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Vitamin D status in children with type one diabetes mellitus and it's therapeutic effect on glycemic control (Hospital based study)

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Abstract
Background: Vitamin D is often described as a fat-soluble vitamin, but it also exhibits hormonal properties in its active form through its action via vitamin D receptors found in most tissues in the human body. Vitamin D can directly enhance insulin synthesis and its release from pancreatic β-cells as well as increase the expression of the insulin receptor in peripheral tissues.
Aim of the study: To assess vitamin D level in children with type one diabetes and to evaluate the effect of vitamin D supplement therapy on the level of HbA1c.
Patient and method: This study included (125) patients with type one diabetes, aged (2-15 years); selected between November 2021 and September 2022. Five patients had celiac disease and were excluded, 61 patients were newly diagnosed, 59 patients had established type one diabetes and 33 controls. Vitamin D and HbA1c were measured for all patients and healthy matched control, vitamin D deficient patients received supplement for three months, and vitamin D level and HbA1c were measured after treatment.
Results: Study included 61 patients with newly diagnosed diabetes; 26 male and 35 female, and 33 healthy matched control, 15 male and 18 female, and 59 patients with established diabetes, 28 male and 31 female, serum vitamin D was low in all groups, vitamin D status was not associated with age, sex, duration of the disease, body mass index, HbA1c, seasonal distribution, family income and education in newly and established diabetic patients, after three months treatment; HbA1c significantly reduced with increased serum vitamin D (p value < 0.05).
Conclusion: Study revealed vitamin D level is low in newly, established diabetes and in control subjects, and it is not associated with patient's clinical, demographic and laberatory characteristics. Treatment of vitamin D improved glycemic control of patients as observed by the reduction of HbA1c level.

Keywords: One diabetes mellitus, vitamin D, glycemic control

Introduction

Type one (insulin-dependent) diabetes mellitus (T1DM) is an auto immune disease that results in the destruction of beta cells in the pancreas as a result of interactions between different susceptibility genes and environmental exposures. Type one diabetes mellitus accounts for approximately 10% of all cases of diabetes in all ages [1]. The 1st peak may correspond to the time of increased exposure to infectious agents coincident with the beginning of school; the 2nd peak may correspond to the pubertal growth spurt induced by gonadal steroids and the increased pubertal growth hormone secretion (which antagonizes insulin) [2].

The trigger of β-cell autoimmunity *1*) has a seasonal pattern, being more common during the cold season; *2*) shows some temporal variation from year to year; and *3*)
does not necessarily induce β-cell autoimmunity at the same time in all genetically susceptible siblings within the same family.

In addition to viral infections, one should also consider other environmental variables with seasonal variation. There is definitely seasonal variation in the amount of daylight and sunshine hours, especially in Northern Europe, which has the highest incidence of type one diabetes in the world [3].

Although some viral infections may increase the risk of T1DM, infectious agents may also play a protective role against diabetes. Human studies have found that the gut microbiome inT1DM has decreased diversity of microbial species and contains fewer butyrate-producing organisms compared to healthy controls, Butyrate is a short-chain fatty acid that is thought to be anti-inflammatory and may have a role in protecting the gut epithelium either directly or indirectly through an effect to increase mucin production.

Other dietary factors that have been suggested at various times as playing a role in T1DM risk include omega-3 fatty acids, vitamin D, ascorbic acid, zinc, and vitamin E. Vitamin D is biologically plausible (it has a role in immune regulation), and deficiency is more common in northern countries like Finland where T1DM incidence is highest; however most observational studies have failed to find associations between vitamin D level or supplementation and T1DM risk. Interventional studies to assess effect of vitamin D supplementation on T1DM risk are lacking. Several studies show an increased prevalence of stressful psychological situations among children who subsequently developed T1DM [4].

Vitamin D has been examined as a potentially protective factor because it has an active role in the regulation of the immune system, as well as metabolic pathways relevant to diabetes. Vitamin D has also been shown to shift the balance of the body's T-cell response toward down regulation of the T-helper-1 immune response. The seasonality of birth in children with type 1 diabetes and the seasonal pattern at diagnosis of type 1 diabetes could be explained by seasonal variation in vitamin D production from exposure to the sun [5].

