CLINICAL STUDY

Does an altered leptin axis play a role in obesity among children and adolescents with classical congenital adrenal hyperplasia due to 21-hydroxylase deficiency?

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Abstract

Objectives: Congenital adrenal hyperplasia (CAH) patients are at a higher risk to develop obesity. The role of leptin in CAH is still controversial. Our study aimed to evaluate serum levels of leptin, the soluble leptin receptor (sOB-R), and the sOB-R: leptin molar ratios in a cohort of CAH children and adolescents, and their associations with clinical and metabolic parameters.

Methods: We studied 51 CAH patients, aged 5.6–19.6 years (median 11.8, n = 30 females) cross-sectionally. All patients had genetically proven CAH and received standard steroid substitution therapy. Blood specimens were taken after overnight fasting between 0800 and 1000 h. For the analyses of leptin and sOB-R, matched pairs were built with healthy Caucasian patients for sex, Tanner stage (TS), chronologic age (CA), and body mass index (BMI).

Results: BMI and SDS were significantly elevated compared with the reference population. Leptin levels were not different between matched pairs, whereas sOB-R levels were significantly lower in CAH. Consequently, the sOB-R: leptin molar ratios were significantly decreased in CAH. Correlation analyses in CAH patients revealed significant relationship between leptin and CA, TS, BMI, and homeostasis model assessment of insulin resistance. Similar results were obtained for the matched control group. For sOB-R, we found no significant correlation for CA, TS, or BMI in CAH, but we did in the controls. There were significant correlations for androgens within the CAH group. Additional analyses revealed no correlation with steroid medication or metabolic control.

Conclusions: Our data show that an altered leptin axis with normal serum leptin concentrations but decreased sOB-R serum levels may contribute to the increased risk of overweight and obesity in CAH.

Introduction

Patients with the classical form of congenital adrenal hyperplasia due to 21-hydroxylase deficiency (CAH) show signs of androgen excess with or without salt wasting (1, 2). Recent studies provide evidence that these patients are at high risk of becoming overweight and obese. Approximately half of the patients are overweight and up to 16% are obese (3, 4). Both high levels of androgens and obesity interfere with the leptin axis (5).

There are contradictory reports on the role of leptin in CAH. Two papers reported elevated serum leptin levels to be contributable to CAH-associated complications (6, 7), whereas we have shown that the leptin elevations are dependent solely on known factors, i.e., body mass index (BMI), sex, and age (4).

Recent research attributed leptin to be part of the dynamic equilibrium with the soluble leptin receptor (sOB-R) that represents the main leptin-binding activity in human blood (8). This protein circulates in two different N-glycosylated isoforms as a dimer or in an oligomerized state. The molar ratio of complexes of leptin with sOB-R is 1:1 (9). The functional soluble receptor isoform potentially modulates steady-state leptin levels by binding free leptin in the circulation and consequently preventing the hormone from degradation and clearance (10, 11). Additionally, there is evidence that an excess of sOB-R can suppress leptin action in a cell model. Therefore, high serum levels of sOB-R may play a role in the development or progression for at least partial leptin resistance in peripheral tissues (12, 13).

Recently, Hahn et al. found decreased sOB-R levels in women with polycystic ovary syndrome (PCOS). Therefore, they hypothesized that PCOS per se might cause leptin resistance (14). However, there is still limited
information available about whether the leptin axis in any way contributes to these complications in CAH.

Therefore, the aim of this prospective, single centre, matched-pairs study was to analyze serum leptin, sOB-R, and their molar ratio as an indicator of free, bioactive leptin. We studied potential contributing factors like BMI, medication, and the implications of various laboratory parameters such as serum testosterone (T), 17-hydroxyprogesterone (17-OHP), and 24-h urine pregnanetriol excretion.

