

Bone mineral density in young adult women with congenital adrenal hyperplasia

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ABSTRACT

Background: There is equipoise regarding the status of bone mineral density (BMD) in patients with congenital adrenal hyperplasia (CAH), where patients need to be on long-term low-dose steroids. **Objective:** We aimed to evaluate BMD at the hip, spine and forearm in women with CAH and compare it to healthy young adult women of the same age range. **Subjects and Methods:** Fifteen adult women with CAH with age ranging from 18 to 40 years (mean \pm standard deviation = 27.5 \pm 6.2 years) underwent dual-energy X-ray absorptiometry along with laboratory evaluation. BMD at lumbar spine, hip, forearm along with T-scores were measured. Serum total calcium, phosphate, alkaline phosphatase, 25 hydroxy Vitamin D, intact parathyroid hormone, total testosterone, and dehydroepiandrosterone were assayed. History of any fractures in the past was taken. Fifteen healthy women in the same age range were taken as controls for comparison. **Results:** The BMD at hip (0.85 \pm 0.02 g/cm²) in CAH was significantly lower as compared with controls (0.92 \pm 0.03 g/cm², $P = 0.029$). BMD at lumbar spine was also reduced (0.96 \pm 0.02 vs. 1.03 \pm 0.03, $P = 0.057$). The BMD at forearm was not significantly different between CAH and controls. The mean Vitamin D was 9.8 ng/ml (deficient range). There was no history of fractures in CAH. **Conclusion:** Young adult CAH women had lower BMD at spine and hip than healthy young adult women of the same age range. The forearm BMD was not different from controls. No change in fracture frequency was present. Patients with CAH being treated with steroids are at increased risk of osteopenia, and their bone health needs to be monitored.

Key words: Bone mineral density, congenital adrenal hyperplasia, osteopenia

INTRODUCTION

Congenital adrenal hyperplasia (CAH) is a disorder characterized by impaired biosynthesis of adrenal steroids due to various defects in the activity of the enzymes involved in the synthetic pathway. The most common variant of CAH is due to defect in the 21 hydroxylase enzyme. The defects in this enzyme lead to impaired

cortisol and aldosterone synthesis along with diversion of their precursors into adrenal androgens. The patients may present with salt wasting crisis in infancy (salt wasting CAH) or with ambiguous genitalia in a female child (simple virilizing CAH). The therapy includes replacement of glucocorticoids and mineralocorticoids to alleviate the deficiency along with control of androgen excess.

Glucocorticoids can cause a reduction in bone mineral density (BMD). On the other hand, androgens, including adrenal androgens, are important in achieving and preserving peak bone mass. Hence, it is interesting to study the BMD of patients with CAH in whom both these factors are in operation.

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In previous studies on BMD in CAH patients, some have observed normal and while others observed decreased BMD.

The aim of our study is to assess BMD of adult female patients with CAH and compare it with healthy women of similar age.

SUBJECTS AND METHODS

Design: Case-control study

The study group consisted of fifteen female patients with CAH with age ranging from 18 to 40 years (mean \pm standard deviation (SD) = 27.5 \pm 6.2 years) being treated in our endocrine outpatient department. Of these 2 had salt wasting CAH while 13 had been diagnosed with simple virilizing CAH. The diagnosis was based on clinical grounds and raised serum 17-hydroxyprogesterone (OHP) levels. Fifteen healthy women in the same age range were included as controls for comparison.

The study was approved by the Institute Ethics Committee. All patients gave consent for the study. Detailed history including past history of fractures was taken, and physical examination was done. Fasting blood samples were drawn for serum total calcium, phosphate and alkaline phosphatase, serum 25 hydroxy Vitamin D, serum intact parathyroid hormone (PTH), serum total testosterone, and dehydroepiandrosterone (DHEAS). Serum 25 (OH) D and PTH were measured by radioimmunoassay (Diasorin, Stillwater, MN, USA) and electrochemiluminescence assay (Roche diagnostics, GMDH-Manheim, Germany), respectively. BMD at the anteroposterior lumbar spine (L1-L4), femur (total hip), and forearm (33% radius) was measured using the Hologic discovery dual-energy X-ray absorptiometry system (Hologic Inc., Bedford, MA, USA) according to standard protocol. Results were calculated both in g/cm² and T-score. T-score between -1 and -2.5 SD. at any measured site was defined as osteopenia, and values below -2.5 SD. as osteoporosis.

