DIABETES MELLITUS;
FREQUENCY OF VITAMIN D DEFICIENCY IN TYPE I DIABETES MELLITUS.

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ABSTRACT… Background: Type I diabetes mellitus is a chronic illness in which autoimmune destruction of pancreatic beta cells results in the body's inability to produce insulin. Vitamin D has several important roles regarding bone health however, recent studies suggest that Vitamin D3 (the active form of Vitamin D) has potent antiproliferative and immunomodulatory properties which has linked it to many autoimmune disease including Type I Diabetes Melltius. Vitamin D deficiency (serum levels less than 50 nmol/l) has a negative influence on insulin secretion in patients with Type I Diabetes Mellitus, thereby suggesting a role for vitamin D3 in the pathogenesis of Type I Diabetes Mellitus. Vitamin D deficiency is an increasingly recognized comorbidity in patients with Type I diabetes mellitus. We aim to determine the frequency of vitamin D deficiency in Type I Diabetes Mellitus in Pakistani population. **Objectives:** The objective of the study was to determine frequency of Vitamin D deficiency in patients having Type I Diabetes Mellitus in Pakistani Population. **Study Design:** Cross-sectional study. **Setting:** The study was conducted in Diabetes Management Center & Endocrinology Unit (DMC & EU) at Services Hospital Lahore. **Period:** From 20th May to 19th November (6 months). **Materials and Methods:** 200 patients having Type I Diabetes Mellitus presenting to Diabetic Management Center were recruited by non-probability purposive sampling. Informed consent was taken. Pro forma was filled by a skilled interviewer and blood sample for vitamin D levels was drawn. Data was entered in the pro forma given at the end and was analyzed in SPSS. **Results:** Of the 200 subjects 125 were males and 75 were females. Of the males 85.6% and females 88% were vitamin D deficient. The frequency of vitamin D deficiency in newly diagnosed Type I Diabetics is 86.5%. In this study it was seen that higher HbA1c levels are significantly associated with Vitamin D deficiency. **Conclusions:** These results conclude that vitamin D deficiency is significantly frequent at the onset of Type I Diabetes Mellitus . So vitamin D levels should be measured in all Type I diabetics on their first presentation to the hospital especially those with higher HbA1c levels and vitamin D should be replaced in deficient patients. Further prospective studies should be done to evaluate Vitamin D3 as a factor in managing glycemic control.

Key words: Type I Diabetes Mellitus, Pancreatic Beta Cells, Vitamin D Deficiency, Immunomodulatory, Antiproliferative, Autoimmune.

INTRODUCTION

Vitamin D, a fat soluble vitamin, was previously thought to be only involved in calcium metabolism and bone turnover. Recently, there has been appealing evidence on the "nonclassic" role of vitamin D in addition to its skeletal effects and control of calcium homeostasis. In fact, Vitamin D3 (the active form of Vitamin D) has shown potent antiproliferative and immunomodulatory properties in many autoimmune diseases including rheumatoid arthritis, scleroderma, psoriasis[1], multiple sclerosis[2], and especially, Type I Diabetes Mellitus (T1DM)[3], an autoimmune disease occurring in the pancreatic islet cells.

Vitamin D3 plays an immunomodulatory role in the prevention of Type I Diabetes Mellitus, through the vitamin D receptor (VDR) expressed in antigen presenting cells, activated T cells and pancreatic islet β-cells.[4,5,6] Sunlight exposure, strongly related to latitude, determines the body's Vitamin D3 level and many observational studies show increased Type I Diabetes Mellitus prevalence at Northern latitudes where sun exposure is reduced. Vitamin

D has important role in the action of insulin and improvement of glycemic control[5] and its deficiency (serum levels less than 50 nmol/l) has a negative influence on both of these factors. Vitamin D replenishment has shown to improve glycemia and insulin secretion in patients with Type I Diabetes Mellitus with established hypovitaminosis D[7], thereby suggesting a role for vitamin D3 in the pathogenesis of Type I Diabetes Mellitus.