**Methods**

**Patients**

We included 51 Caucasian children and adolescents (30 females, 21 males), aged between 5 and 19 years, who presented regularly at our outpatient endocrine unit. All individuals had classical CAH with 21-hydroxylase deficiency (SW: salt wasting, n = 42; SV: simple virilizing, n = 9) and received glucocorticoid substitution therapy with hydrocortisone (HC; n = 38), prednisone (PR; n = 11), or dexamethasone (DX; n = 2). HC was given thrice daily (~50% of the daily dosage in the early morning, 25% at noon, and 25% in the evening), PR was given twice, and DX once daily. The diagnosis was confirmed in all patients with molecular genetic analyses by direct sequencing (n = 3 patients presented with neonatal Addisonian crisis, but had no detectable mutation on the second allele). Forty-nine patients additionally received fludrocortisone (FC; twice daily) due to mineralocorticoid insufficiency. The quality of therapy was monitored during follow-up visits every 3–6 months by clinical presentation and laboratory measurements according to the current guidelines (follow-up at our department: median 10.3 years; range 4.2–19) (15). At the time of the analysis, none of the patients had obvious signs of any acute or chronic disease, nor did they receive any other medication.

**Study design**

The cross-sectional data of all CAH patients was prospectively ascertained during a regular follow-up visit to our outpatient endocrine unit. All patients presented over a 12-month period between July 2004 and June 2005 on a day off school or work, mostly on Fridays. All of them were seen between 0800 and 0900 h, after an overnight fast. The study was approved by our institutional review board. All subjects and parents gave their written informed consent.

Physical examination included the measurement of height and weight, and the assessment of pubertal status Tanner stage (TS). Height SDS were calculated using German references (16). BMI and SDS were calculated adjusted for age and sex according to the current German reference data (17). According to the Childhood Group of the International Obesity Task Force, a BMI over 2.0 SDS was defined as obesity (18, 19).

Ambulatory measurements within the home setting on a couple of days off school or work were undertaken in each patient with a standard oscillometric ABPM device (Mobil-O-Graph, I.E.M., Stolberg, Germany). Further details have been described elsewhere (20).

Equivalent HC dosages (eHC4.30) were calculated for PR and DX (factors 4 and 30 respectively). With respect to recently published data, we alternatively calculated equivalent HC dosages (eHC15.70) by multiplying with factors 15 (PR) and 70 (DX) (21, 22). The estimate of insulin resistance obtained by homeostasis model assessment (HOMA-IR) was calculated and classified by the formula described by Matthews et al. (23). In a subgroup of children (n = 36), bone age was assessed by an experienced observer using the atlas method of Greulich and Pyle, which has been found to be reliable for central European children (24). For evaluation of the current status of skeletal maturation, we calculated the difference between bone age and chronologic age (CA: bone age delay = BA minus CA in years). Fasting blood sampling was performed for monitoring the therapy. Serum or plasma was then separated by centrifugation and stored at −20°C until assay.

**Laboratory methods**

Leptin was measured by a specific ‘in-house’ RIA (25). The sensitivity of the RIA was 0.2 μg/l (2 s.d. of the leptin-free standard matrix, n = 12). The RIA proved to be precise as its intraassay and interassay coefficients of variation were both below 12.5% in the range between 1 and 8 μg/l leptin. sOB-R was measured with a ligand-immunofunctional assay (26). The lowest detectable sOB-R concentration in the assay was calculated to be less than 2 μg/l. Intraassay and interassay coefficients of variation for two control samples were lower than 11.7% (n = 10).

All other serum parameters were measured with commercially available assays. Serum insulin levels were measured by ELISA (Diagnostics Systems Laboratories, Sinsheim, Germany; intra- and interassay CV: < 7%; sensitivity: 0.26 mU/l; conversion factor from mU/l to μg/l: 0.04). Serum levels of active renin were determined by IRMA (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA; Intra- and interassay CV: < 10%; sensitivity: 0.9 ng/l).

