RESEARCH ARTICLE

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The Importance of 25 Hydroxyvitamin D Level Monitoring in Children Diagnosed with Juvenile Idiopathic Arthritis

ABSTRACT

Objective: In patients with juvenile idiopathic arthritis (JIA), bone metabolism may be negatively affected due to both the activity of the disease and the medications used. Our study aimed to investigate the necessity of evaluating 25 hydroxyvitamin D (25 (OH) Vit D), calcium (Ca), phosphorus (P), alkaline phosphatase (ALP) levels and possible related factors in the follow-up of patients diagnosed with JIA.

Materials and Methods: The records of 68 patients with JIA were retrospectively evaluated. Disease subtypes, medications used, and whether they were in remission or active disease were reviewed.

Results: 25 OH Vit D levels were low in 14.7% of patients with JIA compared to the control group. 66.6% of the patients with systemic arthritis had high ALP levels. 25 OH Vit D level was low in 16.6% of steroid users, and Vitamin D level was low in 55.5% of the patients in the active disease group. It was determined that patients in the active disease group had the highest ALP and lowest vitamin D levels compared to patients in remission with and without medication.

Conclusions: Bone metabolism in patients with JIA is negatively affected. Since vitamin D plays a crucial role in bone metabolism, it was emphasized that vitamin D levels should be evaluated especially during active disease and supplements should be provided for patients with low vitamin D levels.

Keywords: Juvenile Idiopathic Arthritis, Vitamin D, Bone Metabolism.

Juvenil İdiyopatik Artrit Tanılı Çocuklarda 25 Hidroksivitamin D Düzey Takibinin Önemi

ÖZET

Amaç: Juvenil idiyopatik artrit (JİA)'li hastalarda gerek hastalığın aktivitesi gerekse kullanılan ilaçlar nedeni ile kemik metabolizması olumsuz etkilenebilir. Çalışmamızda JİA tanılı hastaların takibinde 25 hidroksivitamin D (25 (OH) Vit D), kalsiyum (Ca), fosfor (P), alkalen fosfataz (ALP) düzeyleri ve ilişkili olabilecek faktörlerin değerlendirilmesinin gerekliliğini araştırmak amaçlandı.

Gereç ve Yöntem: JİA tanılı 68 hastanın kayıtları retrospektif olarak değerlendirildi. Hastalık alt tipleri, remisyon durumu, kullanılan ilaçlar incelendi.

Bulgular: Kontrol grubuna kıyasla JİA hastalarının %14,7'sinde vitamin D düzeyinin düşük olduğu bulundu. Sistemik artriti olan hastaların %66,6'sında ALP düzeyinin yüksek olduğu saptandı. Steroid kullananların %16,6'sında vitamin D düzeyi düşük bulundu. İlaçlı ve ilaçsız remisyondaki hastalarla kontrol grubu arasında biyokimyasal parametreler açısından fark yoktu. Aktif hastalık grubundaki hastaların %55,5'inde vitamin D düzeyleri düşük saptandı. Aktif hastalık grubundaki hastaların, ilaçlı ve ilaçsız remisyondaki hastalar ile karşılaştırıldığında, en yüksek ALP ve en düşük vitamin D düzeyine sahip oldukları saptandı.

Sonuç: JİA'lı hastalarda kemik metabolizması olumsuz etkilenmektedir. D vitamininin kemik metabolizması üzerinde önemli rol oynaması nedeni ile bu hasta grubunda özellikle aktif hastalık sırasında vitamin D düzeylerinin bakılması ve D vitamini düşük saptanan hastalara vitamin D desteği verilmesi gerekliliği vurgulandı.

Anahtar Kelimeler: Juvenil İdiyopatik Artrit, D Vitamini, Kemik Metabolizması.

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INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a systemic disease characterized by chronic idiopathic synovitis and the presence of extra-articular manifestations (1). Although the actual prevalence of JIA remains unclear, the average incidence and prevalence of JIA are 9-25/100000 and 12-113/100000, respectively (2). The prevalence in our country was determined to be 64/100000 in one study (3). Although the disease is generally twice as common in females than males, it is more common in boys in developing countries.

Etiology of JIA is not known with certainty but many genetic, hormonal, environmental, and infectious factors are considered to be involved in its pathogenesis (1, 4). Infiltration of activated lymphocytes and macrophages into the synovium and cytokines released from these cells are thought to play a role in the pathogenesis of JIA (5). Tumor necrosis factor-alpha (TNF-α), a cytokine released from macrophages, has a critical role in developing local inflammation and tissue damage. TNF-α stimulates the production of Interleukin 8 (IL-8), monocyte chemotactic protein (MCP) and collagenase. IL-8 stimulates leukocyte infiltration, and mitogen-activated protein kinase phosphatase (MKP) stimulates macrophage activation. Collagenase is the key enzyme in collagen degradation and destroys the extracellular matrix in the synovium. TNF-α exerts its effect through its two receptors at the cellular level: TNF Receptor 1 (TNFR1) (p55) and TNF Receptor 2 (TNFR2) (p75). Other cytokines responsible for the development of inflammation and tissue damage, although not as much as TNF-α, are IL-1, IL-2, IL-4, IL-6, and transforming growth factor-P (TGF-P) (4, 5).

