CORRELATION BETWEEN VITAMIN D DEFICIENCY AND TYPE 1 DIABETES IN CHILDREN

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ABSTRACT

Background: Vitamin D is an organic compound with an important role in bone metabolism and ability to modulate the immune function. Epidemiology research have recently suggested vitamin D's role in the etiology of type 1 and type 2 diabetes in children. Vitamin D controls insulin secretion in pancreatic islets and insulin sensitivity in several peripheral metabolic organs by acting through the vitamin D receptor (VDR). Recent studies have reported an increased prevalence of vitamin D deficiency among patients diagnosed with type 1 diabetes. **The aim of the study** is to identify the correlation between vitamin D deficiency and the frequency, severity, and control of type 1 diabetes in children. **Material and Methods:** The retrospective study was performed on 40 subjects with type 1 diabetes, which associated vitamin D deficiency at the onset of the disease or during the investigation period, at Pediatric Clinic of Constanta County Clinical Emergency Hospital. The strategy used involved the collection of certain parameters from the observation sheets, in order to evaluate, compare and illustrate the correlation between vitamin D deficiency and type 1 diabetes. **Results:** Male subjects represented the majority of cases (55%). The seasonal incidence may be explained by exposure to a reduced amount of ultraviolet radiation in the cold season, which contributes to the decrease in the level of 25-hydroxyvitamin D. Viral infections had an increased incidence in the winter, which may contribute to the onset of type 1 diabetes. An optimal level of serum 25-hydroxyvitamin D was found in 17% cases, insufficient level in 63% cases and deficiency in 20% cases. In evolution, 24 cases had poor glycemic control, registering values higher than 7% of glycosylated hemoglobin. The dosage of 25 hydroxyvitamin D in these subjects indicated vitamin D deficiency in 7 cases and insufficiency in 17 cases. None of the patients with a glycosylated hemoglobin value >7 had an optimal 25-hydroxyvitamin D level. Out of 16 patients with optimal glycosylated hemoglobin values (<7%), 2 cases presented vitamin D deficiency, 6 cases insufficient level, and 8 cases had an optimal value of 25-hydroxyvitamin D. **Conclusions:** Vitamin D deficiency is associated with the evolution of type 1 diabetes in children. The evaluation of vitamin D levels is a potential disease-modifying factor in type I diabetes therapeutic management.

Keywords: type 1 diabetes, vitamin D, deficiency, children

INTRODUCTION

Type 1 diabetes is a complex metabolic condition characterized by the loss of insulin production capacity. This deficiency is due to the destruction of pancreatic β-cells. Insulin-dependent diabetes is frequently diagnosed in childhood and young adulthood, the age at presentation having a bimodal distribution (a

first peak at 4-6 years and a second peak at 10-14 years) [1]. More than one million children and adolescents are diagnosed with type 1 diabetes mellitus. Worldwide approximately 132,600 children and adolescents may develop type 1 diabetes annually [2].

Vitamin D, called calciferol, is part of a group of vitamins (D1, D2, D3, D4, D5, D6, D7) with an important role in the metabolism of calcium and phosphorus, which are found in nature in the form of provitamins. [3]

Hypovitaminosis D and vitamin D deficiency, regardless of narrow definitions, have a higher prevalence worldwide at any age. In pediatrics, US data from the National Health and Nutrition Examination Survey cohort indicate a prevalence of vitamin D deficiency and hypovitaminosis D ranging from 9–18% to 51–61%, respectively [4,5].

The main action of vitamin D in the body is to regulate the concentration and ratio of calcium/phosphorus [6]. From absorption and transport to the use of these elements in the bones, vitamin D constantly intervenes through its hydroxylated compounds. Thus, any metabolic process involving calcium and phosphorus depends directly or indirectly on presence, quality, and functionality of vitamin D [7]. Recent studies on vitamin D have demonstrated significant interactions between vitamin D and immune system cells, both innate and adaptive [8].

The influence on the development of the immune system is determined by factors such as mode of delivery, host genotype, breastfeeding, and gut microbiome [9,10]. Children born by C-section have an increased risk for altered immune development [10]. Specific mechanisms are implied in the determinism of gut microbiome in diseases related to altered immune development and potential therapeutic targets for immune related-disorders [11,12]. Gut microbiota has potent modulators of immune cells function and a role in initiating autoimmune conditions [13-16]. Neonatal diabetes mellitus is encountered in infants under six months of age and newborns, with difficulties related to therapeutic management [17].

A relationship between type 1 diabetes and vitamin D deficiency has been reported [18,19]. There is evidence that vitamin D is important in preventing islet cell death and may be useful in improving the survival of islet cell grafts and improving insulin production. According to epidemiologic data, having enough vitamin D may help delay or prevent the onset of diabetes [20].