Statistical analysis was carried out using software SPSS for windows version 20.0 (SPSS, Inc., Chicago, IL, USA). Data were presented as mean \pm SD or number (%) unless specified. All parametric data were analyzed by independent student's *t*-test. All nonparametric data were analyzed by Mann-Whitney's test. BMD was adjusted for age and body mass index (BMI) and mean BMD was compared using analysis of covariance test. *P* < 0.05 was considered statistically significant.

RESULTS

The cases included 15 women, 13 with simple virilizing and 2 with salt-wasting CAH. The mean age of cases was 27.5 \pm 6.2 years while that of the controls was 27.2 \pm 5.2 years. The period of steroid intake varied from 6 months to 28 years.

None of the patients had history of fracture. The mean serum calcium level was 8.6 mg/dL (normal range: 8.5–10.5 mg/dL), serum phosphorus 2.9 mg/dL (normal range: 2.5–5.5 mg/dL), serum alkaline phosphatase 120 IU/L (normal range: <240), serum DHEAS 186 ng/dL (normal range: 98–340 ng/dL), and mean serum testosterone 0.9 ng/ml (normal range: 0.08–0.48 ng/ml). The mean PTH was 76.29 pg/ml (normal range: 10–65 pg/mL) and mean 25 hydroxy Vitamin D was 9.8 ng/ml (reference range: <10 ng/dL - deficient, 10–30 ng/dL insufficient, >30 ng/dL sufficient). The age, BMI, BMD at hip, lumbar spine, and forearm of the CAH patients are shown in Table 1.

The most commonly used drug was dexamethasone which was used by 14 out of 15 cases. One case had been managed on prednisolone alone. Among the cases managed with dexamethasone, six cases received prednisolone and five received hydrocortisone for varying periods during the course of the disease. Exact data on doses of steroids used in these cases was not available since that was to be obtained from patient records which were not available in few patients. Being a disease for which patients had been on steroids for long, (many since childhood) patients did not remember the exact period of default.

The mean age and BMI of patients and controls were comparable [Table 2]. Among controls, the mean BMD at hip, spine and for arm was 0.92 \pm 0.07, 1.02 \pm 0.08, and 0.56 \pm 0.04 g/cm² respectively. The T-score at the hip, spine and for arm were -0.9 (-1.8, 0.5), -0.7 (-2.2, 0.7) and -0.4 (-2.4, 2.1), respectively.

Among cases, the mean BMD at the hip was 0.84 \pm 0.09 g/cm² which were significantly lower when compared to healthy controls. BMD at spine among cases was lower (0.96 \pm 0.09 g/cm²) than among controls (1.02 \pm 0.08 g/cm²). BMD at forearm was not significantly different between cases and controls [Table 3]. The median T-scores were -0.9 and -0.7 at the hip and lumbar spine, respectively. Osteopenia was noted in 4 out of 15 CAH patients [Table 1].

After adjusting for age and BMI, BMD in CAH was significantly lower at the hip (*P* = 0.039), low at the spine

Table 1: Characteristics of CAH cases

Patient number	Age	SV/SW	BMI (kg/m ²)	BMD hip (g/cm ²)	T-score hip	BMD spine (g/cm ²)	T-score spine	BMD forearm (g/cm ²)	T-score forearm
1	30	SV	23.8	0.717	-1.8	0.933	-1	0.479	-1.7
2	32	SV	27.7	0.808	-1.1	0.885	-1.5	0.61	0.9
3	29	SV	23.1	0.835	-0.9	0.824	-2	0.607	0.8
4	28	SV	21.8	0.923	-0.92	0.965	-0.96	0.669	2.1
5	24	SV	34.7	0.93	-0.1	1.037	-0.1	0.561	-0.1
6	22	SW	26.8	0.83	-0.9	0.85	-2.2	0.443	-2.4
7	18	SV	36.1	0.584	-0.6	1.006	-0.4	0.494	-1.4
8	30	SV	37.3	0.836	-0.83	1.069	0.2	0.650	-0.65
9	30	SV	28	0.865	-0.6	0.981	-0.6	0.506	-1.1
10	25	SV	29.3	0.880	-0.88	0.927	-0.92	0.646	1.6
11	18	SV	19.04	0.840	-0.84	0.923	-0.92	0.533	-0.53
12	40	SV	33.26	0.883	-0.88	1.128	0.7	0.581	0.9
13	36	SV	29.2	0.812	-0.81	0.915	-0.91	0.615	-0.61
14	21	SV	29.13	0.999	0.5	1.123	0.7	0.565	-0.56
15	29	SW	35.13	0.924	-0.92	0.878	-0.87	0.924	-0.92