Although the role of vitamin D in bone metabolism has been well accepted for a long time, studies have also indicated that it has an immune system regulatory effect. Vitamin D inhibits the immune response of Type 1 T helper (Th1) cells and reduces the production of inflammatory cytokines such as IL-17, IL-1, IL-6, and TNF-α. Therefore, the risk of infections and autoimmune diseases increases in vitamin D deficiency (6). Bone metabolism is adversely affected in patients with JIA due to disease activity, duration, medications, restriction of physical activity, and malnutrition. Since vitamin D deficiency is a preventable and treatable condition, the present study investigated the levels of 25(OH) vitamin D, calcium, phosphorus, and alkaline phosphatase in pediatric patients with JIA followed up in our clinic and evaluated possible related factors.

MATERIAL AND METHODS

The records of 68 patients diagnosed with JIA were retrospectively evaluated according to the International League of Associations for Rheumatology (ILAR) criteria in the pediatric rheumatology outpatient clinic between 1995 and 2009. A control group was formed with thirty-nine healthy children. Consent was obtained from the families of both groups. Disease subtypes, medications used, and whether they were in remission or active disease were evaluated. Ca, P, ALP, and 25(OH) vitamin D levels were evaluated in all patients, and these values were compared with those of the control group. The relationship of Ca, P, ALP, 25(OH) vitamin D values with disease subtypes, disease activity, and medications used was investigated, and statistical studies were performed. The normal limits of the laboratory parameters were 8.8-10.6 mg/dl for calcium, 2.5-4.5 mg/dl for phosphorus, 3.5-5.2 g/dl for albumin, 30-120 U/L for alkaline phosphatase and 10-44 ng/ml for 25(OH) vitamin D measured by RIA method. Values outside these reference ranges were considered pathological. Demographic characteristics of the patients (age, gender, height, weight, and body mass index percentiles), JRA subtypes, medications used in the last year, whether osteoporotic doses of steroids were used, last clinical status (remission with or without medication and active disease) and the relationships of the laboratory parameters we examined were statistically evaluated. SPSS (Statistical Package for the Social Sciences) version 13 assessed the study's findings. While evaluating the study data, in addition to descriptive statistical methods (Mean, Standard deviation), the Chi-Square test and Fisher's Exact Chi-Square test were used to compare qualitative data. The statistical significance was evaluated at the $p<0.05$ level.

RESULTS

Of the 68 patients with JIA included in the study, 42 were female, and 26 were male. The mean age was 4.5±2.12 years (3-21). There were 16 females and 23 males in the control group. No difference was determined between the mean ages of both groups ($p>0.005$). Similarly, there was no difference between the two groups regarding height, weight, body mass index, and follow-up periods. The latest status of the patients in terms of disease activities is presented in Table 1.

Table 1. Current status of patients

Final status	Number of patients (n)	Ratio (%)
Active disease	14	20.5
Remission w/medication	27	39.7
Remission w/o medication	27	39.7

w/: with w/o: without

When the calcium, phosphorus, ALP, and 25(OH) Vit D values of the patient group and the control group were compared, it was observed that the 25(OH) Vit D value in the patient group was lower than in the healthy group and the difference was statistically significant ($p=0.013$) (Table 2).

Table 2. Biochemical analysis of patients diagnosed with JIA and the control group

	Ca			P			ALP			25 (OH) Vit D		
	N	H	L	N	H	L	N	H	L	N	H	L
Patients	64	0	4	51	16	1	63	5	0	58	0	10
Control group	36	1	2	35	4	0	36	3	0	39	0	0
p-value	0.41			0.16			1.00			0.013		

Ca: calcium, P: phosphorus, ALP: alkaline phosphatase, 25 (OH) Vit D: 25 Hydroxyvitamin D, N: normal, L: low, H: high

Steroid use above the physiological dose (<5 mg/m²/day prednisolone and equivalent) was considered an osteoporotic dose. When a comparison was made between steroid users and non-users at osteoporotic doses among patients with JIA, it was statistically significant that serum 25 (OH) Vit D levels were lower in the steroid users (p=0.013). There was no statistically significant difference between the serum calcium, phosphorus, ALP, and 25 (OH) Vit D values of patients using steroids and patients using other medications. When patients with active disease were compared with the healthy group, ALP level was statistically significantly higher (p=0.04), and 25(OH) Vit D level was lower, which was statistically significant (p=0.001) (Table 3).