A meta-analysis of the results of observational studies suggests that the risk of Type I Diabetes Mellitus is reduced in those who were supplemented in childhood with vitamin D compared to those who were not.[8] Further evidence is available in the form of another study conducted in Hammad General Hospital, Qatar revealing 90.6% cases of Type I Diabetes Mellitus also having vitamin D deficiency[8] and a similar study in Northern India showing Vitamin D3 deficiency in 58% of Type I Diabetes Mellitus patients.[9] In Switzerland, in a cross-sectional study, 60–84% of Type I Diabetes Mellitus were 25-OH D deficient.[10]

All this evidence strongly links Vitamin D3 deficiency with Type I Diabetes Mellitus.

The rationale of my research is to address this deficiency and determine the level of Vitamin D3 deficiency in Type I Diabetes Mellitus patients in Pakistani population. Both Type I Diabetes and vitamin D deficiency are widespread in Pakistani population but unfortunately, research data that links these two conditions in our population is inadequate. Vitamin D levels vary with latitude and ethnicity and the above mentioned studies show variation in the percentage of vitamin D deficiency in different areas. My study will establish the percentage of this deficiency in Pakistani population with Type I Diabetes Mellitus, which will allow significant insight into management of Type I Diabetes Mellitus in local population, since current regimens do not consider Vitamin D3 levels as a factor in managing glycemic control or preventing/delaying the onset of Type I Diabetes Mellitus. The objective of the study is to determine frequency of Vitamin D deficiency in patients having Type I Diabetes Mellitus.

MATERIAL AND METHODS
Setting
The study was conducted in Diabetes Management Center & Endocrinology Unit (DMC & EU) at Services Hospital Lahore.

Duration of Study
6 months.

Sample Size
The evaluated sample size was 200 patients with 7 % margin of error, 95% confidence level taking expected percentage of frequency of vitamin D deficiency in Type I Diabetes Mellitus as 58%[9] using online calculator www.quantitativeskills.com

Study Design
Cross-sectional study.

Sampling Technique
Non-probability purposive sampling.

Inclusion Criteria
1. Patient diagnosed with Type I Diabetes Mellitus on clinical criteria
2. BMI 18-21 kg/m^2
3. Age between 12-30 years
4. Patient is willing to participate in the research.

Exclusion Criteria
1. Current vitamin D therapy or depot vitamin D injection in last 3 months
2. Taking steroids or any hormone replacement therapy
3. Any other endocrine disorder other than Type I Diabetes Mellitus (e.g hypoparathyroidism, hyperthyroidism etc excluded on history and examination.)
4. Advance liver disease assessed by Liver Function Tests (serum blood test) showing bilirubin more than 1.2mg/dl, and ALT more than 41IU/L, AST more than 45IU/L.
5. Advance renal disease assessed by Renal Function Tests (blood test) showing serum creatinine more than 1mg/dl.
6. Pregnancy

DATA COLLECTION

Patients attending the outdoor of Diabetes Management Center & Endocrinology Unit (DMC & EU) of Services Hospital Lahore were selected according to the inclusion and exclusion criteria mentioned above. The patient was informed that the information collected from him/her will be used in a study and that the confidentiality and anonymity related issues will be taken care of accordingly. After obtaining consent, the samples for the vitamin D levels were taken and sent to the SIMS laboratory. The patient information and results obtained from SIMS laboratory were recorded in Patient Pro forma (attached as annexure A).

DATA ANALYSIS

Data was collected, compiled and analyzed statistically using SPSS version 16 for windows. The quantitative variables like BMI, age have been expressed in mean and standard deviation. Quantitative data like BMI, age has been compared with Student t-test. A 'p' value more than 0.05 was considered statistically significant. Qualitative variables like gender and vitamin D deficiency have been expressed in frequencies and percentages.

Security and confidentiality of the data was ensured.

RESULTS

In this study 200 patients with Type I Diabetes Mellitus attending the diabetes center of Services Hospital were selected through the already defined inclusion and exclusion criteria.

In current study the total number of patients recruited was 200. All of the patients were newly diagnosed Type I diabetics with a BMI between 18 to 21 kg/m². Of the 200 patients 173 were found to be vitamin D deficient (i.e. < 50 nmol/L) and 27 patients had normal vitamin D levels. This depicts that 86.5 % of the Type I diabetics are vitamin D deficient and 13.5 % had sufficient vitamin D levels.

