Sexual Difference in Bone Geometry of Adult Patients with Classical Congenital Adrenal Hyperplasia: Data Using Peripheral Quantitative Computed Tomography

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Key Words
Bone geometry · Congenital adrenal hyperplasia · Androgens · Periosteal bone apposition · Glucocorticoids · Osteoporosis

Abstract
Background/Aims: Glucocorticoid treatment may influence bone and muscle development in patients with congenital adrenal hyperplasia (CAH). This study evaluated bone mineral density (BMD), bone geometry and muscle mass. Methods: 73 adult patients with classical CAH were followed. BMD, bone geometry and muscle mass were measured using peripheral quantitative computed tomography (pQCT). Glucocorticoid-equivalent doses throughout life were calculated and at the time pQCT androgen levels were measured. Results: In males the mean standard deviation (SD) score for trabecular BMD (–0.33 ± 0.71) was reduced, whereas mean cortical BMD (1.05 ± 1.11) was elevated. Mean total (0.86 ± 1.12) and medullary cross-sectional area (CSA; 1.12 ± 1.17) were significantly increased (p < 0.001). In all patients SD scores for cortical thickness (–0.65 ± 0.91) and muscle CSA (–0.83 ± 0.91) were reduced. Treatment duration was associated with lower trabecular BMD in males (r = –0.63, p < 0.001). Suppressed androgens and simple virilizing CAH had an adverse effect on the muscle CSA SD score (OR 0.58 and 0.46, respectively, p < 0.05). Conclusion: There was a sexual difference with enlarged total and medullary CSA in females, whereas in males trabecular BMD was reduced and cortical BMD elevated. Cortical thickness and muscle CSA were reduced in all CAH patients with a possible long-term impact on bone development and stability. Monitoring of bone and muscle development might be warranted.

Introduction
Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders resulting from deficiency of one of the five enzymes required for cortisol synthesis in the adrenal cortex. 21-Hydroxylase deficiency is the most frequent cause, accounting for more than 90% of all CAH cases. The majority of patients have a severe enzyme deficiency that results in the salt wasting (SW) form with insufficient aldosterone and cortisol biosynthesis. The result of a less severe deficiency is the simple virilizing (SV) form with insufficient production of cortisol. Patients with 21-hydroxylase deficiency require long-term glucocorticoid (GC) treatment. Most patients need the addi-
tion of mineralocorticoids. GCs both replace the deficient cortisol and reduce the overstimulation of the adrenal cortex [1]. It is quite difficult to reduce excess androgen without giving higher GC doses [2]. Finding the balance between too much and too little GC treatment is especially difficult because current available GCs do not allow to replicate the physiological circadian rhythm of cortisol secretion [3].

Evidence exists regarding the potential impact of long-term GC treatment on bone mineral density (BMD), bone geometry and muscle development in adults with CAH [4]. Chronic GC therapy is a known risk factor for osteoporosis [5]. On the other hand, androgens may be osteoprotective. The osteoblastic effect of androgens is thought to be mediated by estrogen receptors with stimulation of bone formation [6, 7]. In patients with CAH, published data are conflicting with BMD values being reported as unachanged, elevated or reduced [8–10]. A wide range of age at investigation, heterogeneous groups including classical and non-classical forms, variable GC dose and form, and inclusion of pre- and postpubertal patients might explain in part the differences between studies [8, 11, 12].

Most studies on BMD in CAH used dual-energy X-ray absorptiometry (DXA) measurements [4]. However, since the densitometric data obtained by DXA are greatly influenced by bone size, the height and weight of the subjects must be considered. This is an important issue as CAH patients have a final height at the lower limit of normal [13]. Peripheral quantitative computed tomography (pQCT) images a cross-sectional view of the limb and provides volumetric, three-dimensional assessment of the structural (BMD) and geometric properties (bone size) of the appendicular skeleton – information which is not provided by DXA. A further advantage of pQCT is its ability to measure the muscle cross-sectional area (CSA) of the limb.

