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Vitamin D Deficiency/Insufficiency in Children and Adolescents with Chronic Disease

Kronik Hastalığı Olan Çocuk ve Adölesanlarda Vitamin D Eksiklik/Yetersizliği

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ABSTRACT

Objective: The effect of vitamin D on bone metabolism is well known. It has recently been shown to be also associated with cardiovascular diseases, obesity, infections, autoimmunity, and cancer. The aim of our study was to evaluate vitamin D deficiency in childhood chronic diseases.

Material and Methods: A total of 438 cases followed-up for vitamin D deficiency/insufficiency (25 OHD level < 30 ng/mL) in our clinic between 2005 and 2011 and who had an additional chronic disorder were evaluated retrospectively.

Results: The mean age of the cases was 12.8±4.6 years and the female/male ratio 1.29 Accompanying disorders included diabetes mellitus, obesity, Turner syndrome, congenital adrenal hyperplasia, myopathy, autoimmune and rheumatic diseases, central nervous system diseases and malignancies. The vitamin D deficiency/insufficiency incidence ranged between 62.5 and 95.0% in the children/adolescents with chronic disease. The mean 25 OHD level was 17±6.6 ng/ml. Hypocalcemia or a similar ion imbalance was not found in any group.

Conclusion: Considering the multisystemic effects of vitamin D, 25 OHD levels should be monitored in chronic diseases in childhood and supplementation provided if necessary. This may lead to an improvement in the course of the underlying disease as well.

Key Words: Adolescence, Children, Chronic disease, Vitamin D deficiency

ÖZET

Amaç: D vitamininin kemik metabolizması üzerindeki etkisi iyi bilinmektedir. Son dönemlerde D vitaminin kardiyovasküler hastalıklar, obezite, enfeksiyonlar, otoimmünite ve kanser gelişimi ile de ilişkisi olduğu gösterilmeye başlanmıştır. Bu çalışmada, çocukluk çağındaki kronik hastalıklarda D vitamini eksikliğinin değerlendirilmesi amaçlandı.

Gereç ve Yöntemler: 2005-2011 yılları arasında kliniğimizde D vitamini eksiklik/yetersizliği (25OHD < 30 ng/ml) nedeniyle takip edilen ve ek kronik hastalığı olan 438 olgu geriye dönük olarak değerlendirildi.

Bulgular: Olguların yaş ortalaması 12.8±4.6 yıl ve kız/erkek oranı:1.29 olarak bulundu. Eşlik eden hastalıklar arasında diyabetes mellitus, obezite, Turner Sendromu, konjenital adrenal hiperplazi, miyopati, otoimmün ve romatolojik hastalıklar, santral sinir sistemi hastalıkları ve maligniteler yer almaktaydı. Kronik hastalığı olan çocuk/adölesanlarda D vitamini eksiklik/yetersizliği sıklığı 62.5-% 95 arasında değişmekteydi. Olguların ortalama 25OHD düzeyi 17±6.6 ng/ml'di. Hiç bir grupta hipokalsemi ve benzeri iyon dengesizliği saptanmadı.

Sonuç: D vitaminin multisistemik etkileri dikkate alındığında, çocukluk çağındaki kronik hastalıklarda 25OHD düzeyi takip edilmeli ve gereğinde replasman yapılmalıdır. Böylece altta yatan hastalığın seyrinde de düzelme gözlenebilir.

Anahtar Sözcükler: Adölesan dönem, Çocukluk dönemi, Kronik hastalık, D vitamini eksikliği

INTRODUCTION

The effect/significance of the vitamin D level on the bone and mineral metabolism is well known. This vitamin deficiency is mainly associated with skeletal deformities in children and osteoporosis in adults (1). Only one-fifth of the vitamin D requirement can be obtained from animal and nutritional sources through the diet. It is mainly synthesized in the skin by sunlight. The American Endocrine Society accepts 25 OHD

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values between 21 to 29 ng/ml as insufficiency and values <20 ng/ml as deficiency (2). Vitamin D deficiency is still an important public health problem. The prevalence in child and adolescents is estimated to be 29 to 100% (2). This rate was found to be 60-87% in studies conducted on female adolescents in our country (3,4).

An association between Vitamin D and cardiovascular diseases, obesity, infections, autoimmunity, and cancer has been reported (1,2). There are various publications available regarding the presence of a tendency to obesity, insulin resistance, malignancies and susceptibility to autoimmune diseases with vitamin D deficiency (5-10). We aimed to evaluate vitamin D deficiency in childhood chronic diseases in this study.