The role of VD in diabetes became clearer after the discovery of VDR in the pancreas, adipose tissue, skeletal

muscle cells, and immune cells, which indicates a regulatory effect of VD on glucose homeostasis. Vitamin D can directly enhance insulin synthesis and its release from pancreatic β-cells as well as increase the expression of the insulin receptor in peripheral tissues. It can also indirectly exert an anti-diabetic effect by acting on cells of the immune system that secrete pro-inflammatory cytokines as mediators affecting weight gain, systemic inflammation (contributes to insulin resistance), and autoimmune-mediated destruction of pancreatic β-cells. These findings suggested that VD deficiency probably has a causal relationship with diabetes mellitus.

Two meta-analyses of retrospective studies showed that the risk of type 1 diabetes was lower in infants who were supplemented with vitamin D (calcitriol) compared with those who were not supplemented (pooled odds ratio 0·71) [6]. Two clinical trials reported no effect of vitamin D supplementation on sustained insulin production in new-onset type 1 diabetes [7]. In summary, despite continuing interest in vitamin D supplementation as a potential intervention to prevent islet autoimmunity and type 1 diabetes, there is surprisingly little supporting evidence from prospective birth cohort studies [8].

Aim of the study

To assess vitamin D level in children and adolescents with type one diabetes and to evaluate the effect of vitamin D supplement therapy on the level of HbA1c.

Patient and method

This study consists of 2 parts; part one was case control and part two was therapeutic trial, included a group of (125) patients aged between (2-15 years) diagnosed with type one diabetes and were attending the endocrine department in Children Welfare Teaching Hospital/ Medical city in Baghdad; they were selected between November 2021 and September 2022. Five patients were found to have celiac disease and were excluded from the study. The remaining subjects included 61 patients newly diagnosed and 59 patients had type one diabetes for more than 5 months. Diagnostic criteria for type one diabetes were adapted from the Report of the Expert committee on the Diagnosis and Classification of Diabetes Mellitus [9]. In addition (33) healthy control were enrolled in this study. They were selected from general outpatient clinic in same hospital; they had no chronic diseases and did not take vitamin D supplement before.

Detailed history reported from all patients including age, duration of diabetes, seasonal distribution were analyzed after pooling the data from summer months (May to October) and winter months (November to April), family education was evaluated by obtaining information on the educational background of the one who care the child (mostly the mother), and family income was evaluated according to the family monthly income; low income if its below 500$ and high income if it's above this [10].

Vitamin D and HbA1c were measured for all patients and healthy matched control. Vitamin D level in serum were considered sufficient when it's more than 29 ng/ml, insufficient when it's between 21 – 29 ng/ml and deficient if it's below 21 ng/ml according to the guidelines of the task force of the endocrine society [11]. Patients with insufficient vitamin D received 600 IU/day PO for 3 months and those with deficient vitamin D received 2000 IU/day PO also for 3 months, patients who have diabetes for more than 5 months; serum vitamin D level and Hba1c were measured after completing three months of treatment, and their previous HbA1c measurements (three months before started treatment) were recorded as control to compare between results. Within the corona pandemic; some patients discontinued their treatment and lost contact with outpatient clinic. Unfortunately, only 29 patients returned back with their results.

Before starting treatment with vitamin D, serum level of calcium, phosphate, alkaline phosphates and renal function tests were measured and found to be normal.

Exclusion criteria in this study were: (1) patients with history of vitamin D supplement or drug use that could affect vitamin D level, such as anticonvulsants or systemic steroids, (2) those with history of chronic diseases; like kidney or hepatic diseases and celiac disease.

Serum 25- hydroxylvitamin D levels were measured using immunoassay with MAGLUIM 800 Cumulascense. Serum HbA1c levels were measured by high performance liquid chromatography (HPLC) method using TOSOH HPLC T8 device.

For ethical consideration, consent was taken from the parents of patients and control.

