Association of Increased Level of HBA1C with Vitamin D Deficiency in Children with Type 1 - Diabetes Mellitus

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Abstract:

Background: Type 1 diabetes mellitus(T1D) is due to β-cells destruction, usually leading to absolute insulin deficiency.T1D is the most common type of diabetes mellitus in children. The occurrence of T1D has been increasing worldwide. The International Diabetes Federation (IDF) has announced that there are 78,000 children in the world develop T1D every year. As of 2017, an estimated 1.1 million of children and adolescents have T1D worldwide, and 132.6 hundred of newly diagnosed cases are reported each year. **Methods:** Overall, 51 samples were collected from patients both genders .The patients composed of (51), (23) of them are males and (28) females with age range 2-12 years old, were seen in Endocrinology and Diabetes Center in Samawa.Those sample were diagnosed clinically by HBA1C to Diagnosis of the type diabetic by cobas c111 and evaluate vitamin- D by cobas e411 technique in diabetic patients. Further, groups consist of 50 samples were collected from apparently healthy individuals (25 males and 25 female) without any history of chronic disease. **Result:** There was no significant difference in mean age between patients group and control group, 8.43 ± 3.13 years versus 8.12 ±2.69 years, respectively ($p = 0.594$). The proportion of males with type 1 diabetes mellitus was 45.1 % while that of girls was 54.9 % and there was no significant difference in frequency distribution according to gender between type 1 diabetes mellitus group and control group ($p = 0.622$). There was no significant difference in mean age between boys and girls with type 1 DM ($p = 0.785$). The mean HbA1c% of patients with type 1 diabetes mellitus was significantly higher than that of control group, 9.75 ±0.80 % versus 4.64 ±0.40 %, respectively ($p < 0.001$). The mean serum vitamin –D in our study was significantly lower in patients with type 1 DM in comparison with control group, 11.14 ±4.65 ng/ml versus 17.16 ±6.39 ng/ml, respectively ($p < 0.001$). Diabetic patients with vitamin deficiency (< 20 ng/ml) accounted for 94.1 %, while control subjects accounted for 64 %, therefore, the prevalence rate of vitamin D deficiency in patients with type DM is higher than that in control group significantly ($p < 0.001$).

Keywords: Diabetes mellitus, Vitamin- D Deficiency, Type 1 - Diabetes Mellitus.

Introduction:

Type 1 diabetes or IDDM, develops most frequently in children; however, type 1 diabetes may also develop in adults. In type 1 diabetes, the body does not make insulin or enough insulin because the body's system has attacked and destroyed the cells (pancreatic Beta cells) that make insulin [1]. An individual with Type 1 diabetes developed the disease because their immune system destroyed the insulin-producing beta cells [2]. Hemoglobin (Hb) consists of four protein subunits, each containing a hem moiety, and is the red-pigmented protein located in the erythrocytes. Its main function is to transport oxygen and carbon dioxide in blood. Each Hb molecule is able to bind four oxygen molecules. Hb consists of a variety of sub fractions and derivatives. Among this heterogeneous group of hemoglobin's HbA1c is one of the glycated hemoglobin's, a sub fraction formed by the attachment of various sugars to the Hb molecule. HbA1c is formed in two steps by the non-enzymatic reaction of glucose with the

N-terminal amino group of the β-chain of normal adult Hb (HbA). The first step is reversible and yields labile HbA1c. This is rearranged to form stable HbA1c in a second reaction step. In the erythrocytes, the relative amount of HbA converted to stable HbA1c increases with the average concentration of glucose in the blood. The conversion to stable HbA1c is limited by the erythrocyte's life span of approximately 100 to 120 days. As a result, HbA1c reflects the average blood glucose level during the preceding 2 to 3 months. HbA1c is thus suitable to monitor long-term blood glucose control in individuals with diabetes mellitus. Glucose levels closer to the time of the assay have a greater influence on the HbA1c level [3]. Four recommended tests for diabetes, including measurement of fasting plasma glucose; 2-hour post load plasma glucose after a 75 g oral glucose tolerance test (OGTT); HbA1c; People with fasting plasma glucose values of ≥ (126 mg/dl), 2-h post-load plasma glucose ≥ (200 mg/dl) [4], HbA1c ≥ 6.5% (48 mmol/mol); or a random blood glucose ≥ (200 mg/dl) in the presence of signs and symptoms are considered to have diabetes [5], [6]. There appears to be a geographic variation in occurrence following a gradient in latitude, which is the reverse of the global distribution of ultraviolet B irradiation, critical for the production of vitamin D within the skin. Studies have shown higher occurrence of vitamin D deficiency in patients with type 1 diabetes mellitus. [7].