MATERIAL and METHODS

All children and adolescents who presented to Dr. Sami Ulus Obstetrics, Children Health and Diseases Research and Training Hospital between January 2005 and December 2011 and were found to have vitamin D deficiency were included in the study. Screening was performed according to the ICD-10 (International Statistical Classification of Diseases and Related Health Problems) diagnostic codes and patients with appropriate diagnostic codes [(Deficiency of calcium in the diet (E58), Active rickets (E55.0), Vitamin D deficiency (E55.9) under the title calcium metabolism disorders.] and /or cases found to have vitamin D deficiency/insufficiency for those whose 25 OHD levels were tested at our hospital (25 OHD level < 30 ng/ml) were evaluated (11). The 25 OHD vitamin level was measured with the tandem (LC-MS/MS) method. The detailed medical history, anthropometric evaluation and laboratory/imaging findings of the cases were obtained from the files.

Statistical Analysis

Descriptive statistics for the continuous variables were presented as mean and standard deviation while count and percentages for categorical variables. The statistical significance level was considered as 5% and SPSS (ver. 13) statistical program was used for all statistical computations.

RESULTS

A total of 834 patients between 1.5 months and 18 years of age and diagnosed with vitamin D deficiency/insufficiency in our clinic were evaluated. These cases, 438 with a history of chronic disease were included in the study. The mean age of the group was 12.8±4.6 years (1 - 18 years) and there were 248 females and 191 males. The female/male ratio was 1.29. The distribution of the cases according to the disorders is presented in Table I.

All patients' calcium, phosphorus, alkaline phosphatase (ALP) values were within normal limits and there was no obvious clinical symptom. The mean laboratory values of the cases are presented in Table II. The mean 25OHD levels according to the disease groups are presented in Figure 1.

A whole body bone mineral densitometer was used in 142 cases with vitamin D deficiency/insufficiency (QDR 1000 / W densitometer Hologic, Waltham, MA, USA) and the mean z score in L1-4 vertebrae was -2,05±1.3 [(-5.1) - (1.2)]. The mean age was 14.4±3.8 (5 - 18) years and the mean total BMD value was 0.699±0.2 (0.260 - 1.300) gm / cm^2. The z scores of these cases were > - 1 (normal) in 23.9%, between - 1 and - 2 in 17.9% and < - 2 in 58.2%. X-rays of the left wrist were present in 27 patients were present and none had active rickets findings.

1. Diabetes mellitus: The 25 OHD level was measured in 211 of the 380 cases who were diagnosed with diabetes mellitus and were under regular follow up in our clinic (mean age: 11.5±4.3 years with 60% females) 194 (91%) were found to

Table I: The distribution of the cases with vitamin D deficiency/insufficiency according to the accompanying diseases.

Accompanying disease	N	Age (year) (mean±SD)
Diabetes mellitus	194	11.5±4.3
Mental-motor retardation, epilepsy	60	10.9±4.8
Malignancy + treatment	31	12.6±3.7
Celiac disease	29	10±4.4
Muscle disease (DMD)	25	10±3
Obesity	22	9.3±4.1
Turner syndrome	19	15.5±2.,2
Thyroid disorders	20	8.2±5.6
Pan/Hypopituitarism	18	15.3±3.4
Congenital adrenal hyperplasia	10	5±5.5
Autoimmune diseases (JRA, FMF)	10	14±3.5
Total	438	12.8 ± 4.6

Table II: Laboratory findings of the cases with vitamin D deficiency/insufficiency.

Laboratory values	Mean±SD (Range)
25OHD (ng/ml)	17± 6.6 (3.5 - 29.7)
Calcium (mg/dl)	9.6 ± 0.44 (7.9 – 10.7)
Phosphorus (mg/dl)	4.8 ± 0.8 (1.3 – 7.4)
ALP (IU/L)	182 ± 95 (39 – 607)
PTH (pg/ml)	49.5 ± 28.8 (3 – 150)

