Vitamin D levels in Saudi children with type 1 diabetes

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ABSTRACT

الأهداف: تقييم مدى انتشار نقص فيتامين د بين الأطفال المصابين بداء السكري من النمط الأول.

الطريقة: أُجريت هذه الدراسة الاستطلاعية المقطعية في عيادة السكري والغدد الصماء بقسم الأطفال، مستشفى قوى الأمن، الرياض، المملكة العربية السعودية، وقد استمرت خلال الفترة من يونيو إلى سبتمبر 2010م. شملت الدراسة مجموعة الأطفال المصابين بالسكري من النمط الأول وكان عددهم 100 طفلاً، ومجموعة الشاهد التي تضمنت الأطفال الذي أتوا إلى قسم الأطفال من أجل التطعيم وكان عددهم 100 طفلاً. لقد قمنا بعمل مقارنة بين مجموعة الأطفال المصابين بالسكري ومجموعة الشاهد التي تماثل هذه المجموعة في العمر والجنس والعرق وذلك اعتماداً على نتائج الاختبارات التالية: قياس تركيز فيتامين د في مصل الدم، وهرمون الغدة جار الدرقية، وفحص أنزيم الفوسفاتيز القلوي، والكالسيوم، والفوسفات.

النتائج: أشارت نتائج الدراسة إلى أن مستوى فيتامين د قد كان منخفضا بصورة واضحة لدى مجموعة الأطفال المصابين بمرض السكري من النمط الأول مقارنةً بمجموعة الشاهد (36.7 ± 14.3 نانومول/لتر مقارنةً بالمعدل 44.8 ± 14.1 نانومول/لتر). لقد كان نقص فيتامين د في مجموعة الأطفال المصابين بالسكري خفيفاً في 46% من أطفال المجموعة، ومتوسطاً في 16%، وحاداً في 4%، وبالمقابل كان نقص هذا الفيتامين في مجموعة الشاهد خفيفاً في 52% من أطفال المجموعة، ومتوسطاً في 6%، وحاداً في 1%. وبصفة عامة كانت نسبة الإصابة بنقص فيتامين د 84% في مجموعة الأطفال المصابين بالسكري من النمط الأول، و59% في مجموعة الشاهد. كما لم يكن هناك علاقة بين التحكم بنسبة السكر في الدم من جهة ومستوى فيتامين د من جهة أخرى وذلك في كلي المجموعتين.

خاتمة: أثبتت الدراسة مدى انتشار نقص فيتامين د بين الأطفال المصابين بمرض السكري من النمط الأول حيث كانت نسبة النقص حادة في هذه المجموعة مقارنةً بمجموعة الشاهد، ولهذا يجب الكشف عن نقص فيتامين د والتعويض عنه بالفيتامينات اللازمة.

Objectives: To assess the prevalence of vitamin D deficiency in type 1 diabetic (T1DM) children.

Methods: In this prospective cross-sectional study, we included 100 Saudi children with T1DM attending the Pediatric Endocrinology and Diabetes Clinics, and 100 healthy controls from the Department of Pediatrics, Security Forces Hospital, Riyadh, Kingdom of Saudi Arabia from June to September 2010. We measured serum 25-hydroxy vitamin D (25OHD), parathyroid hormone, calcium, phosphate, and alkaline phosphatase in these patients, and compared the results with age, gender, and ethnicity-matched control subjects.

Results: The mean levels of 25OHD were significantly lower in the T1DM children compared to the controls (36.7 ± 14.3 nmol/l versus 44.8 ± 14.1 nmol/l). In the T1DM children, 64% were mildly, 16% were moderately, and 4% were severely vitamin D deficient as compared with 52% (mildly), 6% (moderately), and 1% (severely) in the control group. Overall, 84% of the T1DM children, and 59% of the healthy children were vitamin D deficient. There was no correlation between glycemic control and 25OHD level.