Vitamin D is a fat-soluble vitamin that is found in dietary supplement, and also produced endogenously. Solar UV-B irradiates 7-dehydrocholesterol present in the skin to generate cholecalciferol. Activation of cholecalciferol requires hydroxylation in the liver (25-hydroxylases) and kidney (1a-hydroxylase to 1.25(OH)2 D3). Active hormonal form of vitamin D (1.25(OH)2 D3) binds and activates the vitamin D receptor (VDR), a nuclear receptor presents in most of nucleated cells. 1.25(OH)2 D3 protects the b-cells from damaging immune attacks, both directly on the b-cells which have receptors for 1.25(OH)2 D3 (VDR) and indirectly by acting on different immune cells, including inflammatory macrophages, dendritic cells, and T-cells [8].

Vitamin D could be a secosteroid hormone, which is understood to be associated with the regulation of the system. It affects calcium and phosphate metabolism and is said to bone health. Recently, the additional skeletal effects of ergocalciferol are under intense research and have attracted the interest of the scientific community [9]. In humans, Vitamin. D is predominantly produced within the skin during exposure to the daylight. However, a tiny low proportion of viosterol (~20%) is obtained through diet [10].

Materials and methods:

Patients and Control: patients group composed of (51), (23) of them are males and (28) females with age range 2-12 years old, were seen in Endocrinology and Diabetes Center in Samawa. Other groups consist of (50) apparently healthy individuals (25 males and 25 female) without any history of chronic disease were clinically considered as healthy also included in this study as a control group.

Cobas HBA1C Test: The blood sample is diluted and mixed with TRIS buffer to release hemoglobin from the erythrocytes. A fraction of the sample is conveyed into a reaction chamber where it is mixed with sodium lauryl sulfate (SLS).

Cobas Vitamin (D) Test: This assay is intended for the quantitative determination of total 25-hydroxyvitamin D in human serum. This assay is to be used as an aid in the assessment of vitamin D sufficiency. The electrochemiluminescence binding assay is intended for use on cobas e411 immunoassay analyzers.

Result:

Demographic Characteristics of Children with Type 1 Diabetes Mellitus and Control Subjects:

Comparison of mean age and frequency distribution according to age between type 1 diabetes mellitus group and control group. There was no significant difference in mean age between patients group and control group, 8.43 ± 3.13 years versus 8.12 ±2.69 years, respectively (p = 0.594). The proportion of males with type 1 diabetes mellitus was 45.1 % while that of girls was 54.9 % and there was no significant difference in frequency distribution according to gender between type 1 diabetes mellitus group and control group (p = 0.622).

Table 1: Comparison of mean age and frequency distribution according to age between type 1 diabetes mellitus group and control group

Characteristic	**Type 1 DM** ***n*** **= 51**	**Control group** ***n*** **= 50**	***P***
Age (years)			
Mean ±SD	8.43 ± 3.13	8.12 ±2.69	0.594 I NS
Range	2 -12	4 -12	
< 5, *n* (%)	7 (13.7 %)	4 (8.0 %)	0.291 C NS
5-10, *n* (%)	25 (49.0 %)	33 (66.0 %)	
> 10, *n* (%)	19 (37.3 %)	13 (26.0 %)	

n: number of cases; **SD**: standard deviation; **I**: independent samples *t*-test; **C**: chi-square test; **NS**: not significant