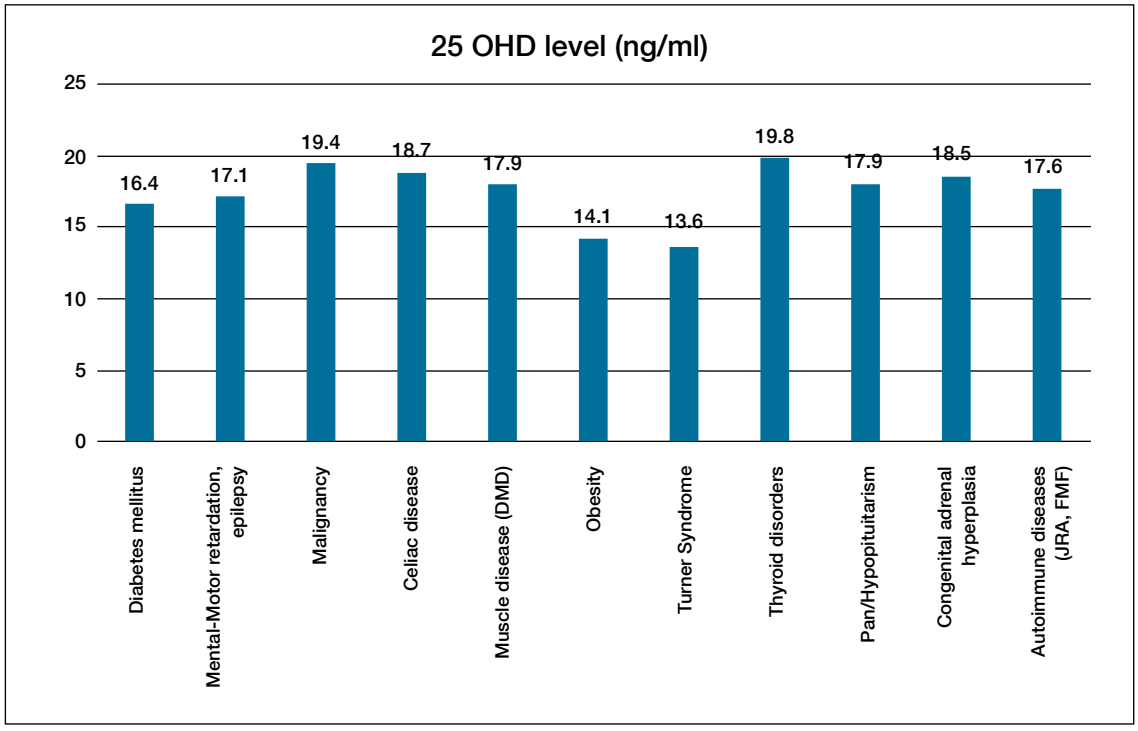

Figure 1: The comparison of the mean 25 OHD level of the cases with vitamin D deficiency/insufficiency according to the disease.

have vitamin D deficiency / insufficiency. The mean 25 OHD level was 16.4 ng/dl and the mean serum calcium was within normal limits; the phosphorus levels of these newly diagnosed patients were low during the ketoacidosis period to be low and improved during follow-up.

2. Obesity: The 25 OHD level was checked in 28 of 712 cases and 22 (78.5 %) were found to have vitamin D deficiency/insufficiency. The mean age was 9.3±4.1 years and 63% were females. The mean 25 OHD level was 14.1 ng/ml.

3. Turner syndrome: The 25 OHD level was checked in 20 of 45 cases with Turner Syndrome 19 (95 %) had vitamin deficiency/insufficiency. The mean age was 15.5±2.2 years. The mean 25 OHD serum level was found 13.6 ng/ml.

4. Panhypopituitarism: The 25 OHD level was checked in 20 (mean age 15.3±3.4 years with 50% females) of the 101 cases and 18 (90%) were found to have vitamin D deficiency/insufficiency. The mean 25 OHD serum level was 17.9 ng/ml.

5. Thyroid disorder: The 25 OHD level was checked in 32 (mean age 8.2±5.6 years and 75% females) of the 997 cases followed-up in our clinic with a diagnosis of thyroid gland disorder (such as congenital hypothyroidism, Hashimoto thyroiditis, iodine deficiency, Graves disease) and 20 (62.5%) were found to have vitamin D deficiency/insufficiency. The mean 25 OHD serum level was found 19.8 ng/ml.

6. Congenital adrenal hyperplasia: The 25 OHD level was checked in 13 (mean age 5.0±5.5 years with 50% females) of 237 cases and 76% were found to have vitamin D deficiency/insufficiency. The mean 25OHD serum level was found 18.5 ng/ml.

7. Motor mental retardation and/or epilepsy: Among this group, 60 cases accompanied by vitamin D deficiency/insufficiency were found to be referred to the endocrine clinic and followed up. The mean age was 10.9±4.8 years and 58% were females. The mean 25 OHD serum level was 17.1 ng / ml. All patients had the history of at least one antiepileptic drug use.

