CLINICAL STUDY

Cardiovascular risk, metabolic profile, and body composition in adult males with congenital adrenal hyperplasia due to 21-hydroxylase deficiency

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Abstract

Objective: Lifelong glucocorticoid therapy in patients with congenital adrenal hyperplasia (CAH) or the disease per se may result in increased cardiovascular risk. We therefore investigated cardiovascular and metabolic risk profiles in adult CAH males.

Subjects and methods: We compared CAH males (n = 30), 19–67 years old, with age- and sex-matched controls (n = 32). Subgroups of different ages (<30 years or older) and CYP21A2 genotypes (null, I2splice, and I172N as the mildest mutation) were studied. Anthropometry, fat and lean mass measured by dual-energy X-ray absorptiometry, lipids, liver function tests, homocysteine, lipoprotein-(a), glucose and insulin during an oral glucose tolerance test (OGTT), urine albumin, adrenal hormones, and 24 h ambulatory blood pressure measurements were studied.

Results: CAH males were shorter. Waist/hip ratio and fat mass were higher in older patients and the I172N group. Heart rate was faster in older patients, the I2splice, and I172N groups. Insulin levels were increased during OGTT in all patients and in the I172N group. γ-glutamyl transpeptidase was increased in older patients and in the I172N group. Testosterone was lower in older patients. Homocysteine was lower in younger patients, which may be cardioprotective. The cardiovascular risk seemed higher with hydrocortisone/cortisone acetate than prednisolone. Urinary epinephrine was lower in all groups of patients except in I172N.

Conclusions: Indications of increased risk were found in CAH males ≥30 years old and in the I172N group. In contrast, younger CAH males did not differ from age-matched controls. This is likely to reflect a better management in recent years.

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Introduction

Congenital adrenal hyperplasia (CAH) causes adrenal androgen excess and varying extent of cortisol and aldosterone deficiency. More than 95% of cases are due to 21-hydroxylase deficiency and three phenotypes are recognized (1). There are two classic forms, the salt-wasting form (SW) manifested neonatally by severe salt loss, and the simple virilizing form (SV) where salt loss is mild or absent. The nonclassic (NC) variant is usually diagnosed with hyperandrogenism later in childhood or adulthood with most males being identified in the course of family investigations (1). There is generally a good phenotype-to-genotype correlation (2), and genotypes may predict outcomes better than phenotypes (3–7).

The consequences of having CAH throughout adult life are incompletely investigated and there are circumstances with the potential to bring about increased cardiovascular morbidity and mortality. Glucocorticoids, the foundation of CAH treatment, is often given in supraphysiological doses to normalize the adrenal androgens, which may lead to unfavorable metabolic consequences: obesity, insulin resistance with type 2 diabetes (T2DM), and hypertension. Long-standing undertreatment with elevation of adrenal androgens may also reduce insulin sensitivity (8, 9) and induce hypogonadism with low testosterone values by gonadotropin suppression. Hypogonadotropic hypogonadism has been shown to be a risk factor for the metabolic syndrome and T2DM and to increase cardiovascular mortality (10). Inadequate mineralocorticoid therapy for aldosterone deficiency may also have negative impact on the vascular system (11). Previous reports on cardiovascular and metabolic profiles in CAH adults have mainly included young females, in spite of the fact that males in general have a higher
cardiovascular risk, and the results have been contradictory (6, 8, 9, 11–22). A very recent publication described however a cohort of 203 individuals with CAH including 62 males reporting adverse metabolic profiles (23).

The aim of this study was to investigate cardiovascular and metabolic parameters in more detail in adult CAH males and to compare them with age- and sex-matched controls. Younger and older patients, and different CYP21A2 mutations were compared to disclose potential changes associated with age and genotype.

Subjects and methods

Subjects

Adult CAH males with genetically confirmed diagnosis were recruited mainly from the two participating University Hospitals. The data were divided into the subgroups aged <30 years or older to allow comparisons with previous studies that had mainly included males below 30 years (9, 14, 16, 17, 19, 21). Moreover, pediatric endocrinology was introduced in Sweden about 30 years before the inclusion of the present cohort, which could affect outcomes.

Data were also divided according to the three most prevalent CYP21A2 mutations: null, I2splice, and I172N. Null refers to mutations completely abolishing enzyme activity and is associated with the SW phenotype. I2splice retains a very low, but measurable, level of activity and is usually associated with SW, whereas I172N is milder and most often found in SV patients.