Statistical analysis was performed by using SPSS (statistical packages for social science version), One-way analysis of variance (ANOVA) and repeated measures ANOVA were conducted to compare the clinical and biochemical parameters of the vitamin D subgroups. Chi-square test was used to assess vitamin D deficiency prevalence. All data were expressed as mean±standard deviation and $P<0.05$ was considered statistically significant.

Results

This study included 125 patients with type one diabetes and 33 healthy control subjects; five patients were found to have celiac disease and were excluded from the study and the remaining 120 divided in two parts: part one included those with newly diagnosed diabetes, and part two included established diabetes.

Part one: prevalence of vitamin D in patients with newly diagnosed diabetes and in healthy controls

This part included 61 patients with newly diagnosed diabetes; 26 patients (43%) were male and 35 (57%) were female, there mean age was 7.93±3.23 years, and 33 healthy matched control, 15 (45%) were male and 18 (55%) were female, their mean age is 8.13±3.88. The age, sex, and time in year of sample aspirate were similar in both groups.

Serum vitamin D level mean was low in both groups (newly and healthy matched control) 16.82, 16.33(ng/ml) respectively with no significant difference (p value 0.288). In the newly diagnosed patients; serum vitamin D was deficient in 44(72%) patients, insufficient in 9(15%) patients and sufficient in 8(13%) patients, and these results were similar in healthy control subjects (25(76%), 3(9%) and 5(15%) respectively) with no significant difference in vitamin D level categories between newly diagnosed diabetes and healthy control (p value 0.699).

The mean age of those with newly diagnosed type 1 diabetes and deficient vitamin D was 8.06±3.32, and those with insufficient was 8.00±2.91 and those with sufficient vitamin D was 7.13±3.82 with no significant correlation with serum vitamin D level (p value 0.198). This study also

showed no correlations between sex, body mass index or diagnosis in summer months with serum level of vitamin D (p value 0.949, 0.516 and 0.271 respectively). The means of Hba1c in newly diagnosed patients were 11.47±2.09, 11.09±1.74 and 10.29±1.06 in deficient, insufficient and sufficient vitamin D respectively, with no significant relationship (p value 0.205); all these results are shown in table.

This study also showed no significant correlation between serum vitamin D level and educational background of the caregivers nor family income.

Part two: prevalence and therapeutic outcome of vitamin D in patients with established diabetes type 1:

This part included 59 patients with type 1 diabetes diagnosed for more than 5 months, 28(47%) were male and 31(53%) were female, their ages were between 3 and 15 years old with mean 9.24 years.

Serum vitamin D levels were deficient in 43(73%), insufficient in 8(13.5%) and sufficient in 8(13.5); and these results also were similar to vitamin D categories in healthy control patients with no significant difference (p value 0.465).

In this study there were no significant relationship between vitamin D level categories in patients with established T1DM and patients' age, sex and BMI standard deviations mean, with p value (0.331, 0.224 and 0.66 respectively).

There was also no correlation between family educational background and family income with serum vitamin D level, p values were 0.941 and 0.424 respectively). also there was no correlation between serum level of vitamin D and Hba1c and the duration of the disease in those patients with type 1 diabetes, p values were 0.09 and 0.47 respectively.

After 3 months from started vitamin D supplement, only 29 patients completed the treatment and the investigations; mainly because of corona pandemic, their vitamin D serum level mean significantly elevated from 10.93 to 22.74 before and after treatment respectively with significant p value below 0.05, and Hba1c level significantly reduced, mean levels of Hba1c were 11.26 and 9.54 before and after treatment respectively, with significant p value < 0.05.

Discussion

Part one: prevalence of vitamin D in subjects with and without diabetes

Age, sex and seasonal time of blood aspirate were not statistically different between healthy controls and patients with type one diabetes. Serum vitamin D level means were suboptimal in both groups (16.82 and 16.33 in newly and control subjects respectively) with no significant difference p value 0.288, and this was compatible with Bierchenk *et al* in Florida 2009 [12], which showed that vitamin D level means in healthy control was 20.1 ng/ml and in new onset type 1 diabetes 21.2ng/ml, with no significant p value 0.87.