8. Malignancy: Vitamin D deficiency/insufficiency was found in 31 of the cases consulted by the Pediatric Oncology Clinic. The mean age was 12.6±3.7 and 32% were female. The mean 25 OHD serum level was 19.4 ng/ml.

9. Coeliac disease: A total of 29 cases who were followed up with a diagnosis of celiac disease and found to have vitamin D deficiency/insufficiency had been consulted to our clinic. The mean age was 10.0±4.4 years and 58% were female, The mean serum 25 OHD level was 18.7 ng/ml.

10. Myopathy clinical features: A total of 25 cases with a diagnosis of muscle disease (such as Duchenne or Becker muscular dystrophy) and had vitamin D deficiency/insufficiency had been consulted to the endocrine clinic. The mean age was 10.0±3.0 years and 4% were female. Steroids were used by 22 cases and all cases were immobile. The mean 25 OHD serum level was 17.9 ng/ml.

11. Autoimmune disease (JRA-Juvenile Rheumatoid Arthritis, FMF - Familial Mediterranean Fever, etc.): A total of 25 cases with autoimmune disease and vitamin D deficiency/insufficiency had been consulted to the endocrine clinic. The mean age was 14.0±3.5 years and 60% were females. Seven cases were using steroids. The mean 25 OHD serum level was 17.6 ng/ml.

DISCUSSION

Holick emphasized in their 2012 article that the optimum vitamin D level should be 30 ng/ml for adults and children (11). We also accepted a 25 OHD level < 30 ng/dl as vitamin D deficiency in this study. Factors affecting serum vitamin D levels include race, vitamin D intake, sun exposure, amount of fatty tissue, age, and physical activity. Even when all factors are taken into account, it is difficult to explain the individual variations of 25 OHD levels. We therefore cannot understand the clinical and biochemical effects of Vitamin D deficiency only by examining the serum 25 OHD level. The duration of vitamin D deficiency, the response of the vitamin D receptors, the calcium amount in the diet and the individual calcium requirement change the clinical features (12). The 25 OHD levels of Hawaian surfers who were exposed to the sunlight at least 15 hours a week for 3 months were shown to vary between 11 and 71 ng/mL in one study. This study shows how much the individual variations are effective on the vitamin D level as sunlight exposure is more effective than dietary vitamin D (13). Genetic variation (polymorphism of certain vitamin D-related genes in the metabolic pathway) explains the varying clinical severity in individuals with the same serum 25 OHD levels.

The optimal level of vitamin D has so far been identified according to the effects of vitamin D on the skeletal system. However, the effects of vitamin D on other systems are also very important and the optimal vitamin D level should be ensured for those systems as well. Studies have been conducted on the association of vitamin D deficiency with chronic diseases and its effect on the prognosis. The risk of type 1 diabetes mellitus was 30 % less in children who took vitamin D supplements in childhood compared to those who did not in a meta-analysis (14). The vitamin D receptor is located in pancreatic beta cells and vitamin D increases insulin secretion and sensitivity. Glucose levels were reported to be higher in adolescents with 25 OHD levels under 15 ng/ml (15). The 25 OHD level was low in 91 % of the 211 patients with diabetes mellitus followed-up in our clinic. This high rate points to harmful effects of vitamin D deficiency/insufficiency on glucose tolerance.

There are many studies on vitamin D and obesity. The 25 OHD level was found to be significantly lower than cases without metabolic syndrome in 528 cases that later went on to develop metabolic syndrome in a large-scale prospective study conducted in 2012 (16). A study from Saudi Arabia reported that adequate calcium and vitamin D taken with diet has positive effects on the body mass index (17). A study on 64 obese adolescent children in 2011 showed 25 OHD under 10 ng/ml levels in 50% of the cases and that the blood sugar was also high in these cases (18). However, comparison of the vitamin D levels of obese and non-obese children in a study from Thailand showed no significant difference (19). Vitamin D deficiency was found in 78 % of the obese cases whose 25 OHD level was checked in our study. Although this result shows that vitamin D deficiency is common in obesity, the cause and effect relationship between obesity and vitamin D deficiency/insufficiency is still being investigated.

