Bone Mineral Density and Body Composition in Prepubertal and Adolescent Patients with the Classical Form of 21-Hydroxylase Deficiency

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Objectives: *To evaluate bone mineral density (BMD) and body composition in prepubertal and adolescent patients with the classical form of 21-hydroxylase deficiency.*
Material and Method: *The authors measured height, weight and used dual energy x-ray absorptiometry (DEXA) to evaluate lumbar spine, whole body BMD and body composition in 10 prepubertal and adolescent patients with the classical form of 21-hydroxylase deficiency. Serum hormone concentrations (17-hydroxyprogesterone, dehydroepiandrosterone sulfate) were also measured. Results were compared with those of age- and sex-matched controls.*
Results: *Seven patients were adolescent (4 girls and 3 boys; age range, 9.0-19.6 years) and three patients were prepubertal. (2 girls and 1 boy; age range, 6.5-8.6 years) There were no significant differences in age, height z-score, weight z-score and body mass index between the patients with congenital adrenal hyperplasia (CAH) and controls. DEXA showed no differences between each group in whole body BMD, but showed significantly elevated areal regional BMD at the lumbar spine (L1-L4) in CAH patients. However, four of the 10 CAH patients and 6 of the 10 controls had osteopenia. The BMD z-score at the lumbar spine was significantly correlated with increasing weight z-score in both CAH patients and controls. When CAH patients with osteopenia were compared with those with normal BMD, there was a trend toward lower weight z-score, higher dose of glucocorticoids and longer duration of treatment among the osteopenic patients, but it did not reach statistical significance.*
Conclusion: *Classical 21-hydroxylase deficiency patients treated with long-term glucocorticoids did not have impaired bone mineral density compared with healthy, age and sex-matched controls. However, the reference data for BMD in the Thai pediatric population is lacking and the number of studied participants was limited so we need further studies.*

Keywords: *Bone mineral density, Body composition, Congenital adrenal hyperplasia, 21-hydroxylase deficiency*

J Med Assoc Thai 2008; 91 (5): 705-10
Full text. e-Journal: *http://www.medassocthai.org/journal*

Congenital adrenal hyperplasia (CAH) is the term applied to a recessive autosomal inherited disorder of steroidogenesis caused by a deficiency of one of five enzymes necessary for the conversion of cholesterol to cortisol. 21-Hydroxylase (21-OH) deficiency is the most common cause of CAH. Management of this disorder consists of lifelong glucocorticoid supplementation to reduce excess levels of adrenal androgens[1-3].

Concern has been raised regarding the deleterious effect of steroids on bone[4] and the fact that the doses usually employed in the past were much higher than those required for physiological hormonal replacement. Previous reports on bone mineral density (BMD) in CAH patients showed discordant data including increased, decreased, or normal BMD[5-13].

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The aims of the present study were to assess skeletal mineralization through measurement of bone mineral density (BMD) in the lumbar spine and body composition, by dual energy x-ray absorptiometry (DEXA), in prepubertal and adolescent CAH patients with the classical form of 21-OH deficiency and to compare these values with those of age- and sex-matched controls from our healthy population.

Material and Method

Ten Thai patients with the classical form of 21-OH deficiency were studied. Seven patients were adolescent (4 girls and 3 boys; age range, 9.0-19.6 years) and three patients were prepubertal (2 girls and 1 boy; age range, 6.5-8.6 years). They had been diagnosed and treated in the first year of life with glucocorticoids and mineralocorticoids. They were followed-up regularly with biochemical and anthropometrical measurements. The control group was recruited by advertisements in the region of the hospital. Inclusion criteria were good health, no medication, and Thai race. The control subjects were matched for age and sex.

All patients and control subjects were assessed auxologically and with densitometry. Clinical data included height, weight, and Tanner stage. Body mass index (BMI) was calculated as weight/(height)^2 (kg/m^2). Total body BMD and areal regional BMD (aBMD, g/cm^2) at the lumbar spine (L1–L4) were assessed with dual energy x-ray absorptiometry, using a QDR 4500W densitometer (Hologic, Waltham, MA).

The duration of treatment was considered as the period in years from the date that treatment began until the last assessment. Data on the type and dosage of glucocorticoid (in mg/m^2/day) were obtained from during consultations that occurred in the 3 years before performing densitometry. All the glucocorticoid dosages used were converted to hydrocortisone dosage (80 mg hydrocortisone = 16 mg prednisone = 1 mg dexamethasone)[14].