The cohort consisted of adolescent and adult male and female patients with classical CAH. Our objective was to study the impact of chronic GC treatment on bone mass, density, geometry and the muscle-bone relation at the radius using pQCT.

**Subjects and Methods**

We followed 73 patients (36 female) born between 1966 and 1992 with 21-hydroxylase deficiency continuously from infancy until adulthood in our tertiary health care center (Division of Endocrinology, University Children’s Hospital of Munich). The diagnosis of classical CAH was based on both clinical symptoms and signs and on hormonal analysis and was confirmed by subsequent comprehensive genotyping [14]. At the time of diagnosis, newborn screening for CAH was not yet available. 41 (20 female) patients had SW CAH and 32 (16 female) had the SV form. Patients with additional diseases possibly affecting bone development were not included in this cross-sectional study (2 patients with seizure and anticonvulsive treatment). All patients had received hydrocortisone (HC) three times daily for GC replacement during their growth period with the exception of 2 who were treated with prednisone. Thereafter, some switched to longer-acting GCs [dexamethasone in 3 (1 female), prednisone in 28 (16 female)]. GC doses were converted to cortisol equivalents using growth-retarding equivalents (80 mg HC = 16 mg prednisone = 1 mg dexamethasone) [15]. Mean daily GC doses per square meter of body surface area were analyzed at start of puberty, at final height and in adolescent/adulthood at the time of pQCT measurement. pQCT measurement was performed between 2002 and 2010 in all adolescent and adult patients before transition to the adult clinic.

Anthropometric data were compared with the cross-sectional growth data of Brandt and Reinken [16]. The pQCT results were compared with data of adult participants of the Donald study or their parents of similar age range (15.0–9.9 years) measured with identical methodology [17, 18]. Additionally, we used height-specific reference data from the same population.

Height was measured in the standing position to the nearest 1 mm using a digital telescopic wall-mounted stadiometer (Ulm Stadiometer; Prof. E. Heinze, Ulm, Germany). Weight was determined to the nearest 0.1 kg using an electronic scale (Seca 753 E; Vogel & Hanke, Hamburg, Germany) with the patients clothed in underwear. Forearm length was measured at the non-dominant forearm as the distance between the ulnar styloid process and the olecranon using a caliper. At start of puberty, defined by Tanner stage B2 in females and testicular volume >3 ml in males [19], bone age was determined on an X-ray of the left hand and wrist by the method of Greulich and Pyle [20].

**Peripheral Quantitative Computed Tomography**

Two sites of the non-dominant radius were analyzed by pQCT (XCT 2000 Scanner; Stratec, Inc., Pforzheim, Germany), the distal metaphysis (‘4% site’) and the proximal diaphysis (‘65% site’) as described before [17, 21]. The measurement was performed on the radius whose distance to the radial articular surface corresponded to 4 and 65% of forearm length. At both sites a 2-mm-thick single tomographic slice was sampled at a voxel size of 0.4 mm. Image processing and calculation of numerical values was done using the manufacturer’s version 5.40 software package (Stratec, Inc.).

At the distal radius (metaphyseal site) trabecular BMD, at the proximal radius (diaphyseal site) cortical BMD, bone mineral content (BMC), total CSA, cortical CSA and cortical thickness were measured. Further, muscle CSA was calculated by the manufacturer’s software.

**Endocrine and Metabolic Assessment**

At the time of bone evaluation a routine blood analysis (blood cell count, electrolytes, and liver and renal function tests) was obtained. Blood samples were taken in the morning in all subjects. 17-Hydroxyprogesterone (17-OHP) was assayed by an enzyme immunoassay (IBL, Hamburg, Germany) and androstenedione and testosterone by commercial enzyme-labeled immunometric chemiluminescence assay (Immulite; Siemens, Eschborn, Germany)
Table 1. Auxology, medication and serological data in adult CAH patients divided by sex and subtype