Control subjects, one for each patient, were recruited by asking subsequent males in the National Population Registry to participate. They were born on the same date as the patient and most of them were living in the same area. The only exclusion criterion used was severe mental or psychiatric disturbance with inability to consent to the study.

The study was approved by the Ethic Committee of the Karolinska Institute, Stockholm, and the University of Gothenburg, Göteborg, Sweden. All participants gave their written informed consent.

Study protocol

Patients and controls were examined as outpatients at the Department of Endocrinology, Metabolism, and Diabetes, Karolinska University Hospital, Stockholm (n = 42) or the Department of Endocrinology, Sahlgrenska University Hospital, Göteborg (n = 20), Sweden. Measurements included height, weight, and waist and hip circumference. Body mass index (BMI) was calculated (kg/m^2). Total and regional fat and lean mass were studied by dual-energy X-ray absorptiometry (DXA). Ambulatory blood pressure and heart rate during 24 h were measured. Blood samples were collected after an overnight fast followed by an oral glucose (75 g) tolerance test (OGTT). A morning urinary spot sample was collected for albumin. Urinary catecholamines were collected during 24 h. In patients, 24 h urinary pregnanetriol and a diurnal 17-hydroxyprogesterone (17OHP) curve (0800, 1400, 1900, 0100, and 0600 h) using dried blood spots were analyzed.

Glucocorticoid supplementation

Glucocorticoids were converted to hydrocortisone equivalents using anti-inflammatory equivalents (30 mg hydrocortisone = 37.5 mg cortisol acetate = 7.5 mg prednisolone = 0.75 mg dexamethasone) (24). Body surface area was calculated as the square root of (height (cm) × weight (kg))/3600 (m^2) and was used to indicate hydrocortisone equivalents in mg/m^2.

Methods

Body composition was estimated by DXA (Lunar Model Prodigy equipment; Lunar Radiation, Madison, WI, USA). The two instruments were calibrated. Lean and fat mass were adjusted for body height (kg/m^2). Ambulatory 24 h blood pressure and heart rate were determined with Meditech ABPM-05 (Meditech Ltd, Budapest, Hungary).

Biochemical assays

Plasma renin was measured by IRMA (Nichols Institute Diagnostics, San Clemente, CA, USA). Serum cholesterol, triglycerides, high-density lipoprotein (HDL), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), lipoprotein-(ii) (Lp(ii)), and plasma homocysteine and glucose were measured on SYNCHRON LX Systems (Beckman Coulter, Inc., Fullerton, CA, USA). The low-density lipoprotein (LDL) concentration was calculated (25). Serum insulin, testosterone, sexual hormone binding globulin (SHBG), and dried blood spot 17OHP were measured by fluoroimmunoasay (AutoDelfia, Perkin-Elmer, Waltham, MA, USA). Urinary pregnanetriol was determined by gas chromatography and gas chromatography–mass spectrometry. HPLC was used for determinations of 24 h urinary epinephrine, and norepinephrine, and HbA1c, the latter by the MonoS method (ref. 3.6–5.3%). Urinary albumin was measured using routine assay.

Statistical analysis

Data were analyzed using SigmaStat for Windows (Jandel Scientific, Erkarath, Germany). Results are presented as the mean ± S.D. if not otherwise stated.
Comparisons between the two groups were made using the unpaired t-test when values were normally distributed. Otherwise, the Mann–Whitney rank-sum test was used and, in these cases, the median and range are reported. When continuous variables were compared in the three groups, one-way ANOVA was used for normal distributions followed by post hoc Bonferroni t-test, otherwise the Kruskal–Wallis test, followed by post hoc Mann–Whitney rank-sum test with Dunn’s method, was performed. \( x^2 \) was used in frequency table calculations or, when the expected frequency was small (<5), Fisher’s exact test. All proportions were calculated discounting missing values. Linear and multiple correlations were used for correlation analyses. Statistical significance was set at \( P < 0.05 \) and trend at 0.05–0.10.

**Results**

**Characteristics of the patients**

The included patients were aged 19–67 (35.7 ± 11.4) years. Nine patients were <30 (23.4 ± 3.3) years and 21 ≥30 (40.9 ± 10.3) years. All 17 patients with the SW phenotype were diagnosed during the first weeks of life (null, \( n = 7 \); 12splice, \( n = 9 \); I172N, \( n = 1 \)) and the 11 patients with the SV phenotype at 3–28 years of age (I172N, \( n = 8 \); 12splice, \( n = 2 \); P453S, \( n = 1 \)). One of them, a 29-year-old male (I172N) was recently diagnosed and used no medication; S-17OHP was 900 nmol/l. Two patients had NC phenotype; a 45-year-old male (V281L) diagnosed at age 30 used prednisolone when acutely ill; a 31-year-old male (I172N) was recently operated on for an abdominal aortic aneurysm and dyslipidemia. One 67-year-old control had been operated on for abdominal aortic aneurysm and dyslipidemia, coronary atherosclerosis, and hyperten-