Rasoul *et al* 2016 study in Kuwait [13] also found the mean serum vitamin D level in Kuwaiti T1DM patients was 13.84 ± 6.66 ng/ml and in the controls, it was 14.98 ± 10.4 ng/ml (p = 0.19). A study from Finland 2016 showed that serum 25(OH) D concentrations are not associated with the development of T1D in Finland [14].

This was incompatible with study from India, Borkar *et al* 2010 [15]; which found serum vitamin D level to be low at the onset of type one diabetes, mean vitamin D level was 20.02 in T1DM patients, compared to 26.16 in healthy control. And also was incompatible with Changwei Liu *et al* in china 2018 [16], the mean serum 25OHD in T1DM children was lower than that of controls (48.69 and 57.93 nmol/l respectively) (P < 0.01).

And this can be explained by that vitamin D deficiency in most Iraqi population is high [17]; and it is affected by many factors (environmental, dietary, skin color and genetic factors), and this likely to result in poor vitamin D status in both T1DM patients and healthy control.

In this study serum vitamin D in newly diagnosed T1DM patients was deficient in 44(72%), insufficient in 9(15%) and sufficient in 8(13%) patients. While Rasoul *et al* 2016 [13] showed more vitamin D deficient than our study, which was deficient in 182/216(84%), insufficient in 31/216(15%) and sufficient in 3/216(1%) of patients. While in Borkar *et al* 2010 [15]. vitamin D was deficient in 58% of T1DM patients compared to control 32%. Much higher vitamin D level showed by Changwei Liu *et al* in china 2018 [16], vitamin D was deficient in 21.5%, insufficient in 42.5% and sufficient in 36% of diabetic patients.

This study found no correlation between serum vitamin D level categories and age (p value 0.198), and this was incompatible with Changwei Liu *et al* [16] and Rasoul *et al* 2016 [13] which found that vitamin D level was lower in older children (p value 0.001).

This study showed that seasonal distribution was not statistically significant (p value 0.271), this was compatible with Bierchenk *et al* in Florida 2009 [12] (p value 0.71) and Rasoul *et al* 2016 in Kuwait [13] (p value 0.228 and 0.403), but incompatible with Changwei Liu *et al* [16] in China which found serum 25OHD level of T1DM was lower than those of controls only in the summer months (P = 0.00).

This can be explained by many factors like duration to sun exposure, race/ ethnicity, latitude variability, and wearing clothes that leave very little area exposed especially in Arabic area.

The means of Hba1c in newly diagnosed patients were 11.47±2.09, 11.09±1.74 and 10.29±1.06 in deficient, insufficient and sufficient vitamin D respectively, with no significant relationship (p value 0.205); and this was compatible with Changwei Liu *et al* [16] which observed no association between 25OHD and HbA1c in newly diagnosed T1DM (P=0.09).

This study also showed no significant correlation between serum vitamin D level and educational background of the caregivers, (with p value 0.776), and there is no correlation between vitamin D status and family income, 19 patients from 44 patients who have vitamin D deficiency are low income, and 25 patients are high income with p value 0.31, and this was compatible with Rasoul *et al* 2016 [13], this attributed to lack of awareness or proper attention to health matters.

Part two: prevalence and therapeutic outcome of vitamin D in patients with established diabetes type 1:

This part included 59 patients with type 1 diabetes diagnosed for more than 5 months, 28(47%) were male and 31(53%) were female, their ages are between 3 and 15 years old with mean 9.24 years.

Serum vitamin D levels were deficient in 43(73%), insufficient in 8(13.5%) and sufficient in 8(13.5); and these results also were similar to vitamin D categories in healthy control subjects with no significant difference (p value 0.465). And this was compatible to Slavcheva *et al* 2012 [18]

in Bulgaria which found vitamin D to be deficient in 36% of patients with type one diabetes and 33% of control, and vitamin D insufficient in 37% in both groups with no significant difference (p value 0.783). And also compatible with Bierchenk L. *et al* in Florida 2009 [12], which observed vitamin D level deficient in 68.5% of patients with established type 1 diabetes and 70.1% in control subjects with no significant difference (p value 0.46). Other studies found vitamin D deficiency prevalence to be higher in patients with type one diabetes than control, Al-Abadi et.al, 2018 from Karbala/ Iraq [19], found vitamin D level mean 11.4 in patients with diabetes while in control was 13.8 with significant p value 0.03.

