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Bone mineral density and vitamin D status in children and adolescents with congenital adrenal hyperplasia

Fatma DEMİREL*, Özlem KARA, Derya TEPE, İhsan ESEN
Department of Pediatric Endocrinology, Ankara Children's Hematology and Oncology Training Hospital, Ankara, Turkey

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Aim: To determine the prevalence of and risk factors for decreased bone mineral density (BMD) and vitamin D deficiency in children and adolescents with congenital adrenal hyperplasia (CAH).

Materials and methods: This study was conducted on 30 girls and 22 boys with CAH (age range = 5–20 years) with median age of 12.0 years. BMD values of lumbar vertebras (L1–L4), which were determined by dual-energy X-ray absorptiometry, were used to calculate z-scores according to chronological age. A serum 25-hydroxyvitamin D level of <15 ng/mL was considered as indicative of vitamin D deficiency.

Results: Mean vitamin D level was 14.8 ng/mL in the whole group. Twenty-seven (51.9%) children had vitamin D deficiency and it was more prevalent during pubertal ages. Vitamin D levels were found to be significantly lower in pubertal females. BMD z-score was below –1 standard deviation in 40.1% of cases with significantly higher mean age and lower vitamin D levels.

Conclusion: Decreased BMD z-score and vitamin D deficiency were common in these children with CAH. Vitamin D levels were significantly lower in girls and pubertal children. Decreased BMD z-score was related to older age and lower levels of vitamin D. Periodical controls of vitamin D status and vitamin D supplementation were recommended in these cases, whenever required.

Key words: Congenital adrenal hyperplasia, bone mineral density, adolescent, vitamin D, children

1. Introduction

Lifelong glucocorticoid replacement should be performed in cases of congenital adrenal hyperplasia (CAH), both to suppress excessive production of adrenal androgens and to meet the daily cortisol requirements (1,2). Adjustment of steroid dose is very important to provide optimal growth and bone health in children. Increased androgen production, peripheral precocious puberty, decreased adult height, and tendency to adrenal crisis are increased in undertreatment conditions. Risks like suppression of growth, obesity, and decreased bone mineral density (BMD) may be encountered in cases of long-term overtreatment with supraphysiological doses of corticosteroid use (1–3). Chronic glucocorticoid use has unfavorable effects on bone health through suppression of osteoblastic activity, decreased intestinal calcium absorption, secondary hyperparathyroidism, increased osteoclastic activity, and oversuppression of androgens (4,5). It is known that osteoporosis risk is higher in adult patients with CAH compared to the normal population (6–9). However, in younger CAH patients there are contradictory results in published studies and case reports that reported that BMD values were not changed or decreased (10–18). This situation may be related to smaller numbers of patients, extensive range of age distribution, and heterogeneous glucocorticoid dose among groups. Since association between children and adolescents with CAH and osteoporosis risk is not clear, follow-up and treatment plans for bone health are not well defined yet (3,19).

Vitamin D is essential for bone health. Association between osteoporosis and vitamin D deficiency in adults is well determined (20). In children with CAH, vitamin D status is not a well-known entity and only 2 studies were found in the current literature with contradictory results (14,21).

In this study it was aimed to determine prevalence and related factors of decreased BMD z-score and vitamin D deficiency by utilizing a larger number of patients with homogeneous age distribution when compared to the previous studies.

* Correspondence: demirelf@gmail.com

2. Material and methods

2.1. Subjects

This study was conducted at the Department of Pediatric Endocrinology at Ankara Children's Hematology and Oncology Training Hospital. In the study, 30 girls and 22 boys with the mean age of 12.8 ± 4.5 (range: 5–20) years and classical CAH were included. Thirty-two of these cases were of the salt-losing type and 20 were of the simple virilizing type.

Body weight, height, and body mass index (BMI) of the patients were recorded as auxological data. For analyses, standard deviation (SD) scores of weight, height, and BMI of all patients were calculated by using standard values for Turkish children (22,23).

The authors confirmed in writing that they have complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects. The study was approved by the hospital ethics board and informed consent was obtained from the families of all patients.

2.2. Laboratory investigation

Serum levels of calcium (Ca), phosphorus (P), magnesium (Mg), alkaline phosphatase (ALP), intact parathyroid hormone (iPTH), and 25-hydroxyvitamin D (25(OH) D) were recorded as laboratory data. Venous blood samples were obtained from all patients after 8–12 h of overnight fasting. Serum Ca, P, Mg, and ALP levels were measured using the spectrophotometry method (Roche Hitachi Modular P). Serum iPTH was evaluated using the chemiluminescence method (Beckman Coulter DXI-800).

Serum 25(OH)D levels were measured by liquid chromatography and tandem mass spectrometry (LC-MS/MS) methods at the end of the winter.

Vitamin D status was assessed according to 25(OH) D levels. Serum 25(OH)D levels of >20 ng/mL were indicative of the normal level. Vitamin D insufficiency and deficiency were defined as 25(OH)D levels of 15–20 ng/mL and lower than 15 ng/mL, respectively (24).

