To determine the mean glycemic changes after vitamin D3 supplement in children with type I diabetes mellitus and vitamin D deficiency presenting at a tertiary care hospital in Karachi

ABSTRACT
INTRODUCTION:

Glucose Homeostasis can potentially be affected by Vitamin D. Vitamin D deficiency has been identified as a global problem with an estimated one billion people worldwide suffering from vitamin D deficiency or insufficiency. Vitamin D deficiency (VDD) is a global health issue and is on the rise in Pakistani pediatric population. Type 1 diabetes (T1D) also negatively impacts bone health and is associated with a modest reduction in bone mineral density (BMD) and strength (7,8) Given the negative impact of vitamin D inadequacy and T1D on bone health, Adolescent with both conditions have multiple risk factors for increased skeletal fragility. In this study we evaluated glycemic changes after vitamin D3 supplement in patients with type I diabetes mellitus and vitamin D deficiency.

OBJECTIVE: To determine the mean glycemic changes after vitamin D3 supplement in children with type I diabetes mellitus and vitamin D deficiency presenting at a tertiary care hospital in Karachi.

METHODOLOGY:

A quasi experimental study design was conducted on 40 children who were presenting in OPD of NICH Karachi for six months. All patients were subjected to demographics and detailed history for Type 1 Diabetes and Vitamin D deficiency. Immunoturbidometry for HbA1C and ELISA for 25OHD was performed. Vitamin D3 supplement was advised as per operational definition. Insulin dose was recorded by parents for three months. 25OHD and HbA1C levels were measured following Vitamin D3 supplements. Statistical analysis was performed to analyze the significance.

RESULTS:

We observed a significant difference in mean HbA1c level at pre-treatment and post treatment was 9.89 ± 2.04 and 8.42 ± 1.87 respectively with Vitamin D3 supplements, with p-value 0.001.

CONCLUSION:

Vitamin D3 supplement improves HbA1C in patients with type I diabetes and vitamin D deficiency.

KEY WORDS:

Vitamin D3, HbA1C, type I diabetes, vitamin D deficiency.

INTRODUCTION:

Vitamin D deficiency (VDD) has been highlighted as a global issue, with an approximately one billion individuals suffering from deficiency or inadequacy of the vitamin D. In Pakistan, a higher incidence of VDD has been found in healthy volunteers and medical clinic patients (Akhtar, 2016). In newborns and children with chronic severe vitamin D deficiency, inadequate mineralization causes bone deformity (i.e., rickets). Vitamin D deficiency prevents children to reach their appropriate peak bone density and increases the risk of fracture later in life (Sahay & Sahay, 2012). In many pediatric groups, vitamin D deficiency is a mostly ignored epidemic. Vitamin D deficiency (VDD) is a global health problem that is becoming more prevalent among Pakistani children.

Type 1 diabetes (T1D) has a deleterious influence on bone health and is linked to a slight decrease in bone mineral density (BMD) and strength (Zhukouskaya et al., 2015). To date, advanced glycation end products in bone collagen, hypercalciuria linked with glycosuria, inflammatory cytokines, and diabetic micro-angiopathy with reduced blood flow to bone have all been hypothesized as potential causes for decreased BMD associated with diabetes (Schwartz, 2003; Ward et al., 2001). However, it's uncertain if rigorous diabetic treatment can assist maintain bone health.

Because both vitamin D deficiency and T1D have a deleterious influence on bone health, adolescents with both disorders have several risk factors for skeletal fragility. Vitamin D deficiency in adolescents with T1D has been studied just a few times. In one Australian investigation, vitamin D deficiency was discovered in 43 percent of adolescents with T1D (Greer et al., 2007). The mean SD HbA1C was 9.731.85 before the trial, but it was reduced to 8.551.91 following vitamin D3 supplement treatment, according to a study done by the Mohammadian shows. This drop is statistically significant (p-value 0.0001) (Mohammadian, Fatahi, Zaeri, & Vakili, 2015).

Several genetic and epidemiologic variables have been identified in type 1 diabetes mellitus. Although there is some epidemiologic evidence that low vitamin D levels during pregnancy or early infancy are linked to a higher risk of diabetes, the data is not definitive. Vitamin D deficiency has also been found to have a deleterious impact on beta cell function (Chiu, Chu, Go, & Saad, 2004). Glycemic alterations following vitamin D3 supplementation in individuals with type 1 diabetes mellitus and vitamin D insufficiency will be evaluated in this study. Furthermore, in a developing nation like Pakistan, where malnutrition is a major concern, it is a global public health issue that places a large strain on health-care resources, and no relevant local evidence has been identified in the literature in this respect.