Thus, 93% (\( n = 28 \)) received glucocorticoids most commonly prednisolone (61%), or hydrocortisone (18%). The mean dose in hydrocortisone equivalents was 17.4 ± 5.2 mg/m² without differences between younger and older patients (16.5 ± 3.8 vs 17.7 ± 5.6 mg/m²; \( P = \text{NS} \)) or genotype groups. The distribution of different glucocorticoids in the subgroups were <30 years of age: prednisolone \( n = 6 \), combination of prednisolone and hydrocortisone \( n = 1 \), dexamethasone \( n = 1 \); ≥30 years of age: prednisolone \( n = 13 \), hydrocortisone \( n = 5 \), cortisone acetate \( n = 2 \); the null group: prednisolone \( n = 5 \), hydrocortisone \( n = 1 \), cortisone acetate \( n = 1 \); the 12splice group: prednisolone \( n = 7 \), hydrocortisone \( n = 2 \), dexamethasone \( n = 1 \): the I172N group: prednisolone \( n = 5 \), hydrocortisone \( n = 2 \), combination of prednisolone and hydrocortisone \( n = 1 \).

Suppressed 17OHP concentrations were frequent and 58% (15/26) of the patients had at least one value below or at the level of detection (≤5 nmol/l). However, the 24 h median 17OHP value was very high (≥96 nmol/l) in 19% (5/26). Urinary pregnanetriol was in the reference range (<6 μmol/24 h) in 39% (11/28) and very high (≥110 μmol/24 h) in 14% (4/28). The majority (\( n = 26 \): 87%) received fludrocortisone, mean dose 0.11 ± 0.06 mg, with similar doses in the different groups. Most renin levels were normal. Testosterone levels were decreased in older compared to younger patients but also compared to controls (Table 1). SHBG was similar in all the groups (not shown).

Cardiovascular disease and/or cardiovascular preventive medications were revealed in two patients and two controls. One 67-year-old patient (I172N) had dyslipidemia, coronary atherosclerosis, and hypertension. One 56-year-old patient (I172N) was treated for dyslipidemia. One 67-year-old control had been operated on for an abdominal aortic aneurysm and dyslipidemia.

### Table 1: Blood Pressure, anthropometry, body composition (by dual-energy X-ray absorptiometry), and hormones in adult males with congenital adrenal hyperplasia due to 21-hydroxylase deficiency younger than 30 and at least 30 years of age and age-matched male controls (mean±s.d. or median and range).

