

Vitamin D Deficiency and Type 2 Diabetes Mellitus

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ABSTRACT: Vitamin D has skeletal as well as non-skeletal effects including those on the endocrine system. Diabetes Mellitus, a leading cause of morbidity and mortality, has recently been linked to vitamin D status. It has been suggested that vitamin D deficiency is one of the modifiable risk factors for diabetes. We therefore designed this study to look at the relationship between vitamin D levels and diabetes control in type 2 South Asian diabetics from Pakistan. The objective of the study was to determine if correcting vitamin D deficiency improves diabetes control in type 2 diabetics. This analytical cross-sectional study, with prospective follow-up, included 200 subjects with type 2 diabetes (age range 27-76 years), who were deficient in vitamin D. 100 of these were treated with vitamin D and were assigned to the study group, while the rest did not receive treatment with vitamin D and so were placed in the control group. The subjects had their history taken and underwent clinical examination, after which, fasting blood was analyzed for HbA1C (using high performance liquid chromatography) and vitamin D levels (by the chemiluminescence technique) at baseline. Then the subjects in the study group only, were given vitamin D treatment for three months, after which, HbA1C and vitamin D levels were rechecked in both groups. In the study group, compared to baseline, the vitamin D levels at 3 months (following vitamin D supplementation) had significantly increased ($p < 0.001$) accompanied by significant decrease in HbA1C values ($P < 0.001$). In the control group, at three months, there was no significant change ($p = 0.219$) in vitamin D levels, but there was significant increase in HbA1C levels ($p < 0.001$) compared to baseline. These results indicate that correcting vitamin D deficiency improves diabetes control in type 2 diabetics. Larger prospective studies are required in the SouthAsian population to corroborate our findings.

Keywords: Vitamin D. Diabetes mellitus. South Asians. Obesity.

INTRODUCTION

Vitamin D is a fat soluble vitamin essential for normal functioning of the skeletal, neuromuscular and other systems [1]. Recently, its deficiency has been implicated in the development of inflammation, cancer and endocrine disorders including diabetes mellitus [2, 3].

The sources of vitamin D include the skin, where it is produced under the influence of sunlight, and diet [4]. Exposure of skin to ultraviolet (UV)-B radiation causes conversion of 7-dehydrocholesterol to cholecalciferol (vitamin D₃) [5]. The dietary form of vitamin D (ergocalciferol) is found in oily fish, liver, egg yolk, plants and fortified foods [5, 6]. The cholecalciferol and ergocalciferol are transported to the liver where they are hydroxylated to form 25-hydroxycholecalciferol [7]. This form circulates in blood bound to proteins and is used for measurement of vitamin D levels [8].

25-hydroxy D₃ is further hydroxylated in the proximal convoluted tubule of the kidney to form 1,25 dihydroxy D₃ [9]. 1,25 dihydroxy D₃, the

active form of vitamin D, has physiological effects of increasing calcium and phosphate absorption from the intestine and mobilization of calcium and phosphate from bone in the presence of the parathyroid (PTH) hormone [10].

It is postulated that vitamin D prevents the development and effects of diabetes mellitus by facilitating insulin secretion from the pancreas in response to glucose stimulation, augmenting the response of peripheral cells to insulin and by promoting survival of beta cells of the pancreas through modulation of the inflammatory effects of cytokines [11]. So, deficiency of vitamin D may lead to the onset and progression of diabetes mellitus [12].

The causes of vitamin D deficiency may be decreased sun exposure, dietary deficiency, a receptor abnormality, isolated deficiency of enzymes required for its synthesis and diseases of the liver, kidney or gastrointestinal tract [13]. Modest exposure of skin (face and arms) to sunlight (for five to thirty minutes between 10 am and 3 pm, twice a week) is enough for



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production of adequate amounts of vitamin D. Still, vitamin D deficiency remains a problem due to decreased sun exposure, particularly in those with an indoor lifestyle, in winter, in those with pigmented skin, in the elderly, in the hospitalized and burn patients etc [14].

Little data exists on the vitamin D status in diabetics and on the effect of correcting vitamin D deficiency on metabolic control of diabetes, particularly in South Asians. Therefore, we proposed to determine the levels of vitamin D and HbA1C (indicating the degree of diabetes control) in type 2 diabetics and to clarify if correcting vitamin D deficiency improves diabetes control.

