



## Serum Vitamin D Levels In Type 2 Diabetes Mellitus - A Missing Link

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### INTRODUCTION

Type 2 diabetes, a significant global health care problem is the fifth leading cause of death and also a major cause of significant morbidity. Although our current methods of treating type 2 DM and its complications are improving, its prevention is preferable. Epidemiological data suggest 9 of 10 cases of type 2 DM are attributed to habits and form of modifiable behavior.

Vitamin D has been traditionally known as anti ricketic factor or sunshine vitamin. It is unique because it is a vitamin synthesized by the body and functions as a hormone. Besides its pivotal role in calcium homeostasis and bone mineral metabolism, vitamin D endocrine system is now recognized to sub-serve a wide range of biological functions in cell differentiation, inhibition of cell growth and immunomodulation.

25-Hydroxyvitamin D serum level (measure of vitamin D status) of less than 20 ng/mL is vitamin D deficiency and 21 to 29 ng/mL is insufficiency. It is currently recognized that. Systemic inflamma-

tion seen in type 2 DM has been linked primarily to insulin resistance, but elevated cytokines may also play a role in beta-cell dysfunction by triggering  $\beta$ -cell apoptosis. Vitamin D may improve insulin sensitivity and promote beta-cell survival by directly modulating the generation and effects of cytokines.

This raises important questions of association between vitamin D and type 2 diabetes hence the purpose of this current study.

### AIM AND OBJECTIVES

AIM- Measure serum vitamin D levels in patients of type 2 Diabetes Mellitus and non-diabetic controls.

### OBJECTIVE

To study the association of serum Vitamin D levels in Type 2 diabetes compared to non-diabetic group.

**BACK GROUND-****Vitamin D & type 2 diabetes**

Accumulating evidences both *in vivo* and *in vitro* studies suggests association between low vitamin D level and the development of type 2 diabetes. This effect is probably explained by role of 1,25 dihydroxy vitamin D<sub>3</sub> in activation of insulin biosynthesis and secretion from  $\beta$ -cells of islets of Langerhans of pancreas and improvement in glucose tolerance.

Vitamin D deficiency and type 2 diabetes share common risk factors, including African-American, Asian, or Hispanic race, obesity, ageing and lack of physical activity<sup>[1,15]</sup>.

Some findings have shown reduction in incidence of type 2 diabetes in individuals with higher vitamin D level. Furthermore, recent studies provide evidence of vitamin D supplements reducing incidence of diabetes and adjustment of insulin dosages. Contrary to these, some findings suggest no clear link between vitamin D and type 2 diabetes.

**Hypovitaminosis D in type 2 diabetes**

A close link between vitamin D deficiency and inhibition of pancreatic insulin secretion and utilization was recorded in early 1980<sup>[3]</sup>.

Animal study by Normal AW et al reported in 1980 suggested vital role of vitamin D in insulin release from a pancreas.<sup>[4]</sup> In 1988, Pietschmann P et al observed vitamin D deficiency and decreased bone formation in type 2 diabetes individuals as compared to normal ones. Study tested serum levels of 25 dihydroxyvitamin D and osteocalcin, both in type 1 and 2 diabetes along with control. As compared to controls, serum osteocalcin and vitamin D levels were significantly decreased in type 2 DM<sup>[5]</sup>.

*In vitro* study conducted by Bourlon PM et al in 1999, confirmed that 1, 25 (OH)<sub>2</sub> D<sub>3</sub> has beneficial effect in two phases of insulin release. First, vitamin D activates islet's protein biosynthesis mechanism and increases insulin synthesis activity of  $\beta$ -cells of pancreas on glucose stimulation.

Second, vitamin D facilitates conversion of proinsulin to insulin<sup>[6]</sup>.

As stated above, vital role of vitamin D in insulin sensitivity and glucose homeostasis might be one of the reasons for such close association<sup>[1,6,7,8]</sup>.

One study by Chiu KC et al in 2004, reported risk of insulin resistance and occurrence of metabolic syndrome in a patient with low vitamin D concentration. On the other hand, vitamin D sufficiency improves insulin sensitivity and facilitates glucose transport. However, the mechanism behind it is still not clear and more studies are required in a future which might explain possible causes<sup>[9]</sup>.