<table>
<thead>
<tr>
<th></th>
<th>Patients (&lt;30 years)</th>
<th>Controls (&lt;30 years)</th>
<th>( P ) value</th>
<th>Patients (≥30 years)</th>
<th>Controls (≥30 years)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Height (cm)</strong></td>
<td>169.0 ± 10.9</td>
<td>180.3 ± 8.0</td>
<td>0.006</td>
<td>168.3 ± 8.7</td>
<td>181.6 ± 6.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.6 ± 2.9</td>
<td>22.3 ± 4.2</td>
<td>NS</td>
<td>28.1 ± 4.5</td>
<td>25.6 ± 6.2</td>
<td>0.031</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.84 ± 0.05</td>
<td>0.86 ± 0.06</td>
<td>NS</td>
<td>0.95 ± 0.05</td>
<td>0.91 ± 0.06</td>
<td>0.022</td>
</tr>
<tr>
<td>T fat mass (kg/m²)</td>
<td>4.39 ± 2.38</td>
<td>4.75 ± 3.04</td>
<td>NS</td>
<td>8.22 ± 3.17</td>
<td>5.85 ± 2.71</td>
<td>0.012</td>
</tr>
<tr>
<td>Trunk fat mass (kg/m²)</td>
<td>2.36 ± 1.61</td>
<td>2.29 ± 1.53</td>
<td>NS</td>
<td>5.07 ± 2.15</td>
<td>3.59 ± 1.75</td>
<td>0.017</td>
</tr>
<tr>
<td>Trunk/T fat mass</td>
<td>0.50 ± 0.07</td>
<td>0.56 ± 0.04</td>
<td>0.055</td>
<td>0.58 ± 0.06</td>
<td>0.58 ± 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>T lean mass (kg/m²)</td>
<td>17.8 ± 2.8</td>
<td>17.2 ± 1.6</td>
<td>NS</td>
<td>18.8 ± 2.3</td>
<td>18.6 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>T fat/T lean mass</td>
<td>0.24 ± 0.14</td>
<td>0.27 ± 0.15</td>
<td>NS</td>
<td>0.44 ± 0.16</td>
<td>0.32 ± 0.15</td>
<td>0.016</td>
</tr>
<tr>
<td>Leg lean mass (kg/m²)</td>
<td>5.54 ± 0.59</td>
<td>6.02 ± 0.62</td>
<td>NS</td>
<td>6.04 ± 0.71</td>
<td>6.33 ± 0.42</td>
<td>0.096</td>
</tr>
<tr>
<td>S-testo (nmol/l)</td>
<td>16.8 ± 3.9</td>
<td>18.7 ± 5.0</td>
<td>NS</td>
<td>13.1 ± 5.1</td>
<td>16.2 ± 4.8</td>
<td>0.045</td>
</tr>
<tr>
<td>P-renin (ng/l)</td>
<td>27.7 ± 18.7</td>
<td>20.6 ± 15.2</td>
<td>NS</td>
<td>22.5 (6.6–303)</td>
<td>8.7 (2.0–25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24 h SBP (mmHg)</td>
<td>130 ± 12</td>
<td>120 ± 10</td>
<td>NS</td>
<td>129 ± 12</td>
<td>125 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>24 h DBP (mmHg)</td>
<td>74 ± 4</td>
<td>70 ± 4</td>
<td>0.081</td>
<td>77 ± 7</td>
<td>75 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>Night SBP (mmHg)</td>
<td>118 ± 5</td>
<td>113 ± 14</td>
<td>NS</td>
<td>117 ± 11</td>
<td>117 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Night DBP (mmHg)</td>
<td>66 ± 7</td>
<td>61 ± 7</td>
<td>NS</td>
<td>69 ± 7</td>
<td>67 ± 6</td>
<td>NS</td>
</tr>
</tbody>
</table>

*\( P < 0.001 \), †\( P < 0.01 \), ‡\( P < 0.05 \), §\( P = 0.05–0.099 \) compared to younger counterparts (patients or controls respectively). SBP, systolic blood pressure; DBP, diastolic blood pressure; 24 h, 24 h ambulatory measurements; NS, not significant; night, all values were measured at 2300–0600 h; BMI, body mass index; T, total; S-testo, serum testostero.
had recovered from stroke. One 61-year-old control was treated for hypertension.

No past or present differences in smoking habits were found between CAH males and controls (current and past smokers 23 vs 25%, \( P=NS \)) or in the different subgroups (not shown).

**Adrenomedullary function**

Urinary epinephrine secretion was reduced in the CAH group compared to controls due to low levels in the null and I2splice groups, whereas concentrations in the milder I172N genotype were similar to those in controls and higher than in the null group (Fig. 1). A tendency to increased excretion of norepinephrine in the I172N group was found. Concentrations were similar in older and younger patients (not shown).

**Body composition**

Patients were shorter than controls (Table 1). Obesity (BMI > 30 kg/m²) was found in 23% (7/30) of patients and 9% (3/32) of controls (\( P=NS \)). Indices of body composition were similar to controls in younger patients, whereas older patients had a higher BMI, waist/hip ratio, total and truncal fat, and fat/lean ratio than both age-matched controls and younger patients. Older controls had a higher BMI and a tendency to a higher waist/hip ratio than younger controls (Table 1). Older patients showed a tendency to decreased leg lean mass.

**Metabolic evaluation**

**Markers of glucose control** None had diabetes, impaired glucose tolerance, or acanthosis nigricans. All investigated parameters were similar in younger patients and controls, while older patients had lower fasting P-glucose. HbA1c tended to be higher in older than in younger patients (Table 2). During OGTT, the area under the curve (AUC) for insulin was increased in all patients compared to controls (3741 (750–8295) vs 2108 (1440–12 267) mU/l \( \times \) min, \( P=0.033 \)). The 2 h insulin level was higher in older patients than in controls.

**Liver enzymes** GGT values were elevated in all CAH males compared to controls (0.36 (0.10–2.10) vs 0.20 (0.10–1.40) \( \mu \)kat/l, \( P=0.020 \)), as well as in older patients compared to controls and to younger patients. GGT was correlated with total and truncal fat mass (\( r=0.521, P=0.003; r=0.488, P=0.006 \)). ALT and ALP concentrations were similar in all CAH groups and controls (not shown). No difference in alcohol intake, defined as standard drinks/week, was found between the different groups (not shown).