Among these individuals recruited for the study 125 were male and 75 were female. This shows that incidence of males is almost double of that of the females. In my study among the males 107 were vitamin D deficient and 18 male patients had normal vitamin D levels, showing that 85.6% of the male Type I diabetics had vitamin D deficiency and 14.4% had normal vitamin D levels. Of the female patients 66 were vitamin D deficient and 9 had no vitamin D deficiency, depicting that 88% of the females had low vitamin D levels while12% had normal levels.

	Minimum	Maximum	Mean (±SD)
Age	4	30	19.15 (±4.91)
BMI	14	21	18.49 (±1.70)
HbA1c	7	11.5	8.81 (±1.02)
Vitamin D levels	20	79	39.79 (±12.65)

Table-I. Characteristics of the Study Population (total population=200)

Vitamin D Deficiency	Frequency	Percent
Yes	173	86.5
No	27	13.5
Total	200	100.0

Table-II. Tabulated form of frequency of Vitamin D deficiency in Type I Diabetes Mellitus. Vitamin D deficiency is found in 86.5% of the subjects.
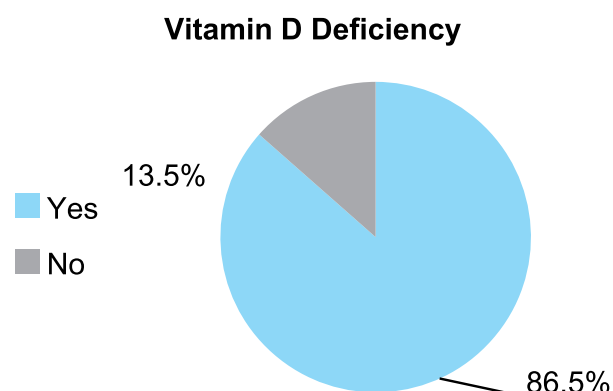
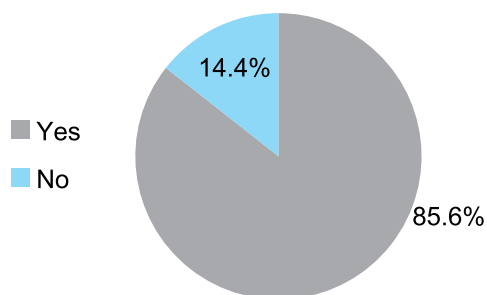## Vitamin D Deficiency

13.5%
■ Yes
■ No
86.5%

The subjects were divided into 4 groups according to their age and maximum individuals (n=69) belonged to the age group 16 to 20 years followed by age group 21-25 years (n=64) age group 12-15 years (n=50) and then 26 to 30 years(n=17) .
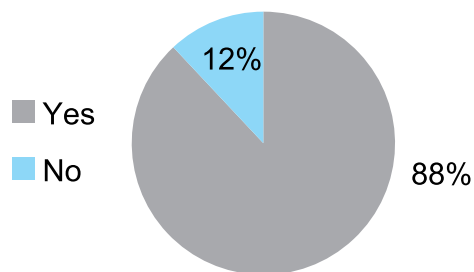
Gender	Vitamin D Deficiency	Freq.	Percent
Male (125)	Yes	107	85.6
	No	18	14.4
Female (75)	Yes	66	88
	No	9	12

Table-III. Shows the gender distribution of the selected subjects, 125 males and 75 female subjects were included in the study. The table shows the distribution of vitamin D deficiency among the male and female subjects. Vitamin D deficiency was observed in 85.6% of males and 88% of the females

Vitamin D Deficiency (Females)

Vitamin D Deficiency (Males)

Frequency of Vitamin D deficiency observed in these groups is: 80 percent, 84.05 percent, 92.18 percent and 94.11 percent respectively.

The HbA1C of the patients was also noted at the time of sampling and the subjects were divided into 4 groups. The patients are divided into 4 groups: 7.0-8.0, 8.1-9.0, 9.1-10 and more than 10. The frequency of Vitamin D deficiency observed is 81.48%, 85.1%, 88.3% and 100% respectively in each group, showing the maximum vitamin D deficiency in patients with high HbA1c.