MATERIALS AND METHODS

This analytical, cross-sectional study with prospective follow up was conducted at the outpatient department of Jinnah Hospital, Lahore, Pakistan. It consisted of 200 male and female subjects with type 2 diabetes mellitus with age greater than 18 years, who were deficient in vitamin D. Sampling was done by the convenient technique. Subjects less than 18 years of age, pregnant and lactating females, those with history of gastrointestinal surgery, those with features of liver or kidney disease and those taking phenobarbital, carbamazepine, isoniazid, theophylline or rifampicin were excluded from the study.

Definition of diabetes mellitus [15] HbA1C in venous blood: $\geq 6.5\%$.

Reference ranges for vitamin D (25 hydroxy cholecalciferol) levels [16] Normal: 31-50 ng/ml. Insufficiency: 20-30 ng/ml. Deficiency: < 20 ng/ml.

Data, sample collection and blood analysis

Each subject underwent a history and clinical examination. Weight and height of the subjects was recorded and the body mass index (BMI) was calculated by the formula weight/height^2 (kg/m^2). Then venous blood was analyzed for HbA1C [by high performance liquid chromatography (HPLC)] at the start of the study. Vitamin D levels were determined (by chemiluminescence) in Vitros EciQ immunodiagnostic system, at baseline. Vitamin D levels were found to be deficient in all the subjects. 100 of the subjects were treated with vitamin D₃ (100,000 international units, orally, every 10 days for first month and then 100,000 international units once a month for next three months) and so were placed in the study group, while the other 100 subjects did not receive vitamin D₃ and were placed in the control group. The groups were followed up and after 3 months, their HbA1C

and vitamin D levels were rechecked (by the above techniques). Treatment of diabetes in the two groups was not changed from the beginning to end of the study.

Ethical considerations

The study was approved by the Ethical Review Committee of Jinnah Hospital, Lahore, Pakistan and was conducted as per the Helsinki Declaration of human rights [17]. Each subject gave written informed consent to participate in the study.

Statistical analysis

The collected data was entered and analyzed using Statistical Package for Social Sciences (SPSS) version 20 software. Qualitative variable was expressed as percentage (%). One-sample Kolmogorov-Smirnov test indicated the normal distribution of our quantitative variables, which were hence expressed as mean \pm standard error of the mean (SEM). The two groups were compared using the independent-samples t-test and chi-square test for the quantitative and qualitative variables respectively, at baseline. Pearson correlation was applied to observe correlations. Paired t-test was used to compare the values of HbA1C and vitamin D at three months to those at baseline. A p value of < 0.05 was considered as statistically significant.

RESULTS

As shown in table 1, the mean \pm SEM age of study group (N = 100) was 52.06 ± 1.30 and of control group (N = 100) was 53.04 ± 1.12 years. There was no statistically significant difference between the ages of the two groups ($p = 0.570$, Independent-Samples t-test). As given in table 1, there were 44.00 % males in the study group and 50 % males in the control group. There was no statistically significant difference between the proportion of males in the two groups ($p = 0.396$, chi-square test). As per table 1, females accounted for 56.00 % of the study group subjects and 50 % of the subjects in the control group. There was no statistically significant difference between the proportion of females in the two groups ($p = 0.396$, chi-square test).

Mean \pm SEM BMI was $32.67 \pm 0.43 \text{ kg/m}^2$ in study group and $34.60 \pm 0.34 \text{ kg/m}^2$ in control group. This difference turned out to be statistically significant ($p = 0.001$, Independent Samples t-test) (table 1). Mean \pm SEM HbA1C was 7.65 ± 0.06 in study group and 7.69 ± 0.05 in the control group, at baseline. This difference was not statistically significant ($p = 0.660$, Independent-Samples t-test) (table 1). Mean \pm SEM vitamin D was $9.97 \pm 0.31 \text{ ng/ml}$ in the study group and $10.81 \pm 0.28 \text{ ng/ml}$ in the control group. This difference was not statistically significant.

Pearson correlation analysis showed that serum HbA1C had a negative but statistically insignificant correlation with vitamin D at baseline (correlation coefficient = - 0.044, $p = 0.532$) in all subjects ($N = 200$) (table 2). Analysis of correlation of HbA1C with vitamin D at 3 months in all subjects showed a statistically significant negative relationship (correlation coefficient = -0.296, $p < 0.001$).

Comparison of HbA1C values at baseline with those at three months showed that mean \pm SEM values in the study group ($N = 100$) significantly decreased (from $7.65 \pm 0.06\%$ to $7.41 \pm 0.05\%$, $p < 0.001$), while in the control group ($N = 100$) they significantly increased (from $7.69 \pm 0.05\%$ to $7.79 \pm 0.05\%$, $p < 0.001$). Comparison of vitamin D values at baseline with those at three months using paired-samples t-test showed that mean \pm SEM values in the study group ($N = 100$) significantly increased (from 9.97 ± 0.31 ng/ml to 35.81 ± 0.49 ng/ml, $p < 0.001$), while in the control group ($N = 100$) there was no significant increase in their levels (from 10.81 ± 0.28 ng/ml to 11.25 ± 0.30 ng/ml, $p = 0.219$) (table 3).