**Serum lipids** No differences were found between CAH and control males. The HDL/LDL ratio was lower and LDL and triglycerides were higher in older patients than in younger ones. Older controls showed higher total cholesterol and LDL values and a tendency to raised triglycerides compared to their younger counterparts (Table 2). The results did not differ when the two patients on statin medication were excluded.

**Other cardiovascular risk markers** Lp(a) was similar in the different age groups. Homocysteine was decreased in younger patients compared to controls and older patients. Urinary albumin tended to be increased in older patients compared to controls (Table 2).

**Heart rate and blood pressure**

The average 24 h heart rate was increased up to 20% in the entire CAH cohort and the older CAH males compared to controls (Fig. 2). Tendencies to higher heart rates in older patients than in younger ones and the opposite among controls were demonstrated. In patients heart rate was negatively correlated with testosterone (\( r=-0.605, P=0.003 \)), positively with
total and truncal fat mass \((r=0.579\) and 0.597, \(P=0.005\) and 0.003\), night 24 h diastolic blood pressure \((r=0.458, P=0.042\), homocysteine \((r=0.430, P=0.046\), and positive tendency with HbA1c \((r=0.417, P=0.060)\) and urinary nor-epinephrine \((r=0.438, P=0.079)\). In multiple regression, the highest correlation with heart rate was with testosterone and HbA1c \((r=0.721, P=0.001)\).

Twenty-four hours ambulatory blood pressure revealed no differences between all CAH males and controls, either regarding average 24 h blood pressure or day or night periods (not shown). There was a tendency of slightly higher mean diastolic blood pressures in younger patients, otherwise all pressures were similar in older and younger patients compared with controls (Table 1). The results did not differ when the patient and the two controls on antihypertensive medication were excluded.

**BMI <25 kg/m²**

If only subjects with BMI <25 kg/m² were compared (14 CAH males versus 17 controls), the only differences that persisted were shorter height \((P<0.001)\) and lower epinephrine \((P=0.002)\), however, tendencies were found in GGT \((0.29 \times 0.10–0.78) vs 0.12 \times 0.10–0.97\) \(\mu\text{kat/l}, P=0.071)\) and HbA1c \((4.1 \pm 0.3 vs 4.4 \pm 0.4\%\), \(P=0.068)\).

**Characteristics of the three most common genotypes**

Indications for increased cardiovascular and metabolic risk were predominantly found in the I172N group. Compared with controls, they had significantly higher waist/hip ratios and GGT and tended to have higher BMI and total fat mass (Table 3). Total lean mass was elevated. Insulin AUC after an oral glucose load was higher than in controls and in the other genotypes. Heart rate was increased (Fig. 1). The mean systolic and night diastolic blood pressure were higher compared with controls, the latter also tended to be elevated compared to the other genotypes. However, there was a tendency to lower homocysteine. Patients in the null group had significantly reduced leg lean mass and fasting insulin levels and a tendency to elevated Lp(a).

In the I2splice group, heart rate was increased and urinary albumin tended to be elevated (Table 3).

**Characteristics of groups on different glucocorticoids**

Increased cardiovascular and metabolic risk were mainly seen in patients on short-acting glucocorticoids (Table 4) in spite of similar doses of hydrocortisone equivalents (hydrocortisone/cortisone acetate versus prednisolone: 19.9 ± 6.3 vs 16.8 ± 4.6 mg/m², \(P=\text{NS}\)). However, GGT was slightly higher in the prednisolone group compared with controls.

**Discussion**

We studied cardiovascular and metabolic risk profiles in a cohort of CAH males where the majority of the patients were ≥30 years old. The prevalence of manifest cardiovascular disease, including hypertension and dyslipidemia, was low, as expected, since only 13% were >50 years old. Nevertheless, there were some indications of increased cardiovascular and metabolic risk profiles in a subset of CAH males.
risk in CAH males ≥ 30 years old. They had higher body fat, serum GGT, insulin responses to glucose administration and heart rates, and lower testosterone levels compared to age-matched controls. In the younger group, none of these parameters differed significantly from controls. With respect to genotypes, indications for increased risk were mainly found in patients with the less severe I172N mutation. If only those with a healthy BMI (i.e. < 25 kg/m²) were compared, most differences in cardiovascular risk between CAH males and controls disappeared.