Table 3. Biochemical comparison of patients with active disease and the control group

	Ca			P			ALP			25 (OH) Vit D		
	N	H	L	N	H	L	N	H	L	N	H	L
Active disease group	12	0	2	9	5	0	10	4	0	9	0	5
Control group	36	1	2	35	4		36	3		39	0	0
p-value	0.46			0.04			0.07			0.001		

Ca: calcium, P: phosphorus, ALP: alkaline phosphatase, 25 (OH) Vit D: 25 Hydroxyvitamin D, N: normal, L: low, H: high

There was no difference between the patients in medicated remission and the control group regarding the examined biochemical values. Similarly, no difference was determined between patients in drug-free remission and the control group. There was no statistical difference between patients in medicated remission and those in drug-free remission regarding serum calcium, phosphorus, ALP, and 25(OH) vitamin D levels. Patients with drug-free remission were compared with those having an active disease, and in the active disease group, higher ALP and lower vitamin D levels were statistically significant (p=0.01 and p=0.03, respectively) (Table 4).

Table 4. Biochemical comparison of drug-free remission and active disease group

	Ca			P			ALP			25 (OH) Vit D		
	N	H	L	N	H	L	N	H	L	N	H	L
Active disease group	12	0	2	9	5	0	10	4	0	9	0	5
Remission w/o medication	26	0	1	23	4	0	27	0	0	25	0	2
p-value	0.26			0.231			0.01			0.03		

Ca: calcium, P: phosphorus, ALP: alkaline phosphatase, 25 (OH) Vit D: 25 Hydroxyvitamin D, N: normal, L: low, H: high

DISCUSSION

Juvenile idiopathic arthritis is a disease characterized by idiopathic, chronic synovial inflammation that is common in childhood. According to the ILAR diagnostic criteria, it is divided into seven subtypes (1). In studies conducted in various countries, the mean incidence was reported to be 9.2-25/100,000 and the prevalence 12-113/100,000 (2). A study from our country determined it to be 64/100.000 (6). Although JIA is more common in girls in developed countries, the disease is more common in boys in developing countries. In our study, female patients were predominant in the gender distribution (42 females, 26 males). There are two peak ages at which the disease occurs most frequently, the first being 1 to 3 years of age and the second being nine years, and the mean age of our patient population was approximately four years, consistent with the literature. While the oligoarticular type is the most common subtype of JIA in developed countries, the polyarticular subtype comes to the fore in developing countries. In our study, the oligoarticular type was 41.1%, and the polyarticular type was 8.4%.

In various studies, laboratory investigations of bone mineralization and physiology of children with JIA have revealed different results (7-10). One study demonstrated that patients with systemic JIA had normal calcium, phosphorus, and osteocalcin levels but elevated ALP levels. This condition is explained by the more severe joint destruction and bone destruction in the systemic form (10). In our study, similar to the literature, we determined that the ALP level was high only in the systemic form of the JIA subgroups.

Vitamin D metabolism is often impaired in patients diagnosed with JIA, both due to lack of intake and as side effects of the medications used. According to the study conducted by Bianchi et al.

on 36 patients diagnosed with JIA, some of whom used steroids, the 25 (OH) Vit D levels of children with polyarticular and systemic diseases were lower than the control group. This decrease is considered to be due to a decrease in 1.25(OH) vitamin D production and receptor number (11). In our study, 25(OH) vitamin D levels were statistically significantly lower in patients diagnosed with JIA compared to the control group (p=0.013).

In severe chronic inflammatory diseases such as JIA, osteoblast-osteoclast balance is disrupted due to the increase in IL-1A, IL-6, IL-7, TNF alpha and beta, and osteoporosis may occur. In addition, corticosteroids used in treatment also negatively affect bone metabolism. Steroids increase bone resorption and the effects of parathormone on bone, suppress the synthesis function of osteoblasts, inhibit intestinal calcium absorption, and cause hypercalciuria. In our study, 25(OH) vitamin D levels were found to be statistically significantly lower in patients diagnosed with JIA who used osteoporotic doses of steroids compared to those who did not, which was consistent with the literature.

When children with active disease and patients in remission with and without medication were compared, respectively, it was revealed that 25(OH) vitamin D levels were low in the group with active disease, while ALP values were high. Studies have reported that patients with JIA have bone mineralization disorders even without steroid use (12-14). Our findings are also compatible with the literature as it was thought that the higher bone destruction in active disease and the use of high doses of steroids were effective (15, 16).

Osteopenia was observed in approximately 40% of patients with JIA, and some of these patients developed pathologic bone fractures at a later age (17).

In our study, vitamin D levels were low in some patients diagnosed with JIA. In this disease, in which bone metabolism is adversely affected, we recommend that vitamin D levels should be evaluated and vitamin D support should be provided together with calcium when necessary.

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