2.3. Bone mineral density measurement

Bone mineral density values of lumbar vertebras (L1–L4) determined by dual-energy X-ray absorptiometry were used for analyses. Bone density measurements were performed with a Hologic QDR-4500A S/N 45130 bone densitometer (Hologic Inc., Bedford, MA, USA).

Bone mineral density values were used to calculate BMD z-scores according to chronological age. Previously published data of Turkish children's BMD, specific for age and sex, were used as normative data (25). According to the International Society for Clinical Densitometry (ISCD) 2007 Pediatric Official Positions and current literature, when BMD z-score was over –1 SD, it was accepted as normal; when it was between –1 and –2 SDs, it was accepted as decreased; and when it was below –2 SD, it was accepted as low BMD (26–28).

2.4. Glucocorticoid dose

The glucocorticoid usage dose was calculated as mg m^{-2} day^{-1}, and the mean value of the last 2 years' doses was calculated. Hydrocortisone use of more than 15 mg m^{-2} day^{-1} was defined as overtreatment or a supraphysiological dose (1).

2.5. Statistical methods

Statistical analysis was performed with SPSS 13.0 (SPSS Inc., Chicago, IL, USA). Chi-square test was used to compare categorical data. For measured data, independent sample t-tests or Mann–Whitney U tests were used when appropriate. The P-value for significance was set at 0.05.

3. Results

Characteristics of the patients are given in Table 1. Mean vitamin D level was 14.8 ng/mL (range: 4–45 ng/mL) in the whole group. Vitamin D levels were below 20 ng/mL in 75.0% (n = 39) of cases. Twelve patients (23.0%) had vitamin D insufficiency, and 27 patients (51.9%) had vitamin D deficiency. In pubertal patients, vitamin D level was significantly lower in females when compared with males (P < 0.05; Table 2).

In total, 32.7% of the patients (n = 17) were receiving steroids at a supraphysiological dose. The mean age of this group was significantly higher than that of patients receiving steroids at the physiological dose (14.6 versus 11.9 years) (P < 0.05). While mean vitamin D level was lower in the patients receiving high levels of steroids than in the counterpart group, there was no significant difference between them (P = 0.059; Table 2).

Calcium, P, Mg, and ALP levels were within normal limits in all cases. However, 7 patients with vitamin D level of <10 ng/mL had iPTH values higher than normal levels (mean: 72.5 ± 7.6 ng/mL), and this condition was defined as secondary hyperparathyroidism.

There was no difference in total BMD and BMD z-scores in clinical typing, sex, pubertal status, and glucocorticoid dose comparisons between the groups (Table 2). Bone mineral density z-score was below –1.0 in 40.1% of patients (n = 21). In this group, mean age was significantly higher (14.5 ± 5.4 vs. 11.7 ± 3.8 years; P = 0.032) and vitamin D level was significantly lower (11.5 ± 7.0 vs. 16.9 ± 12.0 ng/mL; P = 0.047) than those of the others. Low BMD values were detected in 2 adolescents (3.8%) who received supraphysiological doses of glucocorticoids.

4. Discussion

Approximately half of the CAH patients in the age range of 5–20 years who were followed at our clinic had vitamin D deficiency, whereas one-fourth of the patients were diagnosed with vitamin D insufficiency. Vitamin D levels

Table 1. Clinical and demographical characteristics of the study group.

	All patients	Clinical type		P
		Salt-losing	Simple virilizing	
n (%)	52 (100)	33 (61.5)	20 (38.5)	
Age [years, median (range)]	13.0 (5.0–20.0)	10.0 (5.0–20.0)	15.0 (9.0–20.0)	**0.007**
Sex, male/female	22/30	11/21	11/9	0.120
Pubertal state, prepubertal/pubertal	21/31	17/15	4/16	**0.017**
Age at diagnosis, [months, median (range)]	1.0 (1–132)	1.0 (1–36)	15.5 (1–132)	**0.0001**
Glucocorticoid dose, mg m^{-2} day^{-1}	14.7 ± 4.4	15.1 ± 4.2	14.4 ± 4.4	0.37

Bolded values are statistically significant.

Table 2. Laboratory data of the study group.

	25(OH)D (ng/mL)	Total BMD (g/cm^2)	Lumbar BMD z-score
All patients	14.8 ± 10.5	0.730 ± 0.185	–0.26 ± 1.5
Clinical type			
Salt-losing	15.3 ± 10.7	0.691 ± 0.182	–0.17 ± 1.5
Simple virilizing	13.8 ± 10.4	0.793 ± 0.179	–0.41 ± 1.5
Sex			
Male	17.9 ± 11.6*	0.691 ± 0.165	–0.29 ± 1.5
Female	12.5 ± 9.2*	0.759 ± 0.190	–0.24 ± 1.5
Pubertal state			
Prepubertal	18.4 ± 11.6¶	0.561 ± 0.117	–0.05 ± 1.4
Pubertal	12.3 ± 8.9¶	0.640 ± 0.125	–0.40 ± 1.6
Glucocorticoid dose			
≤15 mg m^{-2} day^{-1}	15.9 ± 9.1	0.696 ± 0.193	0.05 ± 1.7
>15 mg m^{-2} day^{-1}	13.0 ± 6.4	0.800 ± 0.148	–0.41 ± 1.4