Serum 17-hydroxyprogesterone (17-OHP), dehydroepiandrosterone sulfate (DHEAS) levels were measured in the fasting state at 08.00 a.m. before the morning corticosteroid dose. A chemiluminescent enzyme immunoassay was performed for DHEAS and 17-OHP.

Basic statistics were used to calculate means and variances. *Z*-scores were calculated by subtracting the corresponding mean age- and sex-matched values and dividing these by the standard deviation. Differences between groups were compared using two-tailed sign-rank test. Data are presented as mean $\pm$ standard deviation (SD). A p-value <.05 was considered statistically significant.

Results

Characteristics of patients and controls

The clinical data of the CAH patients are presented in Table 1. The baseline characteristics of each group are shown in Table 2. There were no significant differences in age, height z-score, weight z-score, and BMI.

BMD and body composition

DEXA showed no differences between patients

Table 1. Raw data in 10 CAH patients

Number of patients/sex	Age (yr)	Weight z-score	Height z-score	BMI (kg/m^2)	aBMD (L1-L4) z-score	Total BMD z-score	Current glucocorticoid dose (mg/m^2/day)	Average glucocorticoid dose in 3 yrs (mg/m^2/day)
Prepubertal								
1/F	6.5	+0.93	+0.23	17.5	+0.1	+0.1	16.6	17.4
2/F	7.3	-0.21	-1.00	15.5	-0.3	-0.6	15.2	17.3
3/M	8.6	-0.04	-1.77	16.3	-1.2	-0.9	21.5	17.2
Pubertal								
4/F	9.0	+1.09	+1.52	17.8	+1.9	+2.4	27.2	24.2
5/F	13.1	+0.97	+0.28	20.8	+0.1	+0.3	21.4	20.4
6/F	15.8	-1.22	-0.38	16.7	-1.3	-0.6	28.6	28.3
7/F	19.6	-0.48	+0.58	18.2	-1.8	-1.8	31.5	28.4
8/M	12.0	+4.54	+1.13	32.5	+0.3	-0.2	20.6	16.3
9/M	15.6	+8.93	-0.77	44.2	+2.3	+1.9	22.2	22.1
10/M	16.9	-0.44	-1.98	20.9	-0.5	-1.6	20.4	28.5

Table 2. Baseline characteristics of patients and controls

Characteristics	CAH patients	Controls	p-value
No.	10	10	
Age (yr)	12.40 (4.50)	12.70 (4.20)	0.124
Weight z-score	1.37 (3.10)	-0.03 (0.68)	0.196
Height z-score	-0.22 (1.17)	0.06 (1.09)	0.595
BMI (kg/m^2)	22.00 (9.20)	17.50 (2.20)	0.125

p-values are from two group comparisons using paired t-test
Data are the frequency or the mean (SD)

Table 3. BMD data and body composition

	CAH patients	Controls	p-value
BMD z-score			
L1-L4	-0.04 (1.32)	-0.95 (1.01)	0.015
Total body BMD	-0.10 (1.36)	-0.87 (1.09)	0.061
Total lean mass (kg)	32.70 (16.21)	28.52 (11.10)	0.202
% lean mass	70.70 (6.90)	73.70 (5.90)	0.440
Total fat mass (kg)	13.93 (12.65)	8.69 (3.59)	0.269
% fat mass	25.90 (7.60)	22.90 (6.30)	0.492

p-values are from two group comparisons using paired t-test
Data are the mean (SD)

and controls in total body BMD, but significantly elevated aBMD at the lumbar spine (L1–L4) in CAH patients. However, four of the 10 CAH patients and 6 of the 10 controls had osteopenia (defined as a z-score between -1 and -2.5). No subjects were found to have osteoporosis. The BMD z-score at the lumbar spine was significantly correlated with increasing weight z-score in both CAH patients and controls (Fig. 1). Total lean mass and total fat mass were not different between patients and controls (Table 3).

Analysis of the factors related to BMD

When CAH patients with osteopenia were compared with those with normal BMD, there was a trend toward lower weight z-score, higher dose of glucocorticoids and longer duration of treatment among