Study from KSA Bin-Abbas *et al* [20] 2011

found vitamin D to be deficient in 84% of patients with type one diabetes while in healthy children was 59%.

Bae KN *et al* 2017 [2] in Korea found that vitamin D deficient in 48%, insufficient in 35% and sufficient in 17% of those with type one diabetes while in control subjects vitamin D levels were 26%, 40% and 34% in deficient, insufficient and sufficient respectively with significant p value less than 0.001. Much higher values of serum vitamin D reported from a study in UK Giri *et al* 2017 [22] which found vitamin D in patients with type one diabetes to be deficient in 14.8%, in sufficient in 31% and sufficient in 54%.

This difference in vitamin D prevalence between many countries is related to geographical environment, skin color and nutritional social habits.

In this study there were no significant relationship between vitamin D level categories in patients with established T1DM and patients' age, sex and BMI standard deviations means, with p value (0.331, 0.224 and 0.66 respectively), and this was compatible with Bin-Abbas *et al* [20] 2011, Mutlu *et al* 2011 in Turkey [23], Hassan *et al* 2016 in Egypt [24], in Bae KN *et al* 2017 [21] there was no significant correlation between sex and BMI with serum vitamin D level categories (p value 0.867 and 0.347 respectively), but vitamin D was more deficient in older children.

In this study there were also no correlation between family educational background or family income with serum vitamin D level, p values were 0.941 and 0.424 respectively), And as mentioned before because of lack in awareness and attention to heath issues.

This study didn't show significant relationship between serum level of vitamin D with Hba1c and the duration of the disease in those patients with established type one diabetes; p values were 0.09 and 0.47 respectively; And this was compatible

with Bin-Abbas *et al* [20] 2011, Hassan *et al* 2016 [24], Bae KN *et al* 2017 [21] (p value 0.451 and 0.868), Mutlu *et al* 2011 [23]. But Elsayed *et al* 2016 in Egypt [25] find a significant inverse correlation between HbA1c and vitamin D (P value 0.003), but with no significant correlation with the duration of diabetes.

After 3 months from started vitamin D supplement, only 29 patients completed the treatment and the investigations, their vitamin D serum level significantly elevated and Hba1c level significantly reduced. And this was compatible with Dehkordi *et al* 2018 in Iran [26], which found significant reduction in HbA1c after 3 months vitamin D supplement (p value 0.04), and also this is matched with Giri *et al* 2017 [22], which found mean serum vitamin D 32.2 nmol/l, 65 mmol/l before and after treatment, with reduction in HbA1c from (73.5 to 65 mmol/l) before and after 3 months of vitamin D treatment.

This inverse relationship because of the effect of vitamin D which play role in insulin production and secretion which may affect glycemic control in children [27]. Supplementation with vitamin D *in vitro* influence on both the secretion and biosynthesis of Insulin in islets B cells of animals. Islets from vitamin D3-deficient rats exhibited a general decrease in the amount of de novo biosynthesised proteins and of [3H] tyrosine-labelled insulin and proinsulin fractions. A 6-h period of 1, 25(OH) 2D3 induction significantly improved the amount of de novo biosynthesized proteins, and particularly of newly synthesized insulin in response to a 2-h glucose stimulation [28].

Conclusion

This study showed low level of vitamin D in patients with newly and established type one diabetes, and also in control subjects with no significant difference between them. There were no correlations between vitamin D status with patient's age, sex, BMI, time of year, duration of diabetes, family educational background or family income. Also, vitamin D deficiency was not associated with the duration of the disease or HbA1c level. Treatment of vitamin D improved glycemic control of patients as observed by the reduction of HbA1c level.

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