Saliva was collected before the morning tablet (0700 h) and stored frozen until measurement. Serum and saliva 17-OHP levels were determined with a commercial RIA (Diagnostics Systems Laboratories; adapted to the use of saliva as sample matrix as previously described (27). Intra- and interassay CV were below 8%; sensitivity was 0.02 μg/l; the conversion factor from μg/l to nmol/l was 3.03).
Levels of pregnanetriol and tetrahydrocortisone in specimens of urine collected during 24 h were simultaneously determined by isotope dilution/gas chromatography-mass spectrometry procedure. Deuterium-labeled analogs of the analytes served as internal standards. Intra- and interassay CV were <6.0%; sensitivity was 10 pg.

**Matched-pairs analysis and statistics**

To analyze serum values of leptin, sOB-R, and leptin: sOB-R, we have built matched pairs (best match) with healthy Caucasian children from a normal representative cohort for sex (exactly), TS, CA (±1 year), and BMI (±2 kg/m²). The 'Leipzig Schoolchildren Project' investigated anthropometric and clinical parameters in 2675 children aged 7.5–18.5 years in 1999–2000 (26). Schools were chosen to cover representative local areas within Leipzig and suburbs (hence social distribution) and an even distribution of school types to establish a representative cohort of German Caucasian children. A careful history and physical exam including anthropometric measurements were obtained in all subjects. The study was approved by the Ethical committee of the University of Leipzig.

Gaussian distribution of the parameters was tested using the D’Agostino-Pearson omnibus normality test ($P > 0.05$). (CA, years), BMI (SDS), skinfold thickness (log(mm)), bone age delay ($\Delta$BA, years), FC dosage ($\mu$g/m² BSA), eHC dosages (log(mg/m² BSA)), serum leptin (log(µg/l)), serum insulin (log(mU/l)) HOMA-IR (1), and serum DHEAS (log(µg/l)) had a Gaussian distribution, whereas (TS, n), skinfold thickness (mm), eHC dosages (mg/m² BSA), and all other laboratory derived variables did not.

To compare each variable between genders, clinical forms (SV and SW), and other subgroups, Mann–Whitney $U$ test was used where appropriate. Different variables within the same subjects or within the matched pairs were compared with the Wilcoxon matched-pairs test. To assess significant deviations from a hypothetical Gaussian distribution, whereas (TS, n), skinfold thickness (mm), and serum levels of the sOB-R were significantly higher for the normal population (expected: 2.27%; $P < 0.0001$) and almost half of the patients ($n = 23$, 45.1%) presented with overweight as defined by a BMI > 90 percentile. There was no difference in age and BMI between genders and clinical form (SW versus SV). Detailed clinical data are shown in Table 1.

As reported previously by our group, mean daytime and night-time systolic blood pressure (BP) levels expressed as SDS for CA and height were significantly elevated (daytime: 0.34 SDS, 0.67 SDS; nighttime: 0.47 SDS, 0.63 SDS, $P < 0.0001$). By contrast, daytime diastolic BP levels were significantly decreased (0.78 SDS, 0.81 SDS, $P < 0.0001$), whereas nighttime diastolic BP was normal (0.13 SDS, 0.11 SDS) (20).

**Leptin axis**

Serum leptin levels were not elevated in CAH patients compared with the matched controls ($P = 0.1874$), whereas serum levels of the sOB-R were significantly lower in CAH patients ($P = 0.0007$). Accordingly, sOB-R: leptin ratios were also lower in CAH than in the controls ($P = 0.0047$) indicating higher levels of ‘free’ serum leptin in CAH patients (Table 2; Fig. 1). Leptin levels and sOB-R: leptin ratios, but not sOB-R levels, were significantly correlated with CA and the progress of puberty (TS) in CAH patients. By contrast, both serum parameters showed significant correlations in the controls (Table 3; Fig. 2). There was no significant difference in any variable of the leptin axis between genders and clinical form (SW versus SV).

**Overweight and obesity**

Similarly, leptin levels and sOB-R:leptin ratios, but not sOB-R levels, were significantly correlated with BMI and skinfold thickness in CAH patients, but all three parameters showed significant correlations with BMI in the controls (Table 3; Fig. 2). BMI was positively correlated with skinfold thickness in CAH patients (mm, $r_s = 0.880$, $P < 0.0001$).