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Females (n = 36)</th>
<th>Males (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SW (n = 20)</td>
<td>SV (n = 16)</td>
</tr>
<tr>
<td></td>
<td>SW (n = 21)</td>
<td>SV (n = 16)</td>
</tr>
<tr>
<td>Age at investigation, years</td>
<td>20.7 (16.7–36.4)</td>
<td>30.4 (16.2–43.7)(^a)</td>
</tr>
<tr>
<td>Age at diagnosis, years</td>
<td>0.19±0.09</td>
<td>1.03±1.66(^c)</td>
</tr>
<tr>
<td>Final height, cm</td>
<td>161.70±4.86</td>
<td>157.50±7.54(^a)</td>
</tr>
<tr>
<td>Final height SD score</td>
<td>–0.45±0.84(^b)</td>
<td>–1.35±1.29(^b)</td>
</tr>
<tr>
<td>BA advanced at puberty start, years</td>
<td>0.09±0.3</td>
<td>0.55±0.52(^a)</td>
</tr>
<tr>
<td>Age at menarche, years</td>
<td>13.82±1.64</td>
<td>13.79±2.11</td>
</tr>
<tr>
<td>HC-E dose at puberty start</td>
<td>15.19±3.61</td>
<td>19.39±5.32(^a)</td>
</tr>
<tr>
<td>HC-E at FH</td>
<td>16.75±4.25</td>
<td>19.84±4.19</td>
</tr>
<tr>
<td>HC-E at present</td>
<td>17.43±5.10</td>
<td>18.00±4.46</td>
</tr>
<tr>
<td>BMI SD score</td>
<td>0.79±1.08(^b)</td>
<td>0.76±1.87(^b)</td>
</tr>
<tr>
<td>17-OHP, nmol/l</td>
<td>6.6 (1.21–297)</td>
<td>7.3 (0.42–248)</td>
</tr>
<tr>
<td>Androstenedione, nmol/l</td>
<td>1.86 (0.66–73.5)</td>
<td>1.96 (0.52–73.5)</td>
</tr>
<tr>
<td>DHEAS, μmol/l</td>
<td>0.20 (0.14–2.70)</td>
<td>0.25 (0.14–2.29)</td>
</tr>
<tr>
<td>Testosterone, nmol/l</td>
<td>1.93 (0.40–13.19)</td>
<td>0.93 (0.52–3.12)</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SD or median (range) as indicated. BA = Bone age. \(^a\) Significant difference between SV and SW CAH (for males and females; Student’s t test or Mann-Whitney U test, if appropriate). \(^b\) Significant difference compared to a healthy reference population (Student’s t test).

Statistical Analysis

Anthropometric measurements of CAH patients were converted into sex-, age- and height-specific standard deviation (SD) scores using the formula: SD score = [(test result for a patient) – (age- or height-specific mean in reference population)]/(age- or height-specific SD in reference population). Results are presented as mean ± SD. Differences from an age-matched healthy population were tested by one-sample t test of the mean SD score against zero. For between-group comparisons (SW vs. SV, female vs. male) we used Student’s t test and in case of non-normally distributed variables the non-parametric Mann-Whitney U test. Correlations between variables were determined by Pearson’s method.

We performed a linear regression analysis to evaluate the associations between different bone parameters such as trabecular BMD, cortical BMD, total bone CSA, cortical thickness and muscle CSA (SD scores) (separate dependent variables) and body mass index (BMI), final height SD score, HC-equivalent dose per square meter body surface area (at start of puberty, at final height and at present), and the binary variables diagnosis (SW = 0 vs. SV = 1) and suppressed adrenal androgens (suppressed = 0 vs. not suppressed = 1) (predictors), additionally adjusted for sex and age. Backward variable selection was also applied based on the Akaike Information Criterion [22].

Throughout the level of significance for each test was set to 0.05. Calculations were performed using the statistical package SPSS for Windows (version 14.0; SPSS, Inc., Chicago, Ill., USA) and R 2.12 (http://cran.r-project.org). The study protocol was approved by the Ethics Committee of Ludwig Maximilians University, Munich, and by the Federal Office for Radiation Protection. Informed consent was obtained from all patients and/or their parents.