MATERIAL AND METHODS

Vitamin D deficiency has been associated with numerous autoimmune and inflammatory disorders, which is why it represents a problem of great interest in the field of health. The objective of this study is to identify a possible association between the level of 25 hydroxyvitamin D and type I diabetes in pediatric patients.

Vitamin D may influence the activity of the immune system, which induces the destruction of insulin-secreting pancreatic β-cells, in genetically susceptible children and may influence metabolic control during the disease. The present study aims to identify the correlation between vitamin D deficiency and the frequency, severity, and control of type 1 diabetes.

The retrospective study was performed on 40 patients with type 1 diabetes and vitamin D deficiency at the onset of the disease or during the investigation period, from Pediatric Clinic of Constanta County Clinical Emergency Hospital. The strategy used

involved the collection of certain parameters from the observation sheets, in order to evaluate, compare and establish a possible association between type 1 diabetes and vitamin D deficiency in children.

RESULTS AND DISCUSSIONS

In 2012 and 2013, 2 cases of type 1 diabetes were registered, equivalent to 5%. In 2016, 2017, and 2021, 4 cases were confirmed annually, equivalent to 10%. In 2018, 8 cases were registered (20% cases), and in 2019, a record was set, identifying 16 subjects (40% cases) (*Table 1*). The number of subjects with type 1 diabetes associated with low vitamin D varied annually.

Table 1. Distribution of cases by year

Year	Number of subjects
2012	2
2013	2
2016	4
2017	4
2018	8
2019	16
2021	4

The distribution of cases according to the season showed that in the winter 17 cases were registered (43%), in the spring the diagnosis was established in 13 cases (32%), whereas during the summer and autumn, the incidence decreased significantly, 7 cases (17%) respectively 3 cases (8%). The seasonal incidence may be explained by exposure to a reduced amount of ultraviolet radiation in the cold season, which contributes to the decrease in the level of 25-hydroxyvitamin D. Also, viral infections had an increased incidence in the winter season, which may contribute to the onset of type 1 diabetes. Considering the gender, the male subjects represented the majority (55% cases), while the females represented 45% cases (*Figure 1*).

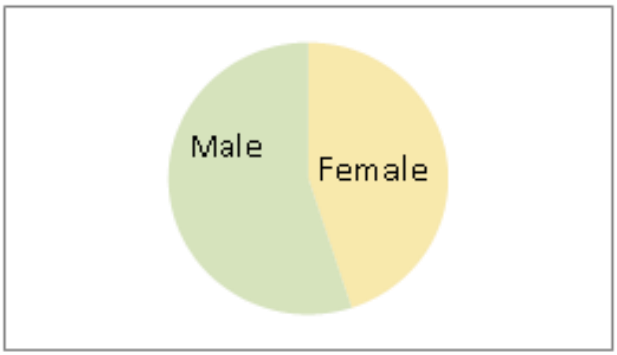

Figure 1. Distribution of cases by gender

According to the onset of the disease, ketoacidosis was identified in 15 cases (9 females and 6 males) equivalent to 37% cases; classic symptomatology was identified in 24 cases (9 females and 15 males), the equivalent of 60% cases, and incidental finding was identified in 1 male (3% cases).

In the studied group, the presence of a relevant family history was observed in 79% cases, a fact that supports the involvement of genetic factors in the occurrence of type 1 diabetes. Heredo-collateral antecedents identified were represented by diabetes, arthritis, thyroid, and cardiac pathology.

Alhonen et al. 2011 showed that diabetes and other autoimmune pathologies are frequently encountered in the extended families of diagnosed patients. The study included 300 families with at least one child diagnosed with insulin-dependent diabetes and 381 control families. According to the analysis, the risk of occurrence was significantly associated with a positive family history [21].

The autoimmune process that induces type I diabetes can also affect other organs.

Thus, screening for certain pathologies is required. Autoimmune thyroiditis was identified in 4 cases at onset and in 6 cases at routine follow-up, meanwhile, Celiac disease was identified in 2 cases a few years after the confirmation of type I diabetes. Krzewska et al. 2016 showed that the most common autoimmune disease associated with type I diabetes is autoimmune thyroiditis (in 15%-30% of cases). Celiac disease affects 1-5.5% of the pediatric population, while children diagnosed with insulin-dependent diabetes mellitus develop celiac disease in 0.6-16.4% of cases [22].

Determination of HbA1c is a necessity in the assessment and monitoring of glycemic balance. Most guidelines recommend a therapeutic target of 6.5-7% for diabetic patients. In the present study, the value of glycosylated hemoglobin was monitored at the onset and during the evolution of the disease. Values between 6.5% and 7% were identified in 2 cases at the time of confirmation of the diagnosis, while the remaining 38 cases presented values higher than 7% (7 determinations in the range of 7-9%, 13 determinations in the range of 9 -12%, 16 determinations in the 12-15% range, and 2 subjects recorded values higher than 15%).