Conclusions: Prevalence of vitamin D deficiency in diabetic children is relatively high. Therefore, screening for vitamin D deficiency and supplementation of children with low vitamin D levels should be warranted.

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Type 1 diabetes mellitus (T1DM) negatively affects bone health, and is associated with a moderate reduction in bone mineral density and strength, as well as an increase in fracture risk. Several potential mechanisms for reduced bone mineral content associated with diabetes have been proposed, including advanced glycation end products in bone collagen, inflammatory cytokines, hypercalciuria associated with glycosuria, and diabetic microangiopathy with reduced blood flow to the bone.[1,2] Several reports[3,4] showed significant vitamin D deficiency in children and adolescent with T1DM. However, studies examining vitamin D inadequacy in diabetic children from the Middle East region is somewhat limited. A recent study from Qatar revealed that the incidence of severe vitamin D deficiency was considerably higher in children with T1DM compared with healthy children.[5] The investigators have shown that the mean serum level of vitamin D was significantly lower in children with T1DM, compared with non-diabetic children, however, both groups belonged to the mild to moderate vitamin D deficiency category.[5] Due to the high prevalence of vitamin D deficiency in children and adolescents with T1DM, some reports[4,6] suggested routine screening for vitamin D insufficiency in these individuals. Optimal vitamin D supply and close follow-up were recommended.[4,6] The aim of this study is to assess the level of vitamin D in Saudi children with T1DM in comparison to healthy children, and its relation to glycemic control and duration of diabetes.

Methods. This study was conducted in T1DM children attending the Pediatric Endocrinology and Diabetes Clinics, Department of Pediatrics, Security Forces Hospital, Riyadh, Kingdom of Saudi Arabia from June to September 2010. One hundred (41 males) Saudi children with established T1DM (more than 5 months duration), and 100 (48 males) age, gender, and ethnicity-matched healthy control subjects were randomly and cross-sectionally selected. The healthy children who came for vaccinations or accompanying their parents to the Primary Care Clinics were randomly selected as the control group. Diabetic children with chronic illnesses, such as gastrointestinal disorders, malabsorption and celiac disease, or those on vitamin D, calcium supplementation, or with diabetic complications, such as diabetic nephropathy were excluded. Likewise, healthy children who were on vitamin D, calcium supplementation, or multivitamins were excluded. The study was approved by the Research Ethics Committee. A written informed consent with the Security Forces Hospital Institutional Board Review approval was obtained from the participants. Clinical evaluation included growth parameters and physical examination. Height and weight were measured using standardized methods. The body mass index (BMI) was calculated as the weight in kilograms divided by height in meters squared. All children in the presence of their parents were interviewed. The questionnaire was designed to meet the objective of the study. The survey was based on standardized interviews performed by trained health professionals, which included demographic and social data, dietary history, daily consumption of dairy products, family, and past medical history of vitamin D deficiency, fractures rate, bone deformities, duration of sun exposure, drug history, and degree of glycemic control. Adequate sun exposure was defined by the investigators as more than 10% body surface area exposed to sunlight for more than 10 minutes a day (adapted with modification from Gilchrest)[7]. Biochemical evaluation including bone profile (calcium, magnesium, phosphorus, and alkaline phosphatase levels), parathyroid hormone level (PTH), 25 hydroxy vitamin D (25OHD) level, albumin level and hemoglobin A1C (HbA1c) was performed. Serum PTH was determined using an electrochemiluminescent immune assay. Serum 25OHD is the standard indicator of vitamin D status, composed of cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2). Levels of 25OHD were measured using the high-performance liquid chromatography method that detects both forms of 25OHD. For inter-assay precision, the coefficient variation was 5.7%; and 4.9% - for high and low pool of patients' samples; for the intra-assay precision, the coefficient variation was 5.6%; and 6% for high and low pool of patients samples. Since there is no consensus on the 25OHD levels that are to be considered sufficient in children, we adopted the cut off limits[8] to define vitamin D as: mild deficiency (<50 nmol/l); moderate deficiency (<25 nmol/l); and severe deficiency (<12.5 nmol/l). Because vitamin D status is associated with sunlight exposure which varies by season, all blood samples were collected during summer (June-September). The HbA1c was measured using high-performance liquid chromatography (reference range: 4-6%).