Results

Auxological Data and Medication

Patients with SW CAH were diagnosed early at a mean age of 0.07±0.19 years (range 0.0–0.5, median 0), whereas patients with the SV form were diagnosed at a mean age of 1.96±1.95 years (range 0.0–6.0, median 1.5). None of the patients had suffered from adrenal crisis once SW CAH was diagnosed. Table 1 summarizes the auxological data of the study population divided by sex and type of CAH.

Females with SV CAH were significantly older than females with SW CAH (p = 0.004). Mean final height was 159.9 ± 6.5 cm (–0.85 ± 1.14 SDS) in females, those with SW being significantly taller (p = 0.017). Mean final height in males was 170.1 ± 6.8 cm (–1.08 ± 0.99). There was no significant height difference between male SW and SV. BMI SD score was significantly higher than in the
reference population in all patients apart from males with SV CAH. Bone age at start of puberty was comparable in male (both groups) and female SV with about +0.5 years advanced. However, bone age was almost identical with chronological age in female SW. In addition, all patients had entered and completed puberty at a normal age range. Females had regular menses with 4 of them being on contraceptives, and boys had a mean testicular volume of 18 ± 2.3 ml with normal adult plasma testosterone values.

**Biochemical Evaluation**

Considering the whole group of CAH patients, the underlying disease was well controlled in the majority of patients, as indicated by the slightly advanced bone age at start of puberty, final height and laboratory parameters. DHEAS concentrations were consistently below normal for age, androstenedione levels mostly within the normal range, whereas 17-OHP levels were significantly elevated in comparison to the reference data but within the accepted range of up to 30 nmol/l in the majority of patients. In a subgroup analysis, 17 patients seem to be overtreated with a combination of suppressed DHEAS levels (≤0.14 μmol/l), 17-OHP levels <5.4 nmol/l as well as low androstenedione values <3.5 nmol/l. In 15 patients, 17-OHP levels were >30 nmol/l combined with elevated androgen levels possibly due to a too low dose or a lack of compliance.

**BMD and Bone Geometry Results**

In male CAH patients there was a significant reduction in trabecular BMD SD score (−0.33 ± 0.71), whereas cortical BMD SD score (1.05 ± 1.11) was elevated. Total CSA SD score was normal (−0.10 ± 0.93) and medullary cavity SD score was slightly elevated (0.21 ± 0.71, p = 0.081), therefore SD scores of cortical CSA (−0.49 ± 1.17) and cortical thickness (−0.54 ± 0.88) were significantly reduced (p = 0.016 and 0.001, respectively) (fig. 1). Muscle CSA SD score (−0.87 ± 0.78) was reduced (p < 0.001), also after adjustment for height (−0.64 ± 0.43, p < 0.05). There was a difference in muscle CSA between male subtype of CAH with significantly higher values in SV (p = 0.05; table 2).

In female patients, BMD parameters (trabecular, cortical) were within the normal range, total (0.86 ± 1.12) and medullary CSA SD score (1.12 ± 1.17) were significantly higher values in SV (p = 0.05; table 2).

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**Table 2. BMD and bone geometry parameters in adult CAH patients divided by sex and subtype**

<table>
<thead>
<tr>
<th>Parameters (SD scores)</th>
<th>Females (n = 36)</th>
<th>Males (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SW (n = 20)</td>
<td>SV (n = 16)</td>
</tr>
<tr>
<td>Trabecular BMD</td>
<td>−0.24 ± 0.74</td>
<td>−0.09 ± 0.94</td>
</tr>
<tr>
<td>Cortical BMD</td>
<td>0.18 ± 1.13</td>
<td>0.07 ± 1.18</td>
</tr>
<tr>
<td>Total CSA</td>
<td>0.94 ± 1.36&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.75 ± 1.07&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Medullary CSA</td>
<td>1.12 ± 1.17&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.11 ± 1.21&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cortical CSA</td>
<td>0.16 ± 1.17</td>
<td>−0.30 ± 1.19</td>
</tr>
<tr>
<td>Cortical thickness</td>
<td>−0.64 ± 0.82&lt;sup&gt;a&lt;/sup&gt;</td>
<td>−0.93 ± 1.08&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>BMC</td>
<td>0.03 ± 1.32</td>
<td>−0.31 ± 1.22</td>
</tr>
<tr>
<td>Muscle CSA</td>
<td>−0.82 ± 1.02&lt;sup&gt;a&lt;/sup&gt;</td>
<td>−0.76 ± 1.08&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SD. <sup>a</sup> Significant difference between CAH patients and a healthy reference population, p < 0.05. <sup>b</sup> Significant difference between CAH subtype within sex groups, p < 0.05.