Many studies have demonstrated elevated BMI (9, 15, 16, 20, 23) in adults with CAH. Measurement of body composition using DXA has previously demonstrated increased fat mass in young adults with CAH (15, 16). Interestingly, two other studies found increased fat mass in male, but not in female, CAH patients (14, 17). We found increased fat mass only in the older males consistent with the latter studies. In contrast, we have previously reported increased lean mass in CAH females ≥ 30 years old as an explanation for elevated BMI (20).

Although no study has demonstrated increased frequency of T2DM in CAH, an increase in gestational diabetes, a strong predictor of future T2DM, has been reported (5, 20). Our patients had increased insulin release during the OGTT and older patients tended to have higher HbA1c than younger ones, suggesting an increased risk of T2DM in the older CAH males. Insulin resistance has been found in adult CAH by all investigators (6, 8, 9, 12, 13, 18, 20–23), but one (18) and has most commonly been expressed as homeostasis model assessment (HOMA) index. We did not calculate this index because fasting glucose was low in our patients, which may lead to a falsely low estimation of insulin resistance.

GGT has been demonstrated to be independently associated with cardiovascular mortality in a dose–response relationship even in the normal range (26). We found elevated GGT in the older male patients and there was a positive association between GGT and body fat. This small increment is probably only of a minor clinical impact and has previously also been found elevated in CAH women (6).

Figure 2 Heart rate measured with 24 h ambulatory monitor in adult males with congenital adrenal hyperplasia, divided into younger than 30 years or older (upper panel), and into the three most common CYP21A2 genotype groups, (Null, I2splice, and I172N) (lower panel) and age- and sex-matched controls. Box plot demonstrates the 10th, 25th, 50th, 75th, and 90th percentiles. All P values compared to controls if not indicated otherwise. P value: *<0.05, **<0.01, ***<0.001, †0.091, ‡0.062.

Increased heart rate is a known risk factor for cardiovascular and noncardiovascular death, especially in men, with some studies finding heart rate being independent of other cardiovascular risk factors (27, 28). Even a small increment of a few beats per minute within the normal range can increase the cardiovascular risk (28). Our younger patients had normal heart rates in accord with previous studies of young patients (29–31). The heart rate in CAH males was correlated with other cardiovascular risk factors. Decreased testosterone levels and the extent of glycemic control explained around 50% of the elevated heart rate.

Single blood pressure measurements in adult CAH, mainly in females, have found values similar to controls (20, 21) or elevated (23). No differences from controls were found by us in 24 h ambulatory measurements with the exception of one genotype group (see below). On the other hand, 24 h ambulatory measurements in children and adolescents have demonstrated elevated day and night time systolic pressures, however, they were more obese than controls (32).
Table 3 Body composition and other cardiovascular and metabolic risk variables in adult male patients representing the three most common CYP21A2 genotype groups and male controls (mean ± s.d. or median and range). Only variables that differ between patients and controls or between genotypes are shown.