DISCUSSION

Recent studies have given evidence that vitamin D deficiency may be associated with increased risk of diabetes mellitus [18]. There is scarcity of data regarding the relationship between vitamin D levels and diabetes control, particularly in South Asia.

The present study was therefore designed to elucidate the effect of correcting vitamin D deficiency on the control of diabetes in the South Asian population of Pakistan.

There was no significant difference between the age and gender distribution of the study and control groups (table 1). The BMI of the study group was slightly less than that of the control group at baseline, however, subjects of both groups had class I obesity (table 1) [19]. Obesity is one of the risk factors for developing diabetes [20].

All the subjects in our study had vitamin D deficiency. Other studies have also shown a high prevalence of vitamin D deficiency in diabetics. [8, 21]

Correlation analysis after three months of vitamin D supplementation showed that, as the vitamin D values increased, the HbA1C values significantly decreased in all subjects (table 2). This indicates that increasing vitamin D values are associated with better control of diabetes [2]. The mechanism

involved may be through the effect of vitamin D to facilitate insulin secretion by the pancreas and to increase the sensitivity of peripheral cells to insulin. [11] A study by Thomas et al has shown that diabetes is associated with decreased vitamin D levels; hence correction of vitamin D deficiency would have beneficial effects on diabetes. [13, 22]

In the study group, after three months of follow up, the HbA1C values had significantly decreased while the vitamin D values had significantly increased (table 3). This indicates that improved diabetes control was associated with treatment of vitamin D deficiency. This can be explained by the fact that vitamin D treatment improves the secretion of insulin and decreases resistance to the peripheral effects of insulin. [23, 24] Studies in humans as well as animals have indicated that vitamin D treatment may improve metabolic control in diabetes. [25]

However, in the control group, there was no significant change in vitamin D levels, while the HbA1C levels significantly increased. This suggests that persisting vitamin D deficiency is linked to worsening of diabetes control. Other studies have demonstrated the link between low vitamin D levels and progression of diabetes [26]

Our study has some limitations. The sample size was small and was limited to Asian subjects. We could not establish a cause and effect relationship between vitamin D deficiency and poor diabetes control, for which, larger prospective studies in different population groups are required. [27]

Nevertheless, the results of our study indicate that treatment of vitamin D deficiency has a significant positive effect on the control of diabetes in Asian subjects. Treatment of vitamin D deficiency is easily managed and tolerated well, the correction of which may be an important modality of diabetes management in the future. [28]

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ETHICAL STANDARDS

The experiments comply with the current laws of Pakistan.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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TABLES

Table 1. Baseline characteristics of the study and control groups.

	Study group (N = 100)	Control group (N = 100)	p value* (N = 100)
Age (years)	52.06 ± 1.30	53.04 ± 1.12	0.570
Gender			
Male (%)	44	50	0.396
Female (%)		50	0.396
BMI (kg/m ²)	32.67 ± 0.43	34.60 ± 0.34	0.001**
HbA1C (%)	7.65 ± 0.06	7.69 ± 0.05	0.660
Vitamin D (ng/ml)	9.97 ± 0.31	10.81 ± 0.28	0.050

Data are given as % or mean ± SEM.

*Determined by independent-samples t-test or chi-square test.

** Significant at 0.001 level.

Table 2. Correlation between HbA1C and vitamin D in all subjects.

		Vitamin D	
		Correlation Coefficient	p value*
HbA1C (%)	Baseline	- 0.044	0.532
	At three months	- 0.296	< 0.001** *

Determined by Pearson Correlation. ** Significant at 0.001 level.

Table 3. Comparison of HbA1C and vitamin D values at baseline and three months.

		Baseline	At three months	p value*
Study group (N=100)	HbA1C (%)	7.65 ± 0.06	7.41 ± 0.05	<0.001**
	Vitamin D (ng/ml)	9.97 ± 0.31	35.81 ± 0.49	<0.001**
Control group (N=100)	HbA1C (%)	7.69 ± 0.05	7.79 ± 0.05	<0.001**
	Vitamin D (ng/ml)	10.81 ± 0.28	11.25 ± 0.30	0.219

*Determined by paired-samples t-test. **Significant at 0.001 level.