**Results**

**Patient group**

The BMI of the whole group ranged between 2.45 and 3.77 SDS (mean 1.05 ± 1.4 s.d.) and was significantly above 0 SDS ($P < 0.0001$). Thirteen subjects (25.5%; $f = 6$, $m = 7$) had a BMI > 2.0 SDS indicating a significantly higher frequency of obesity in CAH patients than expected for the normal population (expected: 2.27%; $P < 0.0001$) and almost half of the patients ($n = 23$, 45.1%) presented with overweight as defined by a BMI > 90 percentile. There was no difference in age and BMI between genders and clinical form (SW versus SV). Detailed clinical data are shown in Table 1.

In addition, in some normally distributed variables we performed linear and non-linear regression analysis using the best-fit model. Observed and expected frequencies were compared with the $\chi^2$-test. All tests were performed two-tailed and a $P < 0.05$ was considered to be significant. For calculation and presentation, we used GraphPad Prism software version 4.03.

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Insulin resistance and serum androgens

In CAH patients, serum leptin levels and sOB-R:leptin ratios, but not sOB-R levels were also correlated significantly with insulin levels and insulin resistance as estimated by HOMA-IR. By contrast, serum sOB-R levels, but not serum leptin levels, were correlated significantly with serum DHEA sulfate (DHEAS) and testosterone levels (Table 3).

Medication and metabolic control

Standard equivalent HC (eHC4,30) dosages ranged between 5.6 and 29.6 mg/m² (Table 1). Serum leptin

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Table 1 Clinical and laboratory cohort data.

<table>
<thead>
<tr>
<th></th>
<th>CAH (n=51)</th>
<th>Controls (n=51)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Quartiles</td>
<td>Median</td>
</tr>
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<td>Chronologic age (years)</td>
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<td>9.0; 15</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>3.8</td>
<td>12</td>
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<td>Tanner stage (n)</td>
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<td>3; 5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2.8</td>
<td>1.8</td>
<td>2.8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
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<td>18; 28</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>7.0</td>
<td>23</td>
</tr>
<tr>
<td>BMI (SDS)</td>
<td>0.93*</td>
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<td>Skinfold (mm)</td>
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<td>18</td>
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<td>Bone age delay (years)</td>
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<td></td>
<td>1.4†</td>
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<td>eHC4,15 dosage (mg/m²)</td>
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<td>16</td>
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<td>eHC15,70 dosage (mg/m²)</td>
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<td></td>
<td>28</td>
<td>29</td>
<td>na</td>
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<td>FC dosage (µg/m²)</td>
<td>47</td>
<td>32; 56</td>
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<td>46</td>
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<td>HOMA-IR (1)</td>
<td>2.7§</td>
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<td>Serum rennin (ng/l)</td>
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<tr>
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<td>35</td>
<td>28</td>
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<tr>
<td>Serum 17-OHP (µg/l)</td>
<td>2.5</td>
<td>1.1; 5.3</td>
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</tr>
<tr>
<td></td>
<td>8.9</td>
<td>21</td>
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<td>Serum DHEAS (µg/l)</td>
<td>85.0</td>
<td>31.0; 144</td>
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<td></td>
<td>175</td>
<td>264</td>
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<tr>
<td>Serum T (µg/l)</td>
<td>0.11</td>
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<tr>
<td></td>
<td>0.81</td>
<td>1.7</td>
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<tr>
<td>Saliva 17-OHP (µg/l)</td>
<td>0.08</td>
<td>0.04; 0.24</td>
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</tr>
<tr>
<td></td>
<td>0.28</td>
<td>0.78</td>
<td>na</td>
</tr>
<tr>
<td>Urine PT:THE (1)</td>
<td>0.31</td>
<td>0.18; 0.52</td>
<td>na</td>
</tr>
<tr>
<td></td>
<td>0.43</td>
<td>0.39</td>
<td>na</td>
</tr>
</tbody>
</table>

ns, non-significant for P<0.05.