		Age in years				Total
		12-15	16-20	21-25	26-30	
Vitamin D level	deficient	40	58	59	16	173
	sufficient	10	11	5	1	27
Total		50	69	64	17	200
Percentage deficiency		80	84.05	92.18	94.11	86.5

Table-V. Vitamin D deficiency observed in different age groups: 12-15 years, 16-20 years, 21-25 years and 26-30 years. Frequency of Vitamin D deficiency observed in these groups is: 80%, 84.05%, 92.18% and 94.11% respectively.

		HbA1c levels				Total
		7.0-8.0	8.1-9.0	9.1-10	>10	
Vitamin D deficiency	deficient	44	46	68	15	173
	sufficient	10	8	9	0	27
Total		54	54	77	15	200
Percentage Deficient		81.48	85.1	88.3	100	86.5

Table-V. Vitamin D deficiency in patients divided into 4 groups according to HbA1c levels: 7.0-8.0, 8.1-9.0, 9.1-10 and >10. The frequency of Vitamin D deficiency observed is 81.48%, 85.1%, 88.3% and 100% respectively in each group.
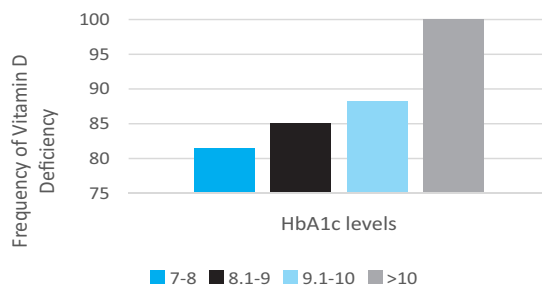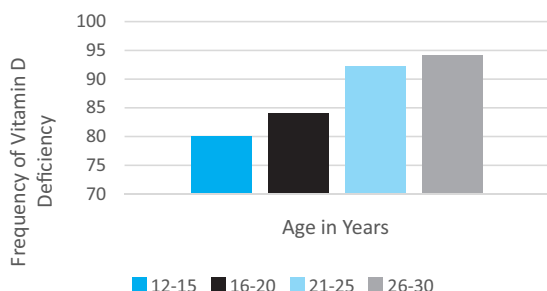
DISCUSSION

The result of my study shows that vitamin D deficiency is quite prevalent in newly diagnosed Type I diabetics. Vitamin D is a fat soluble vitamin and it has a very important role in skeletal muscle development. Vitamin D deficiency leads to increased risk of skeletal fragility due to reduced bone mineral density in adults. The geographical location, diet, exposure to sun and cultural norms tend to play their role in deficiency of this vitamin. In addition to this decrease in intake of vitamin D-fortified milk, use of sugar-free colas, which are frequently consumed by adolescents with diabetes, convey additional risk for poor bone health as they contain phosphoric acid, which is known to reduce intestinal calcium absorption. Hyperglycemia, increased urinary calcium excretion resulting in a calcium deficit, inflammatory cytokines, and microangiopathy could also potentially impair bone strength.

In current study the total number of patients recruited was 200. All of the patients were newly diagnosed Type I diabetics with a BMI between 18 to 21 kg/m^2. Of the 200 patients 173 were found to be vitamin D deficient (i.e. < 50 nmol/L) and 27 patients had normal vitamin D levels. This depicts that 86.5 % of the Type I diabetics are vitamin D deficient and 13.5 % had sufficient vitamin D levels. These results show that vitamin D deficiency is highly prevalent in type I diabetics. This result is in keeping with my reference study "Low levels of vitamin D in North Indian children"[9] with newly diagnosed Type I diabetes where 29 (58%) children in the study group were vitamin D deficient (25-OHD level < 20 ng/mL or < 50 nmol/L). However, in my study 86.5 % Type I diabetics were deficient showing that this deficiency is much more prevalent in our set up than in the Indian population. Further evidence is available in the form of another study conducted by "Bener A, Alsaied A, Al-Ali M, Al-Kubaisi A, Basha B, Abraham A, et al in Hammad General Hospital, Qatar"[8] revealing 90.6% cases of Type I Diabetes Mellitus also having vitamin D deficiency showing results almost similar to my study.

In another study, carried out by "Janner M, Ballinari P, Mullis PE, Flück, the prevalence of vitamin D deficiency in children and adolescents with Type I diabetes"[10] was 60.5%.