A recently conducted meta-analysis of 21 prospective studies confirmed that with each 10 nmol/L increment in 25 (OH) D levels is associated with 4% reduction in type 2 diabetes in diverse population. Meta-analysis involved 76,220 individuals and 4,996 cases of type 2 diabetes. When compared for highest to lowest levels of vitamin D<sub>3</sub> relative risk for type 2 diabetes was 0.62 which indicated higher concentration of vitamin D<sub>3</sub> is protective against type 2 DM. This association is not affected by sex, duration of follow-up, study sample size, diabetes diagnostic criteria or 25 (OH) D assay method<sup>[10]</sup>.

Vitamin D deficiency is more frequent in type 2 diabetes as compared to type 1 cases. Di Cesar DJ et al, in 2006 analyzed data from pilot study investigating vitamin D deficiency in both type 1 and type 2 diabetes. When serum 25 (OH) D concentrations was recorded in both, 63.5% of type 2 individuals were deficient in vitamin D as compared to 36 % of type 1 population irrespective of age, sex and insulin treatment. Vitamin D level exhibit inverse relationship with body mass index. However, Vitamin D deficiency difference still remained same with adjusting BMI<sup>[11]</sup>.

Zoppini G et al in 2013 gives possible mechanisms for such inverse relationship. When they cross-sectionally investigated a cohort of 715 type 2 diabetes people, a negative co-relationship was observed between HbA1c and serum 25 (OH) D

after adjusting for age, sex, HbA1c, BMI, treatment, diabetes duration and nephropathy. Glycemic control can affect a serum vitamin D level by different mechanisms. It may be related to poor diet or lower sun exposure.<sup>[12]</sup>

### Some missing links

Though above evidences support association of vitamin D in type 2 diabetes, exact role of vitamin D in glucose homeostasis is still unclear. Due to influence of vitamin D on insulin sensitivity and  $\beta$ -cell function or both, it might play a role in a pathogenesis of type 2 diabetes<sup>[13]</sup>. Randomized clinical trials have limited and inconclusive reports. As data of negative association is not consistent, recently vitamin D mechanism in type 2 diabetes remains a question.

A new 2011 report produced by Institute of Medicine (IOM), on dietary requirements for calcium and vitamin D supports vital role of these nutrients in maintaining skeletal health. However, for explaining relationship between these nutrients and extra-skeletal manifestations including diabetes, results are inconsistent and uninformative<sup>[14]</sup>.

According to review by Alvarez JA et al in 2010, a direct association between vitamin D and risk of type 2 diabetes is still not clear. Much is unrevealed regarding optimal concentration of vitamin D required for glucose homeostasis. Follow up duration for vitamin supplementation is still to be confirmed to establish an effect of vitamin D on insulin secretion and sensitivity<sup>[15]</sup>.

A cross-sectional survey conducted in largely obese at risk Canadian population didn't show any inverse relationship after adjusting for adiposity<sup>[16]</sup>. Similarly, another cross-sectional study conducted on European subjects with metabolic syndrome serum concentration of vitamin D failed to predict insulin action or secretion<sup>[17]</sup>.

When gender parameter is taken into account, the mean concentration of vitamin D was significantly less in diabetic patients as compared to healthy individuals. Such relationship is strong among women patients. Perhaps, mean concentration of vitamin D is equal in male of both groups<sup>[18]</sup>.

Robinson JE et al did not find any association between 25 (OH) D level and incident of type 2 diabetes in older women. Study involved large cohort of postmenopausal women participated in Women's Health Initiative (WHI). When adjusted for age and ethnicity, higher vitamin D level acts as a protective element in type 2 diabetes but there was no such association when adjusted for BMI, hypertension, fiber and magnesium intake and physical activity. Another important finding was lack of such association in obese women, who are always taken for granted as high risk cases for developing type 2 diabetes<sup>[19]</sup>.

A study conducted on general population of Copenhagen, Denmark demonstrated lack of association between vitamin D and type 2 diabetes after adjustment of confounders. When data from Inter99 study, a population based randomized control trial, was analyzed with adjustment for confounders like age, sex, physical activity, dietary pattern, etc. no significant association was noticed<sup>[20]</sup>.