eHC, equivalent hydrocortisone indexed with factors; FC, fludrocortisone; 17-OHP, 17-hydroxyprogesterone; DHEAS, dehydroepiandrosterone sulf ate; T, testosterone; PT, pregnanetriol; THE, tetrahydrocortisone; ns, non-significant for P<0.05; na, not assessed. * Significantly different from 0 (Wilcoxon signed-rank test, P<0.0001). †Significantly different from 0 (one sample t-test, a: P<0.0001). ‡Significantly different from 0 (Wilcoxon signed-rank test, P<0.05). §Significantly different from 2.0 (Wilcoxon signed-rank test, P<0.0001). ¶Significantly different from 2.0 (one sample t-test, P<0.0001).

Table 2 Detailed data of the leptin axis.

<table>
<thead>
<tr>
<th></th>
<th>CAH (n=51)</th>
<th>Controls (n=51)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Quartiles</td>
<td>Median</td>
</tr>
<tr>
<td>Serum leptin (µg/l)</td>
<td>9.5</td>
<td>4.8; 21</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Serum sOB-R (µg/l)</td>
<td>34</td>
<td>29; 40</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>8.6</td>
<td>45</td>
</tr>
<tr>
<td>sOBR:leptin ratio (1)</td>
<td>0.53</td>
<td>0.21; 0.92</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>0.72</td>
<td>0.67</td>
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</table>

ns, non-significant for P<0.05.
and sOB-R levels did not differ between children receiving HC, PR, or DX. Equivalent HC dosage (eHC) and the FC dosage were not correlated with any variable of the leptin axis. There was no significant difference between the subjects with a lower (eHC 4.30 < 15 mg/m², n = 26) or higher (eHC 4.30 > 15 mg/m², n = 25) dosage. In addition, calculations with the alternative equivalent HC (eHC 15.70) dosage revealed the same results.

To estimate the influence of metabolic control at the time of blood sampling, we performed correlation analyses between serum renin, serum 17-OHP, morning saliva 17-OHP, 24-h urine pregnanetriol, 24-h urine pregnanetriol: tetrahydrocortisone ratio (only in patients with HC), and the bone age delay (bone age minus CA in years) and all variables of the leptin axis: there was no correlation regarding any of these parameters.

**Discussion**

Our results from this prospective, cross-sectional matched-pairs study provide evidence that serum levels of total leptin are normal, but those of sOB-R are decreased in children and adolescents with CAH. However, we cannot exclude some bias in this study with respect to the fact that the serum levels of the patients and the controls were measured 5 years apart. As reported previously, the CAH patients were at high risk for overweight and obesity (4).

There are only few data on leptin in CAH patients in the literature. Charmandari et al. reported on a significantly higher BMI together with elevated serum leptin and insulin levels and reduced catecholamine values, in 18 CAH patients compared with healthy controls. They speculate that these hormones are part of a complex process of interfering hormones resulting in a further increase in androgen production (6). In another study, elevated serum leptin levels were reported after the start of glucocorticoid therapy in CAH patients (7). This appeared to be in line with our findings, since we have also measured higher serum leptin levels in our cohort. However, we have concerns with regard to the methods used, since neither the BMI values nor the leptin data were converted into population-based SDS corrected for age and neither sex nor sufficient pairing was performed. After excluding factors contributing to elevated leptin levels, by building matched pairs for population, CA, sex, TS, and BMI, we did not find elevated serum leptin levels in CAH.