BMI: Body mass index, BMD: Bone mineral density, CAH: Congenital adrenal hyperplasia, SW: Salt wasting, SV: Simple virilism

Table 2: Comparison of mean BMD and T-score in CAH and controls

Characteristics	Mean±SD		P
	CAH patients (n=15)	Control (n=12)	
Age	27.5±6.2	27.2±5.2	0.895
BMI	28.93±5.5	27.8±4.9	0.566
BMD hip (g/cm ²)	0.84±0.09	0.92±0.07	0.029
T-score hip median (minimum, maximum)	-0.9 (-1.8, 0.5)	0.0 (-1, 0.9)	0.003
BMD spine (g/cm ²)	0.96±0.09	1.02±0.08	0.10
T-score spine median (minimum, maximum)	-0.7 (-2.2, 0.7)	-0.35 (-1.3, 1.5)	0.20
BMD forearm (g/cm ²)	0.59±0.11	0.56±0.04	0.29
T-score forearm median (minimum, maximum)	-0.4 (-2.4, 2.1)	0 (-1, 1.5)	0.36

BMI: Body mass index, SD: Standard deviation, BMD: Bone mineral density, CAH: Congenital adrenal hyperplasia

Table 3: Age and BMI adjusted mean BMD at hip, lumbar spine and forearm in CAH and control subjects

Variable	Adjusted mean±SE		P
	Healthy	Disease	
BMD hip	0.92±0.03	0.85±0.02	0.039
BMD spine	1.03±0.03	0.96±0.02	0.057
BMD forearm	0.56±0.03	0.59±0.02	0.351

BMI: Body mass index, SE: Standard error, BMD: Bone mineral density, CAH: Congenital adrenal hyperplasia

(approaching significance; $P = 0.057$) and not different from controls at forearm [Table 3].

DISCUSSION

Our study revealed significantly lower BMD at hip in CAH subjects as compared to healthy controls. The mean BMD at the spine in CAH patients was also lower than healthy controls, almost reaching the level of significance ($P = 0.057$), [Table 3]. However, BMD at forearm was not

different from controls. There was no history of fracture in any of the CAH patients.

Several initial studies of BMD in CAH patients did not report significantly lower BMD compared to controls.^[1-3] Both classical and nonclassical CAH have been reported to have BMD similar to controls after adjusting for confounding variables.^[4] It was proposed that low dose glucocorticoids used in CAH may not predispose to low BMD. The elevated androgens typically present in these patients have a protective effect on BMD. Inhibitory effect of corticosteroid therapy on bone formation could be counteracted by estrogen's effect on the RANK-L/osteoprotegerin system reducing bone resorption.^[5] A study comparing BMD in CAH and central precocious puberty found higher BMD in CAH (after adjusting for bone age) thus suggesting that adrenal androgens either directly or by conversion to estrogens are important determinants of BMD.^[6]

Interestingly, one of these studies showed a reduction in bone turnover markers such as serum osteocalcin, bone alkaline phosphatase, tartrate-resistant acid phosphatase, and urinary cross-linked N-telopeptides of type I collagen despite no significant decline in BMD.^[7] It is plausible that such a biochemical profile would eventually lead to reduced BMD and due to a small sample size, the effect was probably missed.

However, more recent reports have shown low BMD in CAH cases. In a study of 61 female patients with CAH due to 21 hydroxylase deficiency with age ranging from 18 to 63 years, total body, lumbar spine, and femoral neck BMD were lower as compared to matched controls. In that study, the mean age of patients was much more than in our study. This might suggest that patients, who have

been taking corticosteroids for a longer period of time and thereby having a larger cumulative dose, are at increased risk of osteopenia. This is evident from the point that among patients younger than 30 years, 48% were osteopenic versus 12% in controls ($P < 0.009$). On the other hand, in patients 30 years or older, 73% were osteopenic or osteoporotic versus 21% in controls ($P < 0.001$). More fractures were reported in patients than controls. The mean glucocorticoid dose in hydrocortisone equivalents was 16.9 ± 0.9 mg/m².^[8]

The mean age of CAH in our study is lower than studies which show higher fracture rates in CAH. In our study, the mean age of patients was 27.5 ± 6.2 years. Patient group had significantly lower BMD at the hip while BMD at spine was also low. 26.6% of our patients were osteopenic. No fractures occurred in our cases.