### MATERIAL AND METHODS

**Type :** Observational and cross sectional study.

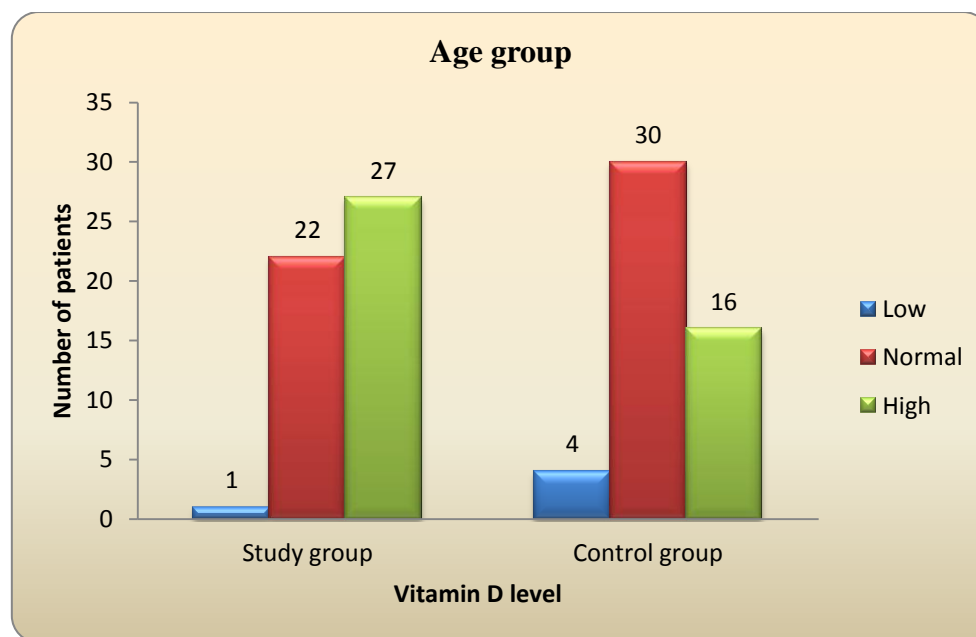
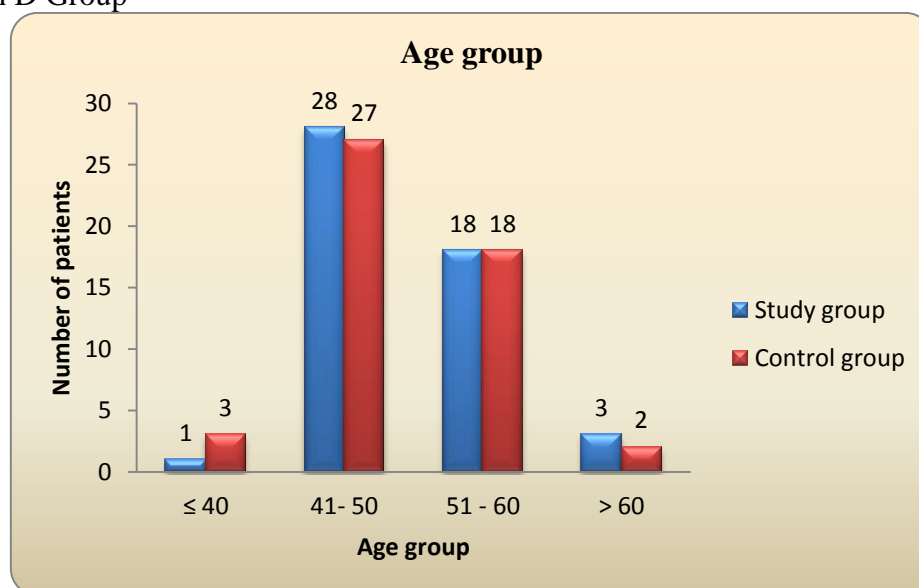
50 patients of Type 2 Diabetes Mellitus between age group of 40-60 years and 50 age and gender matched non diabetic controls without any vitamin D supplements were randomly selected. Serum Vitamin D estimation was done in all cases by standard method (CMIA). Vitamin D Kit - Architect Machine, Maker - Abbott Health Services

Technique Used was CMIA (Chemiluminescent Microparticle Immunoassay)

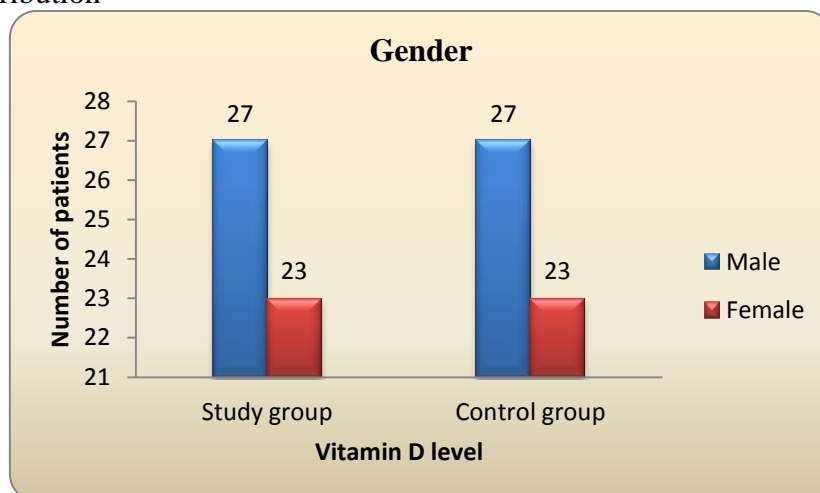
Appropriate statistical methods were applied.