Taken into account that sOB-R is the main binding protein of leptin (8), the levels of free, bioactive leptin are elevated. Since leptin specifically signals a negative energy balance, our CAH patients should be lean or at least normal weight individuals. However, about half of them are overweight. Contrary to this concept of the ‘free leptin index’, higher sOB-R concentrations are found in lean compared with obese individuals (28). By this concept, the leptin clearance and degradation from circulation is delayed, as leptin binds to sOB-R, and this increases the concentration of available circulating leptin (10, 13). A twofold or greater increase of sOB-R has been suggested to cause suppression of leptin action or partial peripheral leptin resistance, as found in common obesity (13). As recently reviewed by Venner et al. this supports the hypothesis of sOB-R as a potential reservoir for bioactive leptin. When sOB-R

![Figure 1](https://www.eje-online.org)
concentrations decrease, there would be higher concentrations of liberated leptin and an overall higher than normal circulating leptin concentration in obesity. These results in the significantly elevated leptin to sOB-R: leptin ratio seen in obese individuals. The low sOB-R concentration found in obesity may be related to a stabilizing feedback mechanism trying to reduce the escalating leptin concentrations (29). On the other hand, it is an interesting observation but the physiological significance of this finding is unclear, particularly given that animal models of increased androgen levels, there is evidence for decreased serum levels of sOB-R, even though there was no significant correlation with androgen levels themselves (14). By contrast, a second study on the leptin axis in PCOS showed a negative correlation of sOB-R with DHEAS concentration (r = 0.35) (35). In our cohort, we demonstrated a negative correlation of androgens, testosterone, and DHEAS. There was no difference between boys and girls. We hypothesize that in CAH boys and girls have elevated serum androgen levels over time and consecutively decreased sOB-R levels. In turn, this might contribute to a higher clearance of leptin leading to an increased rate of obesity.

The therapeutic principle in CAH patients is continuous substitution not pharmacologic therapy with steroids (1, 30). It has been shown that short-term administration of glucocorticoids increases leptin secretion (36–39), whereas long-term intrinsic glucocorticoid excess such as in patients with Cushing’s syndrome has no effect on leptin levels (40). Dagogo-Jack et al. demonstrated that a metyrapone-induced
inhibition of cortisol biosynthesis results in hypoleptinemia (41). In our cohort, we did not find any association of the leptin axis with equivalent HC dosage or the used glucocorticoid. However, we could not exclude a dose-independent effect of glucocorticoids. The effectiveness of glucocorticoid substitution therapy, i.e., the metabolic control, over a period of years is not easy to assess. Monitoring serum and urinary laboratory parameters cover only a few days or weeks, while advanced skeletal maturation as an index of poor metabolic control might be more representative over a longer period of time (4). As an additional parameter, we calculated the pregnanetriol: tetrahydrocortisone ratio which has been shown to be less correlated with age than urine pregnanetriol or serum 17-OHP levels (15, 42). In our cohort, we did not find any correlation of the leptin axis with these parameters.

In conclusion, our data are supportive of an altered leptin axis with decreased serum levels of sOB-R in children and adolescents with CAH. Due to their association with serum androgens, tight metabolic monitoring might be one preventive strategy to avoid decreased sOB-R concentrations in addition to a CAH management adapted to current guidelines.

Declaration of interest

T M K Völkl, D Simm, A Körner, W Rascher have nothing to declare.

Funding

W K receives lecture fees from various pharmaceutical companies (less than US $10,000 per 2 years) and has in the past received unrestricted research grants from Pfizer, Novo Nordisk, and Serono. J Kratzsch received lecture fees from various companies (less than US $1000 USD per 2 years). HGD consults for KIGS Germany Advisory Board (Pfizer, less than US $1000 USD per 2 years) and received lecture fees from various companies (less than US $10,000 USD per 2 years).

Acknowledgements

We appreciate the technical assistance of Mrs Jutta Biskupek-Sigwart and the help of our study nurse Mrs Diana Striegel. Previous presentations. Parts of this study were presented at the 88th Annual Meeting of the Endocrine Society (ENDO), 24–27 June, 2006, Boston, MA, and the 45th Annual Meeting of the European Society for Paediatric Endocrinology (ESPE), 30 June–3 July 2006, Rotterdam, The Netherlands.

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Received 26 October 2008
Accepted 1 November 2008