Statistical analysis was performed using the Statistical Package for Social Sciences program (SPSS Inc. Chicago, IL, USA). Student's t-test was used to ascertain the significance of differences between mean values of 2 continuous variables, and nonparametric Mann-Whitney test was used. Chi-square analysis was performed to test for differences in proportions of categorical variables between 2 or more groups. The Fisher's exact test (2-tailed) replaced the Chi-square test if the assumptions underlying Chi-square violated, that is, in case of small sample size, and where the expected frequency is less than 5 in any of the cells. Pearson's

correlation coefficient was used to evaluate the strength of association between variables. $P<0.05$ was considered as the cut-off value for significance.

Results. Of the total number of children surveyed, 41 T1DM and 48 of the healthy children were males. The mean age for diabetics versus controls was 9.5 ± 3.2 years versus 8.9 ± 2.1 years (**Table 1**). The percentage of children who were dark skinned was 6% in non-diabetic children compared to 4% in T1DM children. The rest of the children had the usual brown whitish skin color. None of the interviewed children, diabetic or healthy, had a history of bone deformities or fractures. Four T1DM children with mild vitamin D deficiency reported generalized bone aches compared with none among the healthy children. Most of T1DM children (92%) and non-diabetic children (89%) had inadequate exposure to sunlight. They reported less than 10 minutes sun exposure a day. Daily consumption of dairy products was focused on milk drinking only. The average daily intake of milk was 200 + 50 ml in T1DM, and healthy children as well. It was difficult to measure other dietary intake sources of vitamin D. Family history of vitamin D deficiency was slightly higher among T1DM children (5%) with a non-significant difference between T1DM and non-diabetic children (4%) (p=0.15). Mean 25OHD level was 44.8 + 14.1 nmol/l in the normal control, and 36.7 + 14.3 nmol/l in T1DM group (p=0.001). Overall, 84% of diabetics and 59% of healthy children were vitamin D deficient (**Table 1**). There was no correlation between HbA1c, BMI, and 25OHD level, however a negative correlation between 25OHD level and duration of diabetes (r=-0.273) was observed. Despite the high prevalence of vitamin D deficiency, we found a low prevalence of secondary hyperparathyroidism in vitamin D deficient healthy control and T1DM children and adolescents. The PTH level was 47.2 + 21.6 pg/ml for T1DM, and 48 + 22.6 pg/ml. All T1DM and healthy children had normal calcium and alkaline phosphatase levels. Calcium levels was 2.3 + 0.12 mmol/l in the healthy control, and 2.3 + 0.10 mmol/l in diabetic children, phosphorus levels was 1.5 + 0.23 mmol/l in the healthy control and 1.6 + 0.19 mmol/l in T1DM children, alkaline phosphatase levels was 274 + 78 U/L in the healthy control, and 233 + 62 U/L in T1DM children.

Table 1 - Vitamin D levels in diabetic and healthy control children.

Variable	Control (n=100)	T1DM (n=100)	*P*-value
Gender			
Males	48	41	
Females	52	59	
Age, years (mean ± SD)	8.9 ± 2.1	9.5 ± 3.2	0.50
BMI, mean ± SD	17.9 ± 3.0	17.6 ± 3.6	0.61
Duration of T1DM	---	38.2 ± 32.0	
25OHD			
Mean ± SD	44.8 ± 14.1	36.7 ± 14.3	0.001
Confidence interval	(43.3-48.8)	(33.9-39.6)	
Vitamin D deficiency (%)			0.001
Mild	(52)	(64)	
Moderate	(6)	(16)	
Severe	(1)	(4)	

T1DM - type 1 diabetes mellitus, SD - standard deviation, BMI - body mass index, 25OHD - 25 hydroxyvitamin D