<table>
<thead>
<tr>
<th>Null (n = 7)</th>
<th>P versus controls</th>
<th>12splice (n = 11)</th>
<th>P versus controls</th>
<th>I172N (n = 9)</th>
<th>P versus control</th>
<th>Controls (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>34.5 ± 9.5</td>
<td>NS</td>
<td>31.6 ± 9.4</td>
<td>NS</td>
<td>41.0 ± 14.9</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.9 ± 3.8</td>
<td>NS</td>
<td>25.1 ± 5.0</td>
<td>NS</td>
<td>28.5 ± 5.2</td>
<td>0.071</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.93 ± 0.07</td>
<td>NS</td>
<td>0.89 ± 0.09</td>
<td>NS</td>
<td>0.95 ± 0.07</td>
<td>0.038</td>
</tr>
<tr>
<td>T fat mass (kg/m²)</td>
<td>6.97 ± 4.10</td>
<td>NS</td>
<td>6.38 ± 3.53</td>
<td>NS</td>
<td>7.78 ± 3.46</td>
<td>0.055</td>
</tr>
<tr>
<td>T lean mass (kg/m²)</td>
<td>18.0 ± 4.2</td>
<td>NS</td>
<td>17.7 ± 4.3</td>
<td>NS</td>
<td>20.2 ± 5.2</td>
<td>0.005</td>
</tr>
<tr>
<td>Leg lean mass (kg/m²)</td>
<td>5.73 ± 0.60</td>
<td>0.019</td>
<td>5.88 ± 0.72</td>
<td>0.065</td>
<td>6.07 ± 0.76</td>
<td>NS</td>
</tr>
<tr>
<td>24 h SBP (mmHg)</td>
<td>128 ± 16</td>
<td>NS</td>
<td>125 ± 8</td>
<td>NS</td>
<td>134 ± 13</td>
<td>0.044</td>
</tr>
<tr>
<td>Night DBP (mmHg)</td>
<td>63 ± 11</td>
<td>NS</td>
<td>69 ± 6</td>
<td>NS</td>
<td>73 ± 5^5</td>
<td>0.042</td>
</tr>
<tr>
<td>S-insulin (mU/l min)^a</td>
<td>4.2 (0.5–6.4)</td>
<td>NS</td>
<td>8.5 (4.1–23)</td>
<td>NS</td>
<td>8.9 (2.3–11)^5</td>
<td>NS</td>
</tr>
<tr>
<td>S-insulin (mU/l min)^b</td>
<td>3030 ± 822</td>
<td>NS</td>
<td>5114 ± 4052</td>
<td>NS</td>
<td>8491 ± 34271^5</td>
<td>0.005</td>
</tr>
<tr>
<td>S-GGT (µkat/l)</td>
<td>0.27 (0.10–0.53)</td>
<td>NS</td>
<td>0.40 (0.10–0.89)</td>
<td>NS</td>
<td>0.40 (0.17–2.1)</td>
<td>0.028</td>
</tr>
<tr>
<td>S-LDL (mmol/l)</td>
<td>1.2 NS 17.7</td>
<td>0.019</td>
<td>5.2 0.071</td>
<td>0.005</td>
<td>19.7 ± 3.6</td>
<td>12.0 ± 2.1^4</td>
</tr>
<tr>
<td>U-albumin (mg/l)</td>
<td>10.0 (6.0–24)</td>
<td>NS</td>
<td>12.0 (6.9–20)</td>
<td>NS</td>
<td>11.0 (6.6–12)</td>
<td>0.063</td>
</tr>
<tr>
<td>U-albumin (mg/l)</td>
<td>8 ± 3 (1–19)</td>
<td>NS</td>
<td>10 (2–74)</td>
<td>0.061</td>
<td>5.4 (2.4–49)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*P < 0.001, †P < 0.01, ‡P < 0.05, §P = 0.05–0.099 compared to other genotypes. BMI, body mass index; T, total; B, blood; S, serum; P, plasma; U, urinary; GGT, γ-glutamyl transpeptidase; TC, total cholesterol; TG, triglyceride; Lp(a), lipoprotein-(a); homocyst, homocysteine; NS, not significant; SBP, systolic blood pressure; DBP, diastolic blood pressure; 24 h, 24 h ambulatory measurements; night, all values were measured at 2300–0600 h. ^Post hoc null versus I172N, P = 0.072 and 12splice versus I172N, P = 0.038. Post hoc null versus I172N, P = 0.018.

Both in the present cohort and in our previous report on CAH females (20), we found that the younger patients apart from a shorter height were similar to controls with respect to body composition and metabolic and cardiovascular risk markers whereas the older patients had more unfavorable profiles (20). These differences still persisted even if the division between younger and older males was set at 35 years of age to make the groups more even (data not shown). The reason is not known, but it can be speculated whether the higher lifetime glucocorticoid exposure may be of importance. To explore that further more individuals need to be included. The management of therapy in the two groups may also differ. The majority of the older patients were treated in general pediatric care during childhood, but the younger ones have been treated within or with backup from pediatric endocrinology units, most likely with a more optimal corticosteroid therapy and access to lifestyle interventions. With national neonatal screening introduced in Sweden 1986 (33), all patients with classic CAH can be identified during the first weeks of life and be adequately treated onward. Therefore, outcome will hopefully improve gradually.

In children, the preferred glucocorticoid is hydrocortisone due to less growth-suppressive effects (1), while in adults longer acting preparations such as prednisolone is often used (20. 23). Interestingly, more cardiovascular and metabolic risk factors were found in those treated with short-acting glucocorticoids.

Table 4 Body composition and other cardiovascular and metabolic risk variables in adult male patients on different glucocorticoids and male controls (mean ± s.d. or median and range). Only variables that differ between patients and controls or between the glucocorticoids are shown.