Table 2 : Comparison of frequency distribution according to gender between type 1 diabetes mellitus group and control group

Characteristic	**Type 1 DM** ***n*** **= 51**	**Control group** ***n*** **= 50**	***P***
Gender			
Male, *n* (%)	23 (45.1 %)	25 (50.0 %)	0.622 C NS
Female, *n* (%)	28 (54.9 %)	25 (50.0 %)	

n: number of cases; **C**: chi-square test; **NS**: not significant

Table 3 : Comparison of mean age between males and females with type 1 diabetes mellitus:

Characteristic	**Male** ***n*** **= 23**	**Female** ***n*** **= 28**	***P***
Age (years)			
Mean ±SD	8.57 ±2.92	8.32 ±3.35	0.785 I NS
Range	2 -12	2 -12	

n: number of cases; **SD**: standard deviation; **I**: independent samples *t*-test; **NS**: not significant

Comparison of mean age between males and females with type 1 diabetes mellitus. There was no significant difference in mean age between boys and girls with type 1 DM (p = 0.785).

Comparison of mean HbA1c% between patients with type 1 diabetes mellitus and control group is shown in table 3.4. The mean HbA1c% of patients with type 1 diabetes mellitus was significantly higher than that of control group, 9.75 ±0.80 % versus 4.64 ±0.40 %, respectively (p < 0.001). All control group members had HbA1c % level within normal range 4-5.6%; however, all patients with type 1 diabetes mellitus had HbA1c % level within diabetic range (≥ 6.5%). In our study, HbA1c % was higher in type 1 DM and all patients were poorly controlled since the level of HbA1c % was within diabetic range despite receiving insulin therapy. The mean serum vitamin –D in our study was significantly lower in patients with type 1 DM in comparison with control group, 11.14 ±4.65 ng/ml versus 17.16 ±6.39 ng/ml, respectively (p < 0.001). Diabetic patients with vitamin deficiency (< 20 ng/ml) accounted for 94.1 %, while control subjects accounted for 64 %, therefore, the prevalence rate of vitamin D deficiency in patients with type DM is higher than that in control group significantly (p < 0.001. Patients with type 1 DM in our study showed vitamin d deficiency in significantly high rate, but the rate of vitamin deficiency in control group was also high.

Table 4 : Comparison of mean HbA1c% between patients with type 1 diabetes mellitus and control group

Characteristic	**Type 1 DM *n* = 51**	**Control group *n* = 50**	***P***
HbA1c %			
Mean ±SD	9.75 ±0.80	4.64 ±0.40	< 0.001 I **
Range	8 -12	4 -5.3	
4-5.6% (normal range)	0 (0.0 %)	50 (98.0 %)	< 0.001 C **
5.7-6.4% (pre-diabetic range)	0 (0.0 %)	0 (0.0 %)	
≥ 6.5% (Diabetic range)	51 (100.0 %)	0 (0.0 %)	

n: number of cases; **SD**: standard deviation; **I**: independent samples *t*-test; **C**: chi-square test; **: significant at $p \leq 0.01$

Table 5: Comparison of mean serum vitamin D between patients with type 1 diabetes mellitus and control group

Characteristic	**Type 1 DM *n* = 51**	**Control group *n* = 50**	***p***
Serum Vitamin D (ng/ml)			
Mean ±SD	11.14 ±4.65	17.16 ±6.39	< 0.001 I **
Range	3 -22.7	4.9 -30.1	
Normal (≥ 20 ng/ml)	3 (5.9 %)	18 (36.0 %)	< 0.001 C **
Deficiency (< 20 ng/ml)	48 (94.1 %)	32 (64.0 %)	

n: number of cases; **SD**: standard deviation; **I**: independent samples *t*-test; **C**: chi-square test; **: significant at $p \leq 0.01$