All these results show that Vitamin D deficiency is higher in Type I diabetics and it is much higher in our set up.

Among these individuals recruited for the study 125 were male and 75 were female. This shows that incidence of males is almost the double of that of the females. This result is similar to the review article recently published stating that incidence of Type I diabetes mellitus, in age group of 15-39 years, a male preponderance of up to twofold is found.[11] The male preponderance in Type I diabetes from age 15 up to 40 could be due to hormonal influence, with higher peripheral insulin resistance among men in young adults and younger middle age.

In my study among the males 107 were vitamin D deficient and 18 had normal vitamin D levels, showing that 85.6% of the male Type I diabetics had vitamin D deficiency and 14.4% had normal vitamin D levels. Of the female patients 66 were vitamin D deficient and 9 had no vitamin D deficiency, depicting that 88% of the females had low vitamin D levels while 12% had normal levels. Since there is no significant difference between the frequency of Vitamin D deficiency between the male and the female patients we infer that vitamin D deficiency is equally prevalent in both sexes.

The subjects were divided into 4 groups according to their age and maximum individuals (n=69) belonged to the age group 16 to 20 years followed by age group 21-25 years (n=64) age group 12-15 years (n=50) and then 26 to 30 years(n=17). This is in accordance with the general distribution of disease as Type I diabetes is more prevalent between 16 to 25 years of life. Frequency of Vitamin D deficiency observed in these groups is: 80 percent, 84.05 percent, 92.18 percent and 94.11 percent respectively. This shows an increasing trend in vitamin D deficiency with age. It may be due to the decrease in intake of vitamin D containing food products. My results are similar to a review article on "Time trends and

gender differences in incidence and prevalence of Type I diabetes in Sweden by Wändell PE, Carlsson AC."[11]

The HbA1C of the patients was also noted at the time of sampling and the subjects were divided into 4 groups. The patients are divided into 4 groups: 7.0-8.0, 8.1-9.0, 9.1-10 and more than 10. The frequency of Vitamin D deficiency observed is 81.48%, 85.1%, 88.3% and 100% respectively in each group, showing the maximum vitamin D deficiency in patients with high HbA1c. Vitamin D deficient individuals had significantly higher HbA1c levels as compared to the patients with normal Vitamin D levels. This shows that there may be an association between low vitamin D levels and hyperglycemia. This result is similar to a study conducted by "Sarah E. Bennett, Jennifer McPeake, David R. McCance, John G. Manderson on pregnant Type I diabetic mothers" showing that, HbA1c at booking was significantly negatively correlated with maternal 25 hydroxy vitamin D3.[12]

This study shows that Vitamin D deficiency is very frequent in Type I diabetic patients.

As Type I Diabetes Mellitus itself can cause increase in skeletal muscle fragility because of hyperglycemia, hypercalciuria resulting in a calcium deficit, inflammatory cytokines, and microangiopathy of the vessels supplying the bones it is necessary to measure Vitamin D levels and replace this deficiency to prevent increased risk of fractures and musculoskeletal problems.

Future studies need to confirm our findings of vitamin D inadequacy in youth with Type I Diabetes Mellitus, identify mechanisms leading to insufficient or deficient states, and assess BMD in youth with Type I Diabetes Mellitus by DEXA. Sample size was small, because of the limited resources and time limit of 6 months. A larger sample size would probably have strengthened the study results. Another limitation was that control group was not included. For better results, these limitations may be avoided in future trials.

CONCLUSION

It is recommended that all the patients presenting with Type I diabetes mellitus, especially those with high HbA1c levels at the time of presentation, should get their vitamin D levels checked, for better and focused management plan and to replace this vitamin D deficiency to prevent increased risk of fractures and musculoskeletal problems.

We must also carry out future studies to confirm our findings of vitamin D inadequacy in youth with Type I Diabetes Mellitus, identify mechanisms leading to insufficient or deficient states, and assess bone mineral density in youth with Type I Diabetes Mellitus by DEXA.

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Ships don't sink because of the water around them; ships sink because of the water that gets in them. Don't let what's happening around you get inside you and weigh you down.

– Unknown –

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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3	Taimia Ayub	Data collection.	
4	Usman Abdul Ahad	Data collection.	