<table>
<thead>
<tr>
<th>Glucocorticoid</th>
<th>P versus controls</th>
<th>HC or CoAc (n = 8)</th>
<th>P versus controls</th>
<th>Controls (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>25.5 ± 4.6</td>
<td>NS</td>
<td>29.0 ± 4.9^†</td>
<td>0.006</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.89 ± 0.07</td>
<td>NS</td>
<td>0.97 ± 0.06^*</td>
<td>0.005</td>
</tr>
<tr>
<td>T fat mass (kg/m²)</td>
<td>6.57 ± 3.49</td>
<td>NS</td>
<td>8.35 ± 3.62</td>
<td>0.024</td>
</tr>
<tr>
<td>Trunk fat mass (kg/m²)</td>
<td>3.84 ± 2.14</td>
<td>NS</td>
<td>5.39 ± 2.73</td>
<td>0.013</td>
</tr>
<tr>
<td>24 h Heart rate (BPM)</td>
<td>74.4 ± 10.7</td>
<td>0.012</td>
<td>72.7 ± 9.5</td>
<td>0.044</td>
</tr>
<tr>
<td>S-testo (nmol/l)</td>
<td>15.3 ± 5.5</td>
<td>NS</td>
<td>12.3 ± 5.6</td>
<td>0.024</td>
</tr>
<tr>
<td>S-insulin 0 min (mE/l)</td>
<td>5.0 (5.0–11)</td>
<td>NS</td>
<td>11.0 (6.9–15)</td>
<td>0.052</td>
</tr>
<tr>
<td>S-insulin (mU/l min)^a</td>
<td>4.124 ± 2470</td>
<td>NS</td>
<td>7098 ± 4561</td>
<td>0.044</td>
</tr>
<tr>
<td>S-GGT (µkat/l)</td>
<td>0.40 (0.1–1.6)</td>
<td>0.021</td>
<td>0.30 (0.15–2.1)</td>
<td>NS</td>
</tr>
<tr>
<td>S-LDL (mmol/l)</td>
<td>2.97 ± 0.74</td>
<td>NS</td>
<td>2.23 ± 0.75^†</td>
<td>NS</td>
</tr>
<tr>
<td>P-homocyst (µmol/l)</td>
<td>11.5 (6.0–24)</td>
<td>NS</td>
<td>10.0 (6.9–14)</td>
<td>0.056</td>
</tr>
</tbody>
</table>

*P < 0.05, †P = 0.05–0.099 compared to the glucocorticoid group. HC, hydrocortisone; CoAC, cortisone acetate; BPM, beats per min, S-testo, serum testosterone; NS, not significant; GGT, γ-glutamyl transpeptidase; homocyst, homocysteine.

Area under curve 0–120 min in oral glucose tolerance test.
compared with prednisolone maybe due to better compliance and control of androgens. Comparing different glucocorticoids in CAH merits further studies.
Comparisons between the three most common genotypes revealed that the I172N group was the one most negatively affected having indices of increased fat mass, glucose-stimulated insulin release, and GGT as well as higher systolic and diastolic blood pressures. The mean glucocorticoid and mineralocorticoid doses were the same as in the null and I2splice groups. Possibly, the explanation for a more unfavorable profile is that the doses of corticosteroids were too high considering the milder disease. Although the sample was small and some differences were only tendencies, these results can alert us to consider genotype in monitoring corticosteroid dosing in classic CAH.

Moreover, none of the I172N patients had been screened with 17OHP at birth and it can be speculated whether a late diagnosis with prolonged postnatal androgen excess could lead to adverse metabolic effects. In a recent study, NC-CAH boys and girls had more parameters of insulin resistance and higher systolic blood pressure compared with controls, in contrast to classic CAH boys and girls diagnosed on average 5 years earlier (34).

Adrenomedullary function was studied in the present cohort. Epinephrine production has been shown to be impaired in adolescents and young adults with classic CAH (1, 29–31). This defect is certainly the result of insufficient prenatal cortisol secretion from the adrenal cortex, necessary for adrenomedullary organogenesis and epinephrine production (1). We could demonstrate for the first time in an older cohort that only patients with classic CAH having severe mutations had reduced epinephrine production (null and I2splice), whereas those carrying the milder I172N had normo production. Whether differences in epinephrine secretion can influence cardiovascular risk profiles have yet to be explored.

The main limitation of this study is its limited size. This primarily affects the power of the study making differences found difficult to reach statistically significant levels. Another limitation is assessing the impact of steroid treatment. Neither type of steroid used nor their cumulative lifetime dose were available and we used the dose of the present steroid in the calculations. Steroid excess at an early age may certainly have a continuing negative metabolic impact in adult age. For example, Knorr et al. (35) found that overtreatment during infancy increased the risk of obesity later despite adequate treatment for several years thereafter (35).

Conclusion

Indications of an increased cardiovascular risk in CAH males were mainly found in those ≥30 years old and in the I172N genotype group. On the other hand, younger CAH males did not differ from age-matched controls. This is likely to reflect a better management in recent years and the neonatal screening program may lead to further improvements.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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