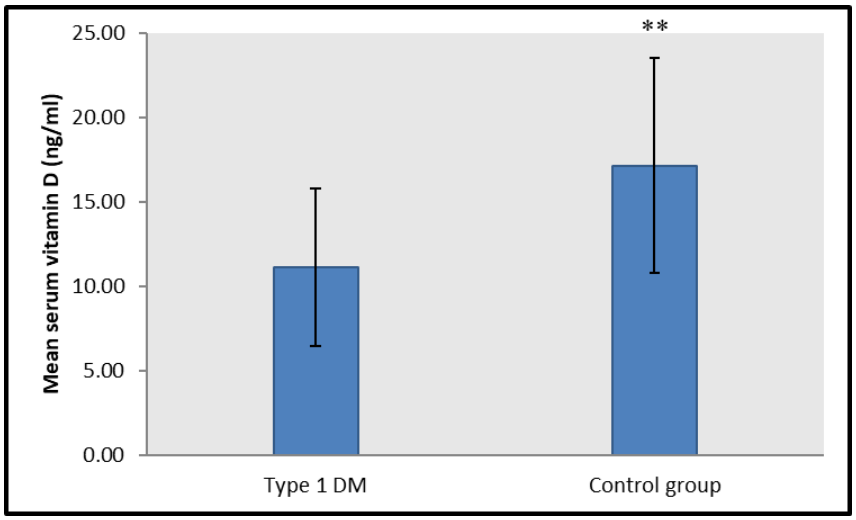

Figure 1: Bar chart showing comparison of mean serum vitamin D between patients with type 1 diabetes mellitus and control group

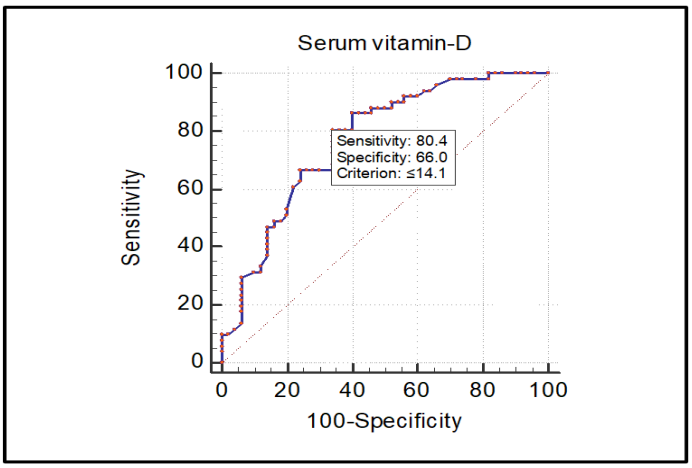

Figure 2: Receiver operator characteristic (ROC) curve analysis to find the cut off value of serum vitamin-D that can predict a diagnosis of type 1 diabetes mellitus

Discussion:

In the current study, the mean age of children with type 1 diabetes mellitus (8.43 ± 3.13 years) was lower than that reported by (Almahfoodh et al., in 2017) [11] in (15.3±9years) in a study done in Basra on 2536 patients with type diabetes mellitus; however, the mean age in another Iraqi study was comparable to our finding since in the Iraqi study the mean age of 60 patients with type 1 DM was 9.8 ± 4.7 years (Mezher et al., 2011) [12]. In line with our study, Haleem in 2019, in Iraq, found that the mean serum vitamin D level of 50 children with type 1 DM was significantly lower than that of 50 control subjects and that the prevalence rate of vitamin D deficiency in children with type 1 diabetes was higher than that in control group, 100 % versus 70 %. Therefore, we agree with Haleem (2019) [13] in the high rate of serum vitamin d

deficiency in both healthy children and diabetic children.

Conclusion:

Our study, is in line with the suggestion that there's a potential underlying relationship between D and glycemic control in diabetes. Therefore, it will be important to bear in mind of the actual fact that viosterol deficiency is common in diabetes and treatment of the identical may help in improving the glycemic control. Children and adolescents with T1D show an increased level of HBA1C and vitamin D deficiency.

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