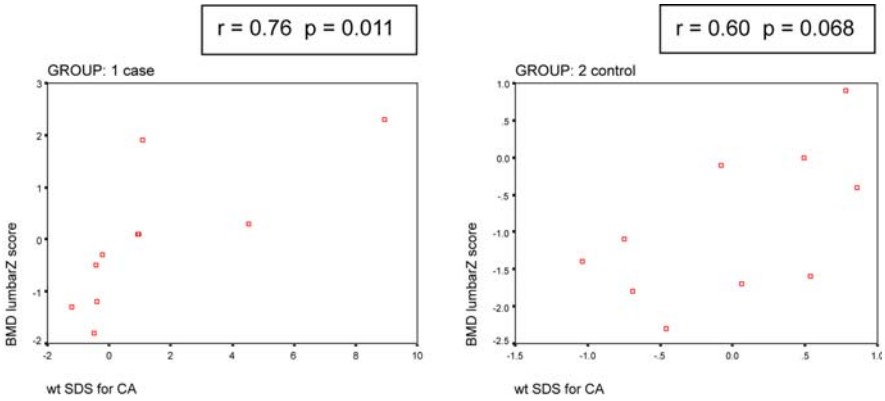

Fig. 1 BMD z-score (L1-L4) as it relates to weight z-score in each group, r is the Pearson correlation coefficient

Table 4. Some factors analyzed in relation to BMD data from 10 CAH patients

	BMD z-score ≤ -1.0 (n = 4)	BMD z-score > -1.0 (n = 6)	p value
Age (yr)	15.2 (4.7)	10.60 (3.6)	0.112
Sex (F/M)	2/2	4/2	1.000
Weight z-score	-0.64 (0.39)	2.71 (3.45)	0.063
Height z-score	-0.89 (1.21)	0.23 (0.99)	0.148
BMI (kg/m^2)	18.00 (2.1)	24.70 (11.3)	0.212
17-OHP (ng/ml)	124.40 (135.3)	84.30 (122.4)	0.668
DHEAS (ug/dL)	92.70 (15.3)	56.40 (64.1)	0.380
Current glucocorticoid dose ($mg/m^2/day$)	25.50 (5.4)	20.50 (4.3)	0.143
Average glucocorticoid dose in 3 yrs ($mg/m^2/day$)	25.60 (5.6)	19.60 (3.1)	0.060
Duration of treatment (yr)	15.10 (4.7)	8.90 (4.2)	0.059

Data are means (SD)

the osteopenic patients, but it did not reach statistical significance. Two of the four osteopenic CAH patients have received dexamethasone in their regimen. 17-OHP and DHEAS levels were not significantly different (Table 4). In the control group, osteopenic subjects had significantly lower weight z-score than subjects with normal BMD.

Discussion

Osteoporosis was one of the expected complications resulting from chronic glucocorticoid treatment[15]. BMD was used as a parameter to monitor this condition. In fact, it may increase in the presence of excessive androgens[5] and decline as a consequence of excessive glucocorticoids[10,11,13]. Previous studies have attempted to address the potential impact of chronic glucocorticoid therapy in CAH patients on BMD, but provided conflicting results[5-13]. The present study population represents a homogeneous group with respect to race, clinical expression of the disease and therapy. The present study shows that long-term glucocorticoid treatment does not impair the height of patients and bone mineral density as total body BMD values in prepubertal and adolescent CAH patients were similar to those of the age- and sex-matched controls, as occurred for height values. However, CAH patients have significantly elevated aBMD at the lumbar spine (L1–L4) compared with controls. These results were probably associated with nutritional status because CAH patients tend to have higher weight z-score and BMI than controls. The other reason was that most of CAH patients had advanced bone age so that BMD may also be evaluated in relation to bone age other than chronological age.

The present results indicate that higher weight z-score are associated with higher BMD in both patients and controls indicating an influence of nutritional status. Previous studies reported a positive correlation between weight and bone mass[16,17]. This effect is probably related to excess adipose tissue through increased conversion of estrogen from adrenal precursors.

The glucocorticoid dosages received by the present osteopenic patients tend to be higher than those of normal BMD. There was no significant association between BMD and 17-OHP or DHEAS values.

Surprisingly, the authors found that six of the 10 healthy controls had osteopenia. The variables that contribute to optimal bone health are genetic factors, physical activity, nutrition, body mass, and hormonal balance[18,19]. Previous studies have shown ethnic differences in bone mass[20,21]. Thus, ethnic-specific reference databases are needed to differentiate normal from impaired bone mineral density in the Thai pediatric population.

The present study had some limitations. Firstly, the present study had a relatively small sample size because CAH is a rare inherited disease and we cannot recruit the patients who are younger than 5 years old since they will not co-operate during the investigation for BMD. Secondly, the reference data for BMD in the Thai pediatric population is lacking. Lastly, this is a crossectional study so it does not rule out that the CAH patients may develop osteoporosis at an older age, especially when sex steroid levels become decreased so the authors need further studies.