In another study of 45 adults with CAH out of which 36 were females, 55% patients had decreased BMD at the femoral neck and/or at the lumbar spine. Subjects with osteopenia had a significantly lower BMI and received higher hydrocortisone dose than those with normal BMD.^[9]

In a recent study of eighty CAH adults (47 classic and 33 nonclassic), lower BMD was noted at all sites. Classic CAH had significantly lower BMD than nonclassic CAH. This difference was most apparent in forearm BMD.^[10] Patients with classic compared to nonclassic CAH, had higher 17-OHP, lower DHEAS, and higher nontraumatic fracture rate. Higher DHEAS was independently associated with higher BMD at the spine, radius, and whole body. Authors of this study suggest that lower DHEAS in classical CAH may be associated with weak cortical bone independent of glucocorticoid exposure.

We did not observe a reduction in BMD at forearm. This could possibly represent a protective effect of adrenal androgens. In our study, mean testosterone was 0.9 ng/ml (normal range: 0.08–0.48) and mean serum DHEAS level was 186 ng/ml (normal for this age 98–340 ng/ml).

In another study, salt wasting CAH was associated with greater risk of low BMD in adult females as compared to simple virilizing and nonclassic CAH. Over suppression of adrenal androgens increased the risk for low BMD.^[11] Our CAH cases had a slightly higher mean testosterone (0.9 ng/ml; normal range: 0.08–0.48 ng/ml).

Majority of our patients had Vitamin D in deficient range. Mean 25 hydroxy Vitamin D was 9.8 ng/ml. Vitamin D deficiency is known to be associated with low BMD. This could be a contributing factor to low BMD in our patients.

Low BMD has been reported in a study of 30 male CAH subjects of age ranging from 19 to 67 years with mean age of 36.5 years. Osteoporosis/osteopenia was present in 81% cases. All skeletal sites were affected when compared to healthy matched controls. The null genotype group and use of prednisolone were associated with worse BMD. Patients with poor control had higher femoral neck BMD. There was no change in fracture frequency.^[12]

In studies in children with CAH, low BMD at lumbar spine and hip have been reported. Poor control, prednisolone use, use of hydrocortisone doses more than 20 mg/m², longer duration, low 25 hydroxy Vitamin D, and higher 17-OHP levels were all associated with low BMD.^[13-15]

In another study, the use of dexamethasone did not by itself increase the risk of low BMD as long as the glucocorticoid dose in hydrocortisone equivalents remained the same.^[16] Total cumulative glucocorticoid dose was an important factor for low BMD in both classic and nonclassic CAH patients.^[17]

There are multiple factors which affect the BMD in CAH. These discrepancies in studies on BMD in CAH could be due to differences in age of patients, type and severity of enzyme deficiencies, and different therapeutic regimes and their duration.

Dexamethasone was the predominant steroid used in our patients. A major limitation of our study is that since data on intake of steroids was collected retrospectively, patient record and prescriptions alone did not confirm steroid intake (especially in simple virilizing CAH who were not sick without steroids). Majority of patients, i.e., 13 out of 15 were simple virilizing and admitted they did not remember how long they had not taken medicine intermittently. Therefore, total dose of steroid received could not be ascertained with surety. Thus, hydrocortisone equivalent doses are not available, and its impact cannot be assessed. Similarly, a single time testosterone and DHEAS level cannot be correlated to the BMD as it will vary with time depending upon a amount of steroids treatment taken. Therefore, we could not correlate the determinants of BMD.

CONCLUSIONS

Our study showed reduced BMD at the hip (significant) and spine (reaching significance) in adult female CAH cases as compared to healthy controls. The forearm BMD was not significantly different. There was no increase in fracture frequency.

Monitoring of bone health is important in CAH women as they have low BMD. Glucocorticoid doses should be optimized, monitored, and adequate Vitamin D prophylaxis and treatment instituted to make patients Vitamin D replete.

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Conflicts of interest

There are no conflicts of interest.

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