Regarding rickets prophylaxis, 45% cases (18 subjects) performed rickets prophylaxis according to the recommended scheme, while 55% cases did not perform prophylaxis (14 subjects) or interrupted recommended therapy (8 subjects). Hypponen et al. 2001 suggested that performing rickets prophylaxis in the first year of life can be crucial in preventing diabetes in children [23].

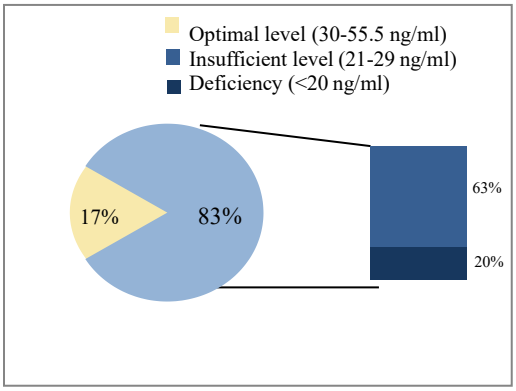

Figure 2. Distribution of cases by vitamin D levels

An optimal level of serum 25-hydroxyvitamin D (30-55.5 ng/ml) was observed in 17% cases; 63% cases (25 subjects) presented an insufficient level (21-29 ng/ml), and 20% cases (8 subjects) had values suggestive for vitamin deficiency (<20 ng/ml) (*Figure 2*).

The study performed by Svoren et al. in 2009 found that 15% of subjects with type I diabetes were deficient in 25-hydroxyvitamin D, and 61% presented insufficient levels [24].

The dynamic evaluation of the level of 25-hydroxyvitamin D led to the following analytical data: 20% (8 cases) presented an optimal level, 57% (23 cases) showed an insufficient level, and 23% (9 cases) presented values for deficiency. It was observed that 25-hydroxyvitamin D deficiency identified at the beginning of the diagnosis can also be maintained dynamically in certain cases.

In evolution, 24 cases had poor glycemic control, registering values higher than 7% of glycosylated hemoglobin. The dosage of 25 hydroxyvitamin D in these subjects indicated deficiency in 7 cases and insufficiency levels in 17 cases. None of the patients with a glycosylated hemoglobin value >7 had an optimal 25-hydroxyvitamin D level. Out of 16 patients with optimal glycosylated hemoglobin values (< 7%), 2 cases presented vitamin D deficiency, 6 cases insufficient level,

and 8 cases had an optimal value of 25-hydroxyvitamin D.

Following a statistical analysis, no subject with HbA1c>7 recorded a 25-hydroxyvitamin D value between the reference parameters, while 49% cases with adequate glycemic control had an optimal level. Values of 25-hydroxyvitamin D between 21-29 ng/ml were recorded in 70% cases with HbA1c >7% and in 38% cases with HbA1c < 7%. Vitamin D deficiency was reported in 30% cases with poor control of type 1 diabetes, compared to 13% in subjects with optimal glycosylated hemoglobin.

In children at high genetic risk, vitamin D insufficiency may increase the risk of type 1 diabetes in the first years of life. Additionally, subjects with type 1 diabetes are frequently deficient in vitamin D. The proof of vitamin D supplementation and the maintenance of beta-cell activity in type 1 diabetes currently is not clear. Future large-scale studies are necessary to fully evaluate vitamin D's potential as a disease-modifying option in type 1 diabetes [25].

CONCLUSIONS

In the families of diagnosed patients, it was observed a significant history of autoimmune pathologies represented by autoimmune thyroiditis and celiac disease. The dosage of specific antibodies revealed the presence of anti-GAD antibodies in 70% cases, anti-IA-2 antibodies in 65% cases, and anti-IAA antibodies in 37% cases. These results support the autoimmune etiology of the disease and the involvement of genetic factors in the pathogenic mechanism.

Confirmation of the diagnosis was carried out mainly in the winter and spring season. During this period, due to exposure to a reduced amount of ultraviolet radiation, children frequently presented serum values of 25-hydroxyvitamin D below the optimal level.

At the time of diagnosis of type I diabetes, 83% cases associated a serum value of 25 hydroxyvitamin D below the recommended level. During the evolution of the disease, 79% cases recorded reduced serum values of 25-hydroxyvitamin D.

In evolution, by measuring glycosylated hemoglobin and 25-hydroxyvitamin D it was observed that inadequate glycemic control was associated with vitamin insufficiency in 70% cases and the presence of deficiency in 30% cases. Subjects with adequate glycemic control presented vitamin insufficiency in 38% cases, deficiency in 13% cases, and optimal levels of 25-hydroxyvitamin D in 49% cases.

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