Conclusion

Classical 21-hydroxylase deficiency patients treated with long-term glucocorticoids did not have impaired bone mineral density compared with healthy, age and sex-matched controls. However, the reference data for BMD in the Thai pediatric population is lacking and the number of studied participants was limited so further studies are needed.

Acknowledgements

The authors wish to thank the patients for participation in this study. The present study was supported by Ratchadapiseksompotch Fund and the Development Grants for New Faculty/Researchers, Chulalongkorn University.

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การศึกษาความหนาแน่นมวลกระดูกและสัดส่วนสารประกอบของร่างกายในผู้ป่วยเด็กและวัยรุ่นที่เป็นโรคขาดเอนไซม์ 21- hydroxylase ชนิด classical

ธนินี สหกิจรุ่งเรือง, สุทธิพงศ์ วัชรสินธุ, วิชิต สุพรศิลป์ชัย, สุมาลี ศรีวัฒนา, คนึงนิจ กิ่งเพชร

วัตถุประสงค์*: เพื่อศึกษาเปรียบเทียบความหนาแน่นมวลกระดูก และสัดส่วนสารประกอบในร่างกายของผู้ป่วยเด็กและวัยรุ่นที่เป็นโรค congenital adrenal hyperplasia กับกลุ่มควบคุมที่มีอายุและเพศเดียวกัน*

วัสดุและวิธีการ*: ผู้ศึกษาได้วัดความสูง น้ำหนัก และตรวจวัดความหนาแน่นมวลกระดูกบริเวณกระดูกสันหลังส่วน lumbar และความหนาแน่นมวลกระดูกรวมทั้งร่างกายและสัดส่วนสารประกอบในร่างกายโดยใช้ dual energy x-ray absorptiometry (DEXA) ในผู้ป่วยเด็กและวัยรุ่นที่เป็นโรค 21-hydroxylase deficiency ชนิด classical จำนวน 10 รายเปรียบเทียบกับกลุ่มควบคุมที่มีอายุและเพศเดียวกัน และวัดระดับฮอร์โมน 17-hydroxyprogesterone, dehydroepiandrosterone sulfate ในกลุ่มผู้ป่วย*

ผลการศึกษา*: ผู้ป่วย 7 รายอยู่ในวัยรุ่น (เพศหญิง 4 ราย เพศชาย 3 ราย อายุ 9.0-19.6 ปี) ผู้ป่วย 3 ราย อยู่ในช่วงก่อนวัยรุ่น (เพศหญิง 2 ราย เพศชาย 1 ราย อายุ 6.5-8.6 ปี) ไม่มีความแตกต่างของอายุ, height z-score, weight z-score และดัชนีมวลกายระหว่างกลุ่มผู้ป่วยและกลุ่มควบคุม ผลการตรวจ DEXA พบว่าความหนาแน่นมวลกระดูกรวมทั้งร่างกายไม่แตกต่างกัน แต่กลุ่มผู้ป่วยมีความหนาแน่นมวลกระดูกบริเวณ lumbar (L1-L4) มากกว่ากลุ่มควบคุมอย่างมีนัยสำคัญ ผู้ป่วย 4 ใน 10 รายและกลุ่มควบคุม 6 ใน 10 รายมีภาวะกระดูกบาง ค่า BMD z-score ทั้งในกลุ่มผู้ป่วยและกลุ่มควบคุมมีความสัมพันธ์เชิงบวกกับค่า weight z-score เมื่อเปรียบเทียบผู้ป่วยที่มีภาวะกระดูกบางกับผู้ป่วยที่มีความหนาแน่นมวลกระดูกปกติ พบว่ากลุ่มที่มีกระดูกบาง มีค่าเฉลี่ย weight z-score ที่ต่ำกว่า ได้รับยา glucocorticoids ขนาดสูงกว่าและระยะเวลาเฉลี่ยที่ได้รับยานานกว่า แต่ไม่มีนัยสำคัญทางสถิติ*

สรุป*: กลุ่มผู้ป่วยโรค21-hydroxylase deficiency ชนิด classical ที่ได้รับการรักษาด้วย glucocorticoids เป็นเวลานาน มีความหนาแน่นมวลกระดูกไม่แตกต่างจากกลุ่มควบคุมที่มีอายุและเพศเดียวกัน อย่างไรก็ตามยังไม่มีค่า BMD ที่ใช้อ้างอิงได้ในเด็กไทยและประชากรที่นำมาศึกษามีจำนวนน้อย จึงควรมีการศึกษาเพิ่มเติมต่อไป*