MATERIALS AND METHODS:

A quasi experimental study design was conducted on 40 children who were presenting in OPD of National Institute of Child Health (NICH) Karachi for six months. Informed consent was taken from guardians or by the patient (considering the age of the patient). All of the patients had their medical histories thoroughly checked for Type 1 Diabetes and Vitamin D deficiency. All of the patients had their medical histories thoroughly checked for Type 1 Diabetes and Vitamin D insufficiency. Weight, diabetes duration, type of treatment, including dose and insulin type, gender, residence, sunlight exposure and family income were all recorded as baseline demographic information. HbA1C and 25OHD tests were performed pre and post Vitamin D3 treatment using Immunoturbidometry with NycoCard, Norway and ELISA strip reader Stat Fax ® 4700 respectively. Vitamin D3 supplements were prescribed and insulin dose was recorded by parents for three months.

The sample size was calculates n= 40, by using Mean ± SD of HbA1C 9.73±1.85 before the treatment and 8.55±1.91 after the treatment. Sample size was calculated using open epi Studies software with 95% confidence interval, 80% power of test. Samples were selected using Non-probability consecutive sampling.

The inclusion criteria for the participants of both genders, age between 06 months to 18 years, having Type I Diabetes Mellitus and Vitamin D levels less than or equal 30 ng/ml. Exclusion criteria includes patients with any other endocrine disease, Chronic Liver Disease (CLD), Chronic Kidney Disease, history of abdominal radiotherapy for any cancer, any steroids administration and who refuse to participate in the study.

Data analysis:

Data was entered and analyzed through Statistical software, SPSS 22. For quantitative variables (age, weight, Vitamin D (25OHD) level, HBA1c level), mean and standard deviation and for qualitative variables (gender, residence, sunlight exposure, family income), frequency and percentage was analyzed. To observe the difference of HbA1c levels pre and post treatment, paired T test was applied with p-value ≤0.05 as significant.

RESULTS:

According to the inclusion criteria, 40 patients were included in this study. Tables 1 illustrate the clinical and demographic features of the patients. Patients had an average age of 4.98±2.89 years, a mean weight of 20.5±5.64 kg, a vitamin D level of 9.87±2.45 at baseline, and a mean duration of type 1 diabetes mellitus of 3.64±2.22 years. In present study, there were 19 (47.5%) females and 21 (52.5%) males, 23 (57.5%) patients were residing in urban areas whereas 17 (42.5%) of the patients were from rural areas. A total of 12 patients (30%) had appropriate sun exposure and

28 individuals (70%) had insufficient solar exposure. In terms of family income, 11 patients (27.5%) came from a low-income family, 16 patients (40%) came from a middle-income family and 13 (32.5%) of the patients were from a high-income category.

Table1: The demographics of the participants including age, weight, Vitamin D level, diabetes duration, gender, residence, sunlight exposure and family income are shown.

Variables	Frequency	Mean± Std. Deviation
Age	40	4.98±2.89
Weight	40	20.5±5.64
Vitamin D level	40	9.87±2.45
Duration of T1DM	140	3.64±2.22

Variables	Frequency	Percentage
Gender		
Female	19	47.5
Male	21	52.5
Total	40	100
Residence		
Urban	23	57.5
Rural	17	42.5
Total	40	100
Sun light exposure		
Adequate	12	30
Inadequate	28	70
Total	40	100
Family income		
Lower income	11	27.5
Middle income	16	40
Upper income	13	32.5
Total	40	100

The mean HbA1c levels before and after intervention were 9.89±2.04 and 8.42±1.87, respectively. A paired t-test was used to determine if there was a significant difference in HbA1c levels before and after treatment in type 1 DM patients with vitamin D insufficiency. With a p-value of 0.001, vitamin D3 supplementation had a substantial effect on glycemic control as shown in Table 2. Age, weight, HBA1c level (baseline), duration of type 1 diabetes, gender, residence, family income, and sunshine exposure were all used to stratify pre and post HbA1c levels. Interestingly, all variables had a significant influence with a P value of 0.05.

Table 2: Stratification of HbA1c level pre and post treatment with respect to age, gender, residence, type I DM duration, weight, family income and sun exposure.