Short stature is one of the dominant clinical characteristics of Turner syndrome. Deficiency in final height and susceptibility to osteoporosis due to lack of estrogen can be seen in these cases. The 25 OHD level was low in 95% of Turner syndrome cases where the 25 OHD level was checked in our endocrine clinic. Turner syndrome already causes short stature so the vitamin D deficiency in these cases, which is a secondary and treatable risk factor, should be promptly corrected.

Vitamin D is known to be an immunomodulator and its deficiency is seen more frequently in autoimmune diseases. The 25 OHD level of 161 Hashimoto thyroiditis cases was found to be significantly lower than in the control group in a study from the Göztepe Training and Research Hospital in 2011 (20). A study from India reported a weak inverse correlation between the serum 25 OHD level and thyroid peroxidase autoantibodies in 2009 (21). The presence of vitamin D deficiency/insufficiency in 62% of the cases being followed-up for a thyroid disorder and whose 25 OHD level was checked in our study is similar to the literature. There are also some studies on other autoimmune diseases. The 25 OHD levels of cases diagnosed with Familial Mediterranean Fever (FMF) were shown to be significantly lower than the control group in a study conducted in 2011 in the Turkish city of Gaziantep (22). The vitamin D level was also shown to be low also in cases with systemic lupus erythematosus (SLE) in a similar study (23). A study on vitamin D in the autoimmune disorder multiple sclerosis showed that the risk of multiple sclerosis increased as the ultraviolet B rays and 25 OHD level decreased (24). We followed 25 cases with autoimmune diseases such as SLE, juvenile rheumatoid arthritis and FMF together with vitamin D deficiency/insufficiency in our clinic.

There are some previous studies on vitamin D and malignant diseases. Sinha et al. found lower 25 OHD levels in childhood cancer cases (25). Another study reported that each 20 ng/ml increase in serum 25 OHD level decreases the colon cancer rate by more than 40% (26). Another study showed that dietary calcium decreased the risk of colon cancer and adenoma formation (27). However, a large study found no protective effect of calcium and vitamin D supplementation on colorectal cancer risk in patients administered calcium and vitamin D supplements and followed for eight years (28). Vitamin D deficiency/insufficiency was found in 31 cases who were referred from the pediatric oncology clinic in our study.

Coeliac disease causes deficiency of oil-soluble vitamins including vitamin D and it is an autoimmune disease as well as an absorption disorder. Numerous studies are available on the decrease of bone mineral density due to vitamin D and calcium deficiency (29). Vitamin D deficiency/insufficiency accompanying celiac disease was present in 29 of our patients.

The use of steroids is a major risk factor for vitamin D deficiency/insufficiency and low bone mineral density. The BMD Z

score was <- 2 in 38 % and the 25 OHD level < 30 ng/ml in 89% of the patients in a study on patients with glomerulopathies using steroids (30). A muscle disease such as Duchenne muscular dystrophy (DMD) and steroid use was present in 25 our patients. These cases were also immobile. Vitamin D deficiency/insufficiency has been reported to be common in DMD cases (31).

Immobilization and antiepileptic drug use in epilepsy and/or motor mental retardation patients causes vitamin D deficiency/insufficiency and low bone mineralization. Antiepileptic drugs cause 4-hydroxylation of 25 OHD in a CYP3A4-dependent pathway in the liver leading to vitamin D deficiency induced by the drug (32). We had 60 epilepsy and/or motor mental retardation cases on antiepileptic drugs who were being followed-up for vitamin D deficiency/insufficiency in our department.

The mean 25 OHD level in our study was 17 ng/ml. In return, the mean serum calcium level was 9.6 mg/dL, mean serum phosphorus level 4.8 mg/dL and the mean serum alkaline phosphatase level 182 IU. The lack of clinical and radiological findings of rickets despite the very low 25 OHD levels in our cases seems to support the genetic polymorphism of vitamin D.

Despite the ongoing research on vitamin D, the cause and effect relationship of vitamin D deficiency/insufficiency with various diseases has not been fully established. However, the deficiency is seen to accompany these diseases and to influence the prognosis. The aim in the treatment of vitamin D deficiency/insufficiency treatment is to raise the 25 OHD level to above 30 ng/ml. Vitamin D has been shown to be optimally available to the skeletal and other systems when the 25 OHD levels are above 30 ng/ml (11). All our cases were started treatment and the serum 25 OHD level was raised above 30 ng/ml. In conclusion, patients with chronic diseases should be investigated for 25 OHD levels and the treatment planned accordingly considering that vitamin D deficiency/insufficiency may be associated with many chronic diseases and can adversely affect the prognosis.

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