D levels in Gp II in pre supplementation group was 13.32 ± 4.07g/ml increased significantly after vitamin D supplementation to 32.26 ± 7.02 ng/ml. Although the mean FPG decreased significantly after Vit D supplementation, there was not a significant change in the mean baseline 2 h plasma glucose (Post-glucose load) level in the pre and post supplement group of Vit D deficient diabetics. Change in HbA1c levels was also not significant probably due to short four week Vitamin D supplementation in our study in contrast to study by Kota SK et al[22] where glycated Hb reduced from 11.1±1.3 to 7.7±0.9 in 12 weeks of Vitamin D supplementation.What was strongly notable from the study was a significant decrease in Serum Insulin levels (from 24.67 ± 14.95 µI U /ml to 18.76 ± 11.00 µIU / ml) and Insulin resistance (from 8.98 ± 6.50 to 5.82 ± 3.70) after supplementation with Vit D in Gp II patients.

Our study supports that Vitamin D supplementation has a positive effect in decreasing insulin levels, improving glycemic controls and decreasing insulin resistance in Vit D deficient diabetics. The meta-analysis conducted by Anastassiosis G. Pittas et al concluded that calcium and vit D levels had negative influence on glycemia.[4] They searched MEDLINE for observational studies on the association between vitamin D / calcium status and T2DM (prevalence or incidence) and for randomized controlled trials of the effect of vitamin D and/or calcium supplementation in non-pregnant adults on outcomes related to glycemic control.

There is a growing evidence that Vitamin-D levels are inversely associated with development of diabetes independent of risk factors like age BMI and race.[25] The NHANES data confirmed the inverse relationship between 25(OH)D levels and diabetes and insulin resistance in the non-Hispanic white and Mexican American, but not in the non-Hispanic black populations.[26,27]

However, gaps in the knowledge exist on dose of vitamin D supplementation and its effect on insulin sensitivity. Significant improvement in insulin secretion and sensitivity has been reported in patients on Vit. D supplementation as

compared to placebo[28,29], but all studies have a different supplementation doses and time intervals. Mitri et al. conducted a 2 x 2 factorial randomized controlled trial of Vit D and calcium supplementation in adults at high risk of diabetes.[28] Participants were randomly assigned in a 1: 1 ratio to receive Vit. D 3 2000 IU per day or a matching placebo and within each category to receive 800 mg of $CaCO_3$ in two divided doses for 16 weeks. Vit D supplementation with or without calcium improved insulin secretion and there was attenuation of the rise in HbA1c in this population. The supplementation with calcium alone did not have any effect on the glucose levels, insulin secretion or HBA1C levels.[28] Kahn et al in their study observed that, vitamin D supplementation improved the disposition index by 26% compared with a worsening of 14% in the group that received no vitamin D. The disposition index is a measure of pancreatic β cell function that captures the hyperbolic relation between insulin secretion and insulin sensitivity.[29] A low disposition index indicates an impaired pancreatic β cell function and is a predictor of diabetes risk.[30] Vitamin D improved the disposition index and insulin secretion, but its effect on insulin sensitivity was not significant, which indicated a predominant effect of vitamin D on the pancreatic β cell. Our study, which was on diabetics, showed significant decrease in fasting glucose levels, fasting insulin levels and insulin resistance too. There have been studies on non diabetics but obese individuals which showed difference in various insulin sensitivity indices. Nagpal et al based on a pilot trial, conducted a double blind RCT in 100 middle aged, centrally obese, non-diabetic, apparently healthy volunteers who were given three doses of Vit D3 120000 IU fortnightly or a placebo and studied the effect on OGIS[31] (oral glucose insulin sensitivity). The results revealed improvement in 3-h OGIS, whereas other insulin sensitivity indices (HOMA and QUICKI -quantitative insulin-sensitivity check index) remained unaffected. They interpreted it as an improvement in postprandial glucose disposal, whereas the basal fasting hepatic insulin sensitivity remained unaffected. There was no significant change in 2 hr plasma glucose and HbA1C levels.

There have been few trials on certain ethnic populations demonstrating no improvement in insulin sensitivity and HbA1c levels after 4 weeks vitamin D supplementation. Study done on Chinese subjects by Luo et al. where they examined the impact of low vit D levels on metabolic status as well as on inflammatory markers – ferritin and hsCRP on ethnic group of Chinese patients with t2DM, found that there was no association of hypovitaminosis D with prevalence of metabolic syndrome and there was no difference in response to vit. D supplementation in patients with metabolic syndrome and those without metabolic syndrome.[32]

The literature is vast on this subject and the results although differ in various ethnic populations, it is clear there might be some association between Vitamin D metabolism and glucose metabolism. Effect of Vitamin D on glycemic control (HbA1c levels) could not be brought out in this study as the supplementation was only for four weeks. The exact factors contributing to development of DM type 2 have always been elusive, however the Vit D supplementation seems to be having some effect on insulin resistance and our study adds further information to the pre-existing limited and conflicting knowledge on this subject.

CONCLUSION

Our pre-post interventional study on 90 Vit. D deficient Diabetic patients showed decreased insulin levels, improved sensitivity and lowered fasting plasma glucose on supplementation. India being the diabetic capital and with syndrome X rampant, Vitamin D supplementation may be of relevance in management of Type 2 DM. There is evidence to leave an impression that vitamin D supplementation could potentially be beneficial.[33] However, there has to be large scale prospective studies to identify which subset of diabetic patients respond and what should the supplementation dosages be, the results should be validated in diverse settings and uniform guidelines need to be formulated to benefit maximally.

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