	HbA1c level	n	Mean ±SD	P-value
HbA1c level	Pre-treatment	40	9.89±2.04	0.001
	Post- treatment	40	8.42±1.87	
	difference	40	1.52±1.75	
Age				
≤10 years	Pre-treatment	25	9.39±2.56	0.001
	Post- treatment		8.56±1.92	
>10 years	Pre-treatment	15	9.88±2.24	0.001
	Post- treatment		8.54±1.96	
Gender				
Male	Pre-treatment	19	9.74±2.45	0.001
	Post- treatment		8.49±2.14	
Female	Pre-treatment	21	9.98±2.05	0.001
	Post- treatment		8.47±1.97	
Residence				
Urban	Pre-treatment	23	9.74±2.21	0.001
	Post- treatment		8.54±1.74	
Rural	Pre-treatment	17	9.96±2.12	0.001
	Post- treatment		8.37±1.74	
Duration of Type 1 DM				
<3 years	Pre-treatment	19	10.02±3.0	0.001
	Post- treatment		9.12±1.92	
≥3 years	Pre-treatment	21	9.23±2.16	0.001
	Post- treatment		8.22±1.89	
Weight				
<20kg	Pre-treatment	22	9.76±2.41	0.001
	Post- treatment		8.49±1.84	
≥20kg	Pre-treatment	18	9.69±2.34	0.001
	Post- treatment		8.49±1.95	
Baseline HbA1c				
<9	Pre-treatment	11	8.6±2.41	0.001
	Post- treatment		9.79±1.74	
≥9	Pre-treatment	29	9.82±2.06	0.001
	Post- treatment		8.54±1.66	
Family income				
Lower income	Pre-treatment	11	9.87±2.12	0.001
	Post- treatment		8.64±1.90	
Middle income	Pre-treatment	16	9.87±2.41	0.001
	Post- treatment		8.63±1.75	
Upper income	Pre-treatment	13	9.79±2.11	0.001
	Post- treatment		8.33±1.69	
Adequate sunlight exposure				

Yes	Pre-treatment	28	9.74±2.13	0.001
	Post- treatment		8.65±1.46	
No	Pre-treatment	12	9.39±2.21	0.001
	Post- treatment		8.33±1.69	

DISCUSSION:

To our knowledge, only a few researchers have examined at the 25OHD status and glucose metabolism in children with T1DM. Tunc et al. discovered that in individuals with T1DM and poor metabolic control, 25OHD levels were lower and insulin requirements were greater (Tunc, Cetinkaya, Kızılgün, & Aycan, 2011). Limited studies have evaluated the effect of vitamin D therapy on glycemic control in T2DM and T1DM patients, and the results are still inconclusive. After three months of ergocalciferol or cholecalciferol supplementation, Nwosu and Maranda found a substantial decrease in HbA1c in children and adolescents with T2DM, but not in those with T1DM (Nwosu & Maranda, 2014).

Treatment with vitamin D3 improves glycemic control in people with type 1 diabetes, according to this study. Furthermore, supplementing with vitamin D3 improves HbA1C in all glycemic groups, including low, middle and high income. Vitamin D deficit or insufficiency is perhaps more common in diabetes individuals with micro-albuminuria, according to Thraikill et al., notably with the rise in urine vitamin D Binding protein excretion. (Thrailkill, Jo, Cockrell, Moreau, & Fowlkes, 2011). The children in our study, had their microalbuminuria levels examined and found to be normal. Polymorphism of vitamin D receptor genes in type I diabetes mellitus has been discovered in two Iranian investigations. (Bonakdaran, Abbaszadegan, Dadkhah, & Dalouie, 2012; Mohammadnejad et al., 2012) . In our study, 38.73 percent of people had a positive family history for two forms of diabetes, and increases in HbA1C and 25OHD did not vary between relatives and non-relatives (p-value>0.05).

Finally, we recommend a daily dose of 400 to 1000 IU of vitamin D and a maintenance dose of 3.5-9 gr/m2 elemental calcium for individuals with diabetes and vitamin D insufficiency (Mohammadian et al., 2015). The family members of a vitamin D deficient patient was likewise vitamin D deficient. We urge that their family undergo a diagnostic examination and, if necessary, therapy.

We discovered inconsistent results in this study comparing migrants and Italian youngsters, with the first presenting the severe 25OHD insufficiency, which was linked to a more severe diabetic keto-acidosis (DKA) at onset. (Savastio et al., 2016). This finding might explain the findings of a prior multicenter research in Italy, suggesting that 25OHD deficiency is an environmental factor that triggers the onset of diabetes and worsens the clinical presentation. Indeed, as previously demonstrated, the decrease in 25OHD levels appears to be greater in diabetic ketoacidosis patients upon presentation (Franchi et al., 2014; Huynh et al., 2009).

Our findings suggest that a normal 25OHD level could prevent a severe onset of T1DM, possibly through a slower decline in β-cell function due to vitamin D's specific immuno-modulatory action, as suggested by a recent study that found that vitamin D3 given as a therapy to patients with T1DM had positive effects on cytokine, regulatory T cell levels, and residual β-cell function. Furthermore, the immunological activity of vitamin D has recently been documented in healthy persons treated with cholecalciferol (140.000 IU/month vs placebo) for three months (Savastio et al., 2016).