**OBSERVATIONS AND RESULTS****Table 1 : Vitamin D Group**

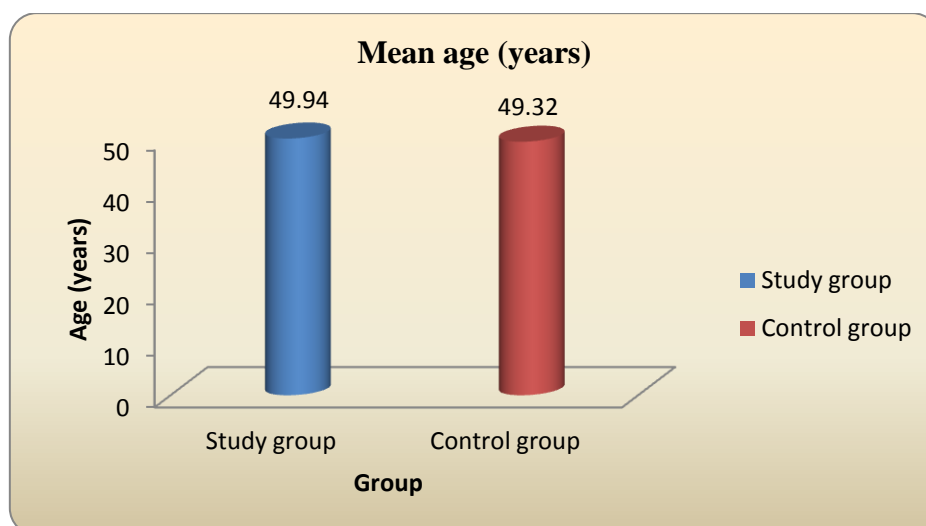
		Group		Total	P-value
		Study group	Control group		
Vitamin D group	Low	1	4	5	0.058
	Normal	22	30	52	
	High	27	16	43	
Total		50	50	100	