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**Fig. 1.** Schematic, cross-sectional view of the appendicular skeleton in male and female CAH adults: the result of an enlarged medullary cavity is a smaller cortical thickness. In females, total CSA of the bone is larger in relation to a healthy reference population (left side). In males, cortical BMD is elevated indicated by a reduced number of points within the cortex (less porosity).
larger (<0.001) than in the reference population, with the
consequence of a reduced cortical thickness (–0.77 ± 0.94,
p < 0.001) (fig. 1). As in male patients the muscle CSA SD
score was reduced (–0.79 ± 1.03, p < 0.001).

Relationship between BMD/Bone Geometry and
Other Parameters
In the whole patient population no significant influ-
ence on bone parameters by present HC-equivalent dose,
dose at onset of puberty or at the age near final height was
detectable. When we built groups using a cut-off level for
HC-equivalent dose at the different time points (onset of
puberty, at final height and at present) of 17 mg/m², as
recommended in the literature [2], again no significant
differences were detectable. 23 patients were overweight
and had a BMI above the 90th percentile. No significant
difference with regard to bone parameters between nor-
mal and overweight patients was observed. The BMI cor-
related with the muscle mass in all (r = 0.38 for males and
r = 0.55 for females, p < 0.02), leading to a trend for a
higher muscle mass with increasing BMI. Treatment du-
ration and age at evaluation might play a role. In males,
duration of GC treatment was negatively associated with
trabecular BMD (r = −0.63, p < 0.001) and BMC (r =
−0.33, p = 0.048), while no association was found in fe-
males (fig. 2).

Some of our patients were considered to be overtreat-
ed with androgen levels almost suppressed. Performing a
comparison between overtreated (n = 17), normal treated
(n = 43) and undertreated or less compliant (n = 15) pa-
tients, those with overtreatment had the smallest muscle
CSA (−1.30 ± 0.69 vs. −0.52 ± 0.66 for undertreated, p <
0.001). Patients with serological signs of undertreatment
were more prone to be treated by HC (74%), whereas in
normal or overtreated CAH patients, 40 and 50%, respec-
tively, were on long-acting GC (prednisone or dexameth-
asone).

In multiple regression models (table 3) adjusted for
age and sex, HC-equivalent dose per square meter at final
height was positively associated with trabecular BMD SD
score (β = 0.07; 95% CI 0.00, 0.13) but negatively with
cortical thickness (β = −0.07; 95% CI −0.13, −0.01) after
backward selection. The present HC-equivalent dose did
not show a significant influence on bone density or geom-
etry (data not shown). Lower muscle CSA SD score was
associated negatively with the diagnosis of SV (β = −0.46;
95% CI −0.81, −0.11), but positively with BMI (β = 0.13;
95% CI 0.09, 0.17) and suppressed androgens (β = 0.57;
95% CI 0.12, 1.03). There were no significant associations
between cortical BMD and total CSA and any of the pre-
dictors (data not shown).

Discussion
To the best of our knowledge this is the first study us-
ing pQCT for the evaluation of bone density and geom-
etry in classical CAH patients. The most striking findings
of this study were reduced cortical thickness and muscle CSA in all patients. In females bone geometry was altered with enlarged total and medullary CSA, whereas in males trabecular BMD was reduced and cortical BMD elevated.