Discussion. The prevalence of vitamin D deficiency was higher in our cohort (84%) than in previous Western studies[3,4] analyzing subjects with T1DM. The prevalence of vitamin D deficiency was 60.5% in a Swiss study,[6] 43% in an Australian study,[3] approximately 25% in an Italian study,[9] and 15% in a North American study.[4] In Qatari children, a study revealed that vitamin D deficiency was considerably higher in T1DM children (90.6%) compared to non-diabetic children (85.3%).[5] In Australian children and adolescents with T1DM, the mean 25OHD was 64.6 nmol/l (61.3-67.9) in normal children, and 54.7 nmol/l (50.3-58.9) in T1DM children.[3] The proportion of 25OHD deficient were 18% in normal children, and 43% in T1DM children.[3] In a Swedish study, the mean 25OHD levels were 96.7 ± 2.7 nmol/L for the control group, and 82.5 ± 1.3 nmol/L for those with T1DM.[10] In a North American study, 25OHD level was measured in 128 youth with T1DM. Fifteen percent were vitamin D deficient, and 61% were vitamin D insufficient. Adjusted 25OHD mean level was 26.8 + 6.7 ng/dl. The investigators showed that vitamin D deficiency was more prevalent among older children, and those with longer duration of diabetes.[4] In a Swiss prospective cross-sectional study, serum 25OHD level was measured in 129 diabetic children.[6] Sixty percent were vitamin D deficient with a mean 25OHD level of 28.8 nmo/l (26-31.6), and the number rose to 84% during winter, whereas there was no correlation with diabetes control.[6] These differences might be explained by differences in dietary intake, sun avoidance behaviors, geographical environment, skin dark color, or genetic predisposition.

Not all studies showed lower vitamin D level in T1DM children than the control group. Serum samples from 110 T1DM and 153 control subjects were cross-sectionally analyzed, and the 25OHD levels were similar among the 2 groups.[11] The median 25OHD level was 20.1 ng/ml (13-37.4) in the control group, and 23 ng/ml (13.8-33.9) in T1DM. However, both groups had suboptimal 25OHD level.[11] Hypovitaminosis D was also observed in T2DM. In 581 Japanese patients with T2DM, the mean 25OHD concentration was 17.0 +

7.1 ng/ml.[12] The prevalence of hypovitaminosis D (<20 ng/ml) was 70.6%, and was associated with HbA1c and age, but not related to the duration of diabetes.[12] In our study, there was no correlation between glycemic control (HbA1c), BMI, and 25OHD level, however, a negative correlation between 25OHD level and duration of diabetes was observed. Low vitamin D levels were also found in newly diagnosed diabetics. Littorin et al[10] found low 25OHD levels in 459 Swedish patients aged between 15 and 34 years who were newly diagnosed with T1DM compared with age- and place-matched controls. Another study from Italy[9] found low 25OHD levels in 88 newly diagnosed children and adolescents. A recently published paper from India showed similar results.[13] Understanding the nature of low vitamin D levels in children with T1DM is important because it may potentially clarify the mechanisms of autoimmune ß-cell destruction, and may lead to interventions for preventing or delaying insulin dependence by using vitamin D or its analogues.

Several limitations were faced while this current study was conducted, including inaccuracy of milk and food intake measurement, and the exact duration and time of sun exposure, which might affect the results. In our study, the mean 25OHD level in diabetic children, is relatively lower than those published in Western studies.[3,4,6] This might reflect the high prevalence of 25OHD deficiency and insufficiency in our normal population. High prevalence of vitamin D deficiency might be related to low milk intake and decreased sun exposure, which can be partially prevented by increased family awareness.

In conclusion, the present study revealed that vitamin D deficiency was higher in diabetic children compared to healthy controls. Moreover, vitamin D deficiency was found common in the young Saudi population. It will be of interest for future studies to investigate whether vitamin D supplementation will improve glycemic control in Vitamin D deficient diabetic children.

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