**Graph 1 : Age group****Graph 2 : Vitamin D Group**

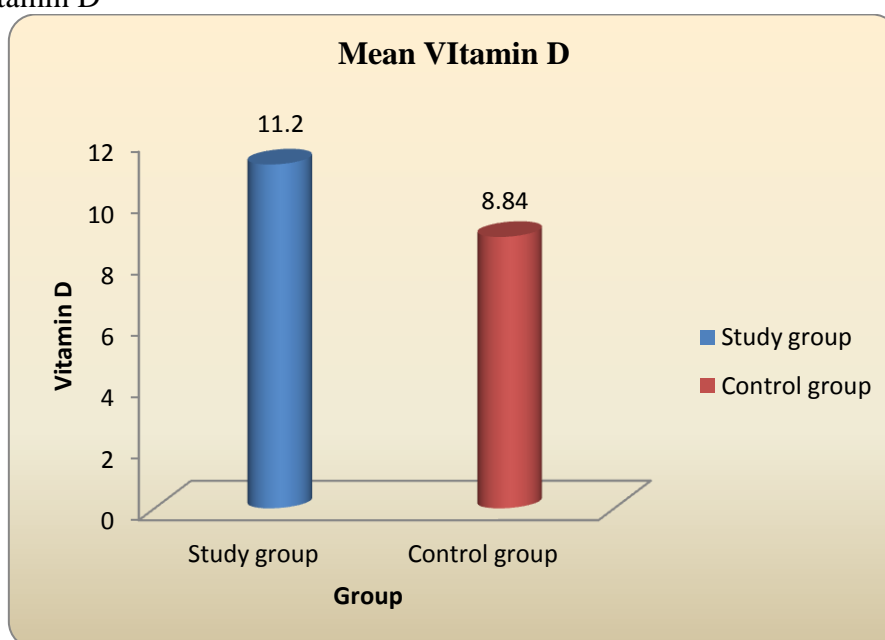
Graph 3 : Gender distribution



Graph 4 : Mean age



Graph 5 : Mean Vitamin D



## RESULTS & DISCUSSION

With respect to age group, 1 in study group and 3 in control group ( $\leq 40$  years); 28 in study group and 27 in control group (41-50 years) ; 18 in study group and 18 in control group (51-60 years) and 3 in study group and 2 in control group ( $> 60$  years) (graph 1) were found ( $p= 0.852$ ) . Fisher's exact test is not statistically significant. Higher number of patients were found in 41-50 years and 51-60 years age group showing that type 2 diabetes is commonly diagnosed in people above 40 years of age. Overall prevalence of diabetes for all age groups was recorded as 2.8%. A population based study demonstrated diabetes prevalence almost gets doubled in both men and women within 40-49 years age group.<sup>[21, 22]</sup>

Vitamin D level was found to be low in 5 patients (study group 1, control group 4), normal in 52 patients (study group 22, control group 30) and high in 43 patients (study group 27, control group 16). Fisher's exact test is not statistically significant ( $p=0.058$ ) (Table 1 & graph 2). Usually level of vitamin D declines with age .This may be correlated with diabetes which increases with age. So there are chances of association between type 2 diabetes and low serum vitamin D level. Animal studies support this association and showed that low vitamin D decreases insulin secretion.<sup>[23]</sup> But many human studies showed mixed results. A recently conducted study by Talaei A et al found significant improvements in serum fasting plasma glucose, insulin level and insulin resistance after treatment with vitamin D suggesting vitamin D supplementation could reduce insulin resistance in type 2 diabetes.<sup>[24]</sup> However, the third National Health and Nutrition Examination Survey (NHANES) data analysis exhibited varying type of relationship between fasting blood glucose (FBG) and 25 (OH) D concentrations among ethnic groups. The survey observed negative relationship between these FBG and vitamin D concentration in non-Hispanic whites and Mexican Americans. However, non-Hispanic blacks didn't exhibit such inverse association.<sup>[25]</sup> Likewise results of our study do

not support any link between low level of vitamin D and presence of type 2 diabetes.

With respect to gender wise distribution of study participants, total male participants were 54 (study group 27, control group 27) and total female participants were 46 (study group 23, control group 23) at ( $p=0.999$ ) with Chi-square test and Fisher's exact test not statistically significant (graph 3). However, Stadlmayr A et al in one of the cross-sectional study found sex-specific effect of vitamin D in pathogenesis of type 2 diabetes. Study suggested strong association between body mass index (BMI) and 25 (OH) D<sub>3</sub> in both genders. The same study observed higher crude or seasonally adjusted vitamin D concentrations in men as compared to women. Seasonally adjusted levels of vitamin D have stronger association with type 2 diabetes in women than men. This inverse relationship persists in women even after adjustment for BMI and other confounding variables but not observed in men.<sup>[26]</sup> Circulating vitamin D levels correlate with age and are in the lower range of normality in most healthy subjects. Levels of vitamin D decreases significantly in middle age and elderly. Alvarez-Rodriguez et al found 5 % of young (20-30 years), 21.7% of middle (31-59 years) and 31.6% of elderly (60-86 years) had decreased level of vitamin D lower than 20 ng/ml.<sup>[27]</sup>

Graph 4 shows in study group age (mean = 49.94, SD = 5.9) and in control group age (mean = 49.32, SD = 6.4) at ( $p= 0.6161$ ) with 2 independent sample t test being not statistically significant.

Graph 5 shows in study group vitamin D count (mean = 11.2, SD = 6.02) and in control group age (mean = 8.84, SD = 3.79) at ( $p= 0.022$ ) with 2 independent sample t test is statistically significant. It is in contrast to a recent Indian study recorded mean value of vitamin D in cases ( $21.01 \pm 8.67$ ) and in control as ( $19.46 \pm 9.42$ ) which was not statistically significant.<sup>[28]</sup>

Overall the result of our study shows no link between diabetes and vitamin D. This may be related to small sample and at single centre study and hence the results can't be generalized. We



have not taken into consideration other demographic (except age and sex) and socio-cultural factors that can have impact on both vitamin D level and diabetes status. Many other studies from literature have mixed findings.

## CONCLUSIONS

1. The result of this study is inconclusive raising doubts regarding low vitamin D level and occurrence of Type 2 diabetes mellitus.
2. Further studies are required to establish a clear co-relation between low vitamin D level and type 2 diabetes mellitus as most of the past studies also have mixed results.

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