* and ¶: $P < 0.05$.

were significantly lower in girls and pubertal patients than in boys and prepubertal patients. It is known that prevalence of vitamin D deficiency is remarkable during childhood and adolescence throughout the world (24,29). In Turkey, vitamin D prophylaxis is applied as the national health policy starting from the neonatal period during the first year of life, due to high vitamin D deficiency prevalence in childhood (30–34). In a recent study that was conducted in the same province as our study, vitamin D deficiency rate in healthy children was defined as 25%, whereas prevalence

of vitamin D insufficiency was detected as 15% (31). In our study, vitamin D deficiency and insufficiency rates were higher in patients with CAH when compared to normal healthy children, and the deficiency degree was increased with age. In 2 studies about bone health in children and adolescents with CAH, 2 different results were reported. In the first study, vitamin D levels were found to be lower than those of normal controls, whereas in the second, they were reported to be at similar levels (14,21). In our study group, children were from low-to-middle–income families and vitamin D levels were measured at the end of winter. These factors might contribute to detection of higher rates of vitamin D deficiency. Another reason might be chronic steroid use. Recent laboratory studies showed that steroids may enhance inactivation of 25(OH)D by up-regulating 24-hydroxylase activity (35,36). Skversky et al. reported in their large population screening study based on 2001–2006 National Health and Nutrition Examination Survey data that vitamin D deficiency was more widely seen in patients with chronic steroid use than in the normal population (37). Additionally, significantly lower levels of vitamin D were determined in chronically ill children treated with glucocorticoids (38–40).

As treatment compliance is low in patients with CAH, steroid dose should sometimes be increased to suppress androgen production and to provide better control. Approximately one-third of our patients had used higher doses of steroids than the normal replacement doses during the last 2-year period. In our study, deleterious effects of supraphysiological doses of steroids on BMD and vitamin D levels could not be shown. Limited sample size and relatively shorter treatment duration compared to adults for cumulative effects of glucocorticoids might give rise to these results.

Another reason for vitamin D deficiency may be that patients with CAH isolate themselves as they get older, abstain from group activities, and spend a significant part of their time indoors. In patients with CAH, anatomical and psychological results of feminizing genitoplasty were widely discussed in the literature (41–43). However, no study has been published about socialization and life quality of children and adolescents with CAH in our population. In one of the studies performed on girls with 21-hydroxylase deficiency, it was reported that more behavioral and emotional disorders were observed in these patients when compared to children with other chronic diseases, but no information was given about their social behaviors (44). In a study about the life quality of children with CAH from the Netherlands, it was reported that the Dutch children had no problems related to socialization (45). Studies in identification of life quality and socialization problems in children with CAH will shed light on this issue among our population.

Osteoporosis risk is increased in CAH patients in adulthood with increasing age when compared to the normal population (6–9). Therefore, bone health of these patients should be evaluated starting from childhood. A calcium-rich diet during adolescence, along with prophylactic vitamin D intake, annual screening of vitamin D deficiency, and vitamin D replacement, if required, will have beneficial effects on bone health.

In our study, decreased BMD was detected in 40% of children and adolescents with CAH and low BMD was detected in 3.8%. Since patients with decreased BMD z-scores were older and had significantly lower vitamin D levels, it is thought that BMD started to decrease at puberty, and vitamin D deficiency was one of the precipitating factors in cases of CAH. When studies of BMD and its related factors in children and adolescents with CAH are reviewed, the relatively limited number of cases and wide age ranges of the patients in these studies complicate definitive evaluation of results. We think that our results are significant because the age range was narrow and the case number was relatively high in our study. However, there is no consensus about whether BMD should be examined in children with CAH or who is under risk for decreased BMD. It is obvious that analyzing the results of multicenter, large-scale studies performed with the same standards is required. According to the results of our study, it can be recommended that adolescent patients, especially those from middle-to-low income levels who use long-term supraphysiological doses of glucocorticoids, who have low daily calcium intake, and who are diagnosed with vitamin D deficiency, should be screened for decreased BMD.

Major weaknesses of our study were the lack of a control group and the limitations of a cross-sectional study in determining causality. However, the presence of BMD z-score standards for Turkish children and recent vitamin D research on healthy children in our province helped us to evaluate the results of our study.

In conclusion, bone health of children with CAH is an important concern to which attention should be paid starting from childhood. In these cases, vitamin D deficiency, especially during adolescence, may contribute to decreased bone mineral content. We strongly recommend protection of bone health in these children through calcium-balanced diets, periodical controls of vitamin D levels, and vitamin D supplementations, whenever required.

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