There are a number of studies in the literature that assessed BMD in individuals with CAH with a wide spectrum of results. DXA was the technique mostly used. However, caution is necessary with this technique since it is dependent on bone and body size. CAH adults have a reduced final height and therefore underestimated BMD data might be the consequence of DXA measurement. We therefore used the pQCT method which gives data on real volumetric BMD and bone geometry.

In this population, trabecular BMD appeared to be maintained in female but not in male CAH patients. This is in accordance with previous reports on lower BMD values in males [11, 23]. Further, in male CAH patients cortical BMD was significantly elevated. The reduction in trabecular and elevation in cortical BMD could be the consequence of long-term GC treatment characterized by lower bone turnover [24]. Women with CAH might benefit from the preserving effect of estrogens combined with the additive effect of androgens [25]. In males the elevated adrenal androgens may suppress the hypothalamic-gonadal axis with the result of smaller testes and lower testosterone, thereby influencing bone development [26].

The BMI of CAH patients was significantly higher as in previous studies [13, 23, 27]. BMI also appeared to protect patients with CAH from bone loss. Chakhtoura et al. [23] could show that a higher BMI was associated with a higher bone density in adult patients with CAH. In this study an increase in BMI by 1 point was associated with an increase in muscle mass by 0.13 SD. BMI had no influence on BMD or bone geometry parameters. However, looking at patients below the age of 30 years, there was a significant correlation between BMI and total CSA (r = 0.32) and medullary CSA (r = 0.31).

There seems to be a difference in results with regard to which age group was chosen in the different studies. Disease duration or age is known to be an important confounding factor [28, 29]. In previous studies with a younger patient population (<30 years of age) normal values of trabecular BMD at the spine were described [9, 28, 30, 31]. With increase in age of the population (>30 years of age) lower BMD levels were found [4, 8, 22]. One explanation for this relation might be the cumulative lifelong GC dose [12, 31, 32]. A second explanation might be the higher GC dosing used in infancy in those of older age. Further, in young adults the negative effect of GC on bone could be balanced by the positive effects of androgens [28, 33]. In this study with longer disease duration and therefore higher cumulative GC dose, patients had a lower trabecular BMD and a lower bone mass. In patients with Addison disease, low BMD was found especially in males with low testosterone and in postmenopausal women [34]. This scenario may also apply for older CAH patients.

Cortical thickness was reduced in males and females possibly as a result of increased endosteal bone resorption as a consequence of GC treatment [5]. GC dosing at a single time point as at final height had only a mild influence, e.g. with each increase in HC-equivalent dose at final height of 1 mg/m² a decrease of cortical thickness SD score by 0.07 was associated.

Total and medullary CSA were significantly elevated in female CAH patients, but not in males (apart from a significant elevation of medullary cavity in male SV). In females, bone geometry might be altered in favor of periosteal bone apposition. This could be explained by early influences of androgens on bone development. Androgens enhance osteoblast differentiation and influence osteoclast activity. In both sexes androgens may stimulate periosteal apposition [35]. In males with lower levels of estrogens, periosteal apposition might be upregulated,