CONCLUSION:

Finally, 25OHD deficiency is common in T1DM children and appears to affect metabolic state and glycemic homeostasis. The potential use of vitamin D supplementation as a supportive treatment for improving glycemic control and insulin sensitivity offers up new avenues for improving disease management and patient health. Vitamin D3 is a cheap and widely accessible supplement. In individuals with type 1 diabetes and vitamin D insufficiency, a vitamin D3 supplement improves HbA1C. To investigate if increasing 25-OHD levels from deficit to sufficiency improves glycemic management in type 1 diabetic patients, well-designed clinical studies are necessary.

Consent

As per international standard, parental written consent has been collected and preserved by the author(s).

REFERENCES:

Akhtar, S. (2016). Prevalence and correlates of vitamin D deficiency-perspectives from Pakistan. *Pakistan journal of pharmaceutical sciences, 29*(4).

Bonakdaran, S., Abbaszadegan, M., Dadkhah, E., & Dalouie, M. K. (2012). Vitamin D receptor gene polymorphisms in type 1 diabetes mellitus: a new pattern from Khorasan province, Islamic Republic of Iran. *EMHJ-Eastern Mediterranean Health Journal, 18 (6), 614-619, 2012*.

Chiu, K. C., Chu, A., Go, V. L. W., & Saad, M. F. (2004). Hypovitaminosis D is associated with insulin resistance and β cell dysfunction. *The American journal of clinical nutrition, 79*(5), 820-825.

Franchi, B., Piazza, M., Sandri, M., Mazzei, F., Maffeis, C., & Boner, A. L. (2014). Vitamin D at the onset of type 1 diabetes in Italian children. *European journal of pediatrics, 173*(4), 477-482.

Greer, R. M., Rogers, M. A., Bowling, F. G., Buntain, H. M., Harris, M., Leong, G. M., & Cotterill, A. M. (2007). Australian children and adolescents with type 1 diabetes have low vitamin D levels. *The Medical Journal of Australia, 187*(1), 59-60.

Huynh, T., Greer, R. M., Nyunt, O., Bowling, F., Cowley, D., Leong, G. M., . . . Harris, M. (2009). The association between ketoacidosis and 25 (OH)-vitamin D3 levels at presentation in children with type 1 diabetes mellitus. *Pediatric diabetes, 10*(1), 38-43.

Mohammadian, S., Fatahi, N., Zaeri, H., & Vakili, M. A. (2015). Effect of vitamin d3 supplement in glycemic control of pediatrics with type 1 diabetes mellitus and vitamin d deficiency. *Journal of clinical and diagnostic research: JCDR, 9*(3), SC05.

Mohammadnejad, Z., Ghanbari, M., Ganjali, R., Afshari, J. T., Heydarpour, M., Taghavi, S. M., . . . Rafatpanah, H. (2012). Association between vitamin D receptor gene polymorphisms and type 1 diabetes mellitus in Iranian population. *Molecular biology reports, 39*(2), 831-837.

Nwosu, B. U., & Maranda, L. (2014). The effects of vitamin D supplementation on hepatic dysfunction, vitamin D status, and glycemic control in children and adolescents with vitamin D deficiency and either type 1 or type 2 diabetes mellitus. *PloS one, 9*(6), e99646.

Sahay, M., & Sahay, R. (2012). Rickets–vitamin D deficiency and dependency. *Indian journal of endocrinology and metabolism, 16*(2), 164.

Savastio, S., Cadario, F., Genoni, G., Bellomo, G., Bagnati, M., Secco, G., . . . Bona, G. (2016). Vitamin D deficiency and glycemic status in children and adolescents with type 1 diabetes mellitus. *PloS one, 11*(9), e0162554.

Schwartz, A. (2003). Diabetes mellitus: does it affect bone? *Calcified tissue international, 73*(6), 515-519.

Thrailkill, K. M., Jo, C.-H., Cockrell, G. E., Moreau, C. S., & Fowlkes, J. L. (2011). Enhanced excretion of vitamin D binding protein in type 1 diabetes: a role in vitamin D deficiency? *The Journal of Clinical Endocrinology & Metabolism, 96*(1), 142-149.

Tunc, O., Cetinkaya, S., Kızılgün, M., & Aycan, Z. (2011). Vitamin D status and insulin requirements in children and adolescent with type 1 diabetes.

Ward, D. T., Yau, S. K., Mee, A. P., Mawer, E. B., Miller, C. A., Garland, H. O., & Riccardi, D. (2001). Functional, molecular, and biochemical characterization of streptozotocin-induced diabetes. *Journal of the American Society of Nephrology, 12*(4), 779-790.

Zhukouskaya, V., Eller-Vainicher, C., Shepelkevich, A., Dydyshko, Y., Cairoli, E., & Chiodini, I. (2015). Bone health in type 1 diabetes: focus on evaluation and treatment in clinical practice. *Journal of Endocrinological Investigation, 38*(9), 941-950.