### Table 3. Linear regression models for bone parameters: potential predictive factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Trabecular BMD SD score (β, 95% CI)</th>
<th>Cortical BMD SD score (β, 95% CI)</th>
<th>Total CSA SD score (β, 95% CI)</th>
<th>Cortical thickness SD score (β, 95% CI)</th>
<th>Cortical thickness SD score post-BW (β, 95% CI)</th>
<th>Muscle CSA SD score (β, 95% CI)</th>
<th>Muscle CSA SD score post-BW (β, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>0.02 (–0.03, 0.06)</td>
<td>0.03 (–0.02, 0.06)</td>
<td>0.02 (–0.05, 0.11)</td>
<td>0.05 (–0.01, 0.10)</td>
<td></td>
<td>0.13 (0.06, 0.17)</td>
<td>0.13 (0.09, 0.17)</td>
</tr>
<tr>
<td>HCE puberty</td>
<td>0.01 (–0.05, 0.03)</td>
<td>0.00 (–0.07, 0.05)</td>
<td>0.00 (–0.07, 0.05)</td>
<td>0.02 (–0.03, 0.07)</td>
<td></td>
<td>0.04 (0.00, 0.07)</td>
<td></td>
</tr>
<tr>
<td>HCE at FH</td>
<td>0.07 (0.00, 0.13)</td>
<td>0.05 (–0.06, 0.16)</td>
<td>0.02 (–0.08, 0.12)</td>
<td>0.07 (–0.15, 0.01)</td>
<td>–0.07 (–0.13, –0.01)</td>
<td>0.04 (–0.12, 0.01)</td>
<td></td>
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<tr>
<td>Diagnosis</td>
<td>0.21 (–0.59, 0.17)</td>
<td>0.07 (–0.63, 0.55)</td>
<td>0.04 (–0.60, 0.52)</td>
<td>0.09 (–0.35, 0.54)</td>
<td>–0.46 (–0.81, –0.11)</td>
<td>0.04 (–0.21, 0.11)</td>
<td>–0.48 (–0.84, –0.12)</td>
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<tr>
<td>Suppression</td>
<td>0.24 (–0.26, 0.74)</td>
<td>0.07 (–1.37, 0.12)</td>
<td>0.13 (–0.61, 0.87)</td>
<td>0.38 (–0.21, 0.97)</td>
<td></td>
<td>0.57 (0.11, 1.04)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as β (95% CI). Bold values determine significant associations. β = Regression coefficient; FH = final height (expressed as SD score according to Brandt and Reinken [16]); HCE puberty = HC-equivalent dose per square meter at onset of puberty; HCE at FH = HC-equivalent dose per square meter at final height; Diagnosis = SW CAH classified = 0, SV CAH = 1; Suppression = defined as low DHEAS and androstenedione levels at pQCT evaluation (<0); post-BW = selected variables according to backward selection.
whereas in females endogenous estrogens may inhibit periosteal apposition through interaction with IGF-1 [36]. Recent evidence suggests that the higher IGF-1 levels in males may depend on neonatal androgen action [37]. In females with CAH and elevated androgens from early on in life, it is suggestive that androgens are responsible for an elevated total and medullary CSA.

Androgens additionally increase muscle mass and strength [7]. Surprisingly, muscle mass was low in all CAH patients, especially in SV CAH. This may have long-term consequences on bone development since the largest bone loads come from muscle force. Consequently, chronically reduced muscle forces result in a disuse osteopenia.

There was no significant association between BMD, bone geometry and 17-OHP or androstenedione and also no influence of present HC-equivalent dose. However, overtreated patients had the lowest muscle mass, indicating treatment induced sarcopenia. Previous studies could demonstrate the effect of GC overdosing only on BMD in adult CAH [12]. Future studies have to evaluate if a lower dose in infancy and during pubertal years has an impact on muscle and bone development. In general, overtreatment with GC has to be avoided.

An advantage of our study is a regular follow-up of adolescent and adult patients with classical CAH in a single outpatient clinic treated similarly. Appropriateness of their GC dose was checked based on their steroid serum and urine concentration, growth and development. A weakness is its cross-sectional design and a relatively small sample resulting in small numbers in the four subgroups and a heterogeneous age distribution. No data on physical activity and diet were collected. Further, especially older patients were treated with higher doses in infancy and throughout childhood that might have had an influence on bone development. Serological and morphological measures recorded represent only one window in time. Patient’s compliance and response to medication may greatly vary over time.

To conclude, the population at particular risk might be male patients with a long GC treatment duration, a lower BMI, low muscle mass and suppressed androgens. In females, estrogens and androgens may have an additive effect on bone development leading to bone expansion, at least in the younger age group. We may suppose that with age CAH patients develop lower BMD. Physicians should bear in mind the potential consequences of GC on bone by adjusting the treatment and improve clinical and laboratory surveillance from infancy on [23]. It is important to use the lowest possible GC dose. Lifelong proficient medical care for CAH patients should be assured. Follow-up BMD measurements in adults are justified, even if a normal BMD is found in early adulthood [29].

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References


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