REVIEW ARTICLE

Unfavourable trends in cardiovascular and metabolic risk in paediatric and adult patients with congenital adrenal hyperplasia?

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Summary

Context As a result of the introduction of treatment with glucocorticoids and mineralocorticoids, now 60 years ago, congenital adrenal hyperplasia has become a lifelong chronic disease. Whether long-term treatment of the disease leads to long-term side effects remains unknown. In this respect, especially cardiovascular risk seems to be important.

Evidence synthesis We reviewed the reported prevalence of conventional cardiovascular risk factors, i.e. obesity, insulin resistance, high blood pressure and dyslipidaemia in patients with congenital adrenal hyperplasia. Overall, the studies suggest a tendency towards an increased body mass index and fat mass, the presence of insulin resistance and hypertension, although data are relatively scarce and obtained in heterogeneous populations.

Conclusions Our findings suggest that adult CAH patients tend to have a cluster of metabolic risk factors, which are consistent with the metabolic syndrome. This notion may have consequences for the care for this group of patients.

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Introduction

Congenital adrenal hyperplasia (CAH) is a disorder of adrenal steroidogenesis. Treatment with glucocorticoids and, if necessary, mineralocorticoids prevents adrenal crises and suppresses abnormal secretion of adrenal androgens. As a result of the introduction of treatment with glucocorticoids and mineralocorticoids, now 60 years ago, nearly all CAH patients currently reach adulthood. This renders it possible to unfold the clinical spectrum of CAH as a lifelong chronic disease, with the oldest salt-wasting patients now

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being in their 60s, and long-term consequences of therapy becoming increasingly important. Patients with CAH are at risk of developing signs and symptoms of iatrogenic Cushing's syndrome[1,2] as the therapeutic range of treatment with glucocorticoids is narrow and supraphysiological doses of glucocorticoids are used to suppress hyperandrogenism. As hypercortisolism is associated with cardiovascular morbidity,[3] it is suggested that patients with CAH may show an adverse cardiovascular risk profile.[4] Furthermore, other factors such as obesity and alterations in the leptin axis may contribute to the development of an unfavourable cardiovascular risk profile in CAH patients. In this review, we discuss cardiovascular risk factors in paediatric and adult CAH patients. Data reviewed in this paper are from patients suffering from CAH because of 21-hydroxylase deficiency unless stated otherwise.

Overview of CAH

In 95% of cases, CAH is caused by 21-hydroxylase deficiency.[2] Deficiency of 21-hydroxylase results in impaired adrenal synthesis of cortisol and often also of aldosterone, causing increased secretion of ACTH by the pituitary gland, adrenal hyperplasia and excessive production of adrenal androgens.

The symptoms of CAH depend on the degree of enzyme deficiency. Patients with the classic salt wasting (SW) type of CAH have no residual enzyme activity resulting in disturbed cortisol and aldosterone production typically leading to an Addisonian crisis 7–14 days after birth and prenatal virilization of the external genitalia in females. Patients with the classic simple virilizing (SV) type of CAH have a residual enzyme activity of 1–2% and are considered to have sufficient aldosterone production to prevent severe salt wasting. The simple virilizing form results in prenatal virilization in females and postnatal androgen excess in both sexes, when left untreated, leading to precocious pseudopuberty at a young age. The two classic forms of CAH have an incidence of approximately 1 in 15 000 live births worldwide.[5] The nonclassic or late onset form of CAH with a residual enzyme activity of 30–50% has a prevalence of 0·1% in the general white population,[6] a higher frequency being reported in Eastern European Jews (3–4%), and in Hispanics and Yugoslavs (1–2%).[6] Female patients may be asymptomatic or are characterized by signs and symptoms of hyperandrogenism

such as abnormalities of the menstrual cycle, acne, hirsutism and subfertility. Therefore, signs and symptoms in women with the late onset form of congenital adrenal hyperplasia are comparable with those seen in women with polycystic ovary syndrome.[2,7] Male patients are usually asymptomatic but occasionally, they present with subfertility caused by hypogonadotrophic hypogonadism because of suppression of gonadotrophins by elevated adrenal androgens.

Risk factors for atherosclerotic vascular disease

Atherosclerotic vascular disease is caused by a complex process, to which several risk factors contribute.[8] Traditional risk factors include age, male gender, familial predisposition, obesity, diabetes mellitus, dyslipidaemia, hypertension, smoking and a sedentary lifestyle. In addition, several new nontraditional risk factors have been identified.[8] In the following part, some of these risk factors in CAH patients will be discussed in more detail.

Obesity

An increased fat mass and the presence of abdominal obesity are important factors in the development of cardiovascular disease. Many studies have investigated body mass index (BMI) in CAH patients and most,[9–18] but not all,[19,20] of them report an elevated BMI. Studies regarding body composition in patients with CAH are summarized in Table 1. Most studies used dual X-ray absorptiometry (DXA) scans to evaluate body composition, and one study used skinfold measurements.

In a cross-sectional study, Stikkelbroeck et al.[9] found an elevated BMI in young male and female adult CAH patients (*n* = 30, aged 17–25 years) compared with healthy controls. Increase in BMI was caused by an increase in fat mass. Fat mass adjusted for height and relative fat mass (i.e. fat mass divided by total body mass) was significantly higher in both males and females. Body fat distribution (measured by DXA) did not differ between patients and controls. Falhammar et al.[10] found a higher BMI in female CAH patients aged 30 years or older (*n* = 34) compared with controls. The elevated BMI in female CAH patients was not accompanied by elevation of total fat mass as found by Stikkelbroeck et al.[9] Falhammar et al.[10] did not find differences either in BMI or in body composition in female CAH patients younger than 30 years of age (*n* = 27) compared with controls. Bachelot et al.[11] reported a high BMI in adult male and female CAH patients (*n* = 45), but BMI in CAH patients was not compared with control subjects. BMI did not differ between the various clinical forms of CAH. BMI also showed no correlation with duration of treatment, dosage of hydrocortisone and 17alpha-hydroxyprogesterone (17-OHP) levels.

In a study by Hagenfeldt et al.[12] a significantly higher weight, BMI and absolute amount of body fat were found, but the fat/lean body mass ratio was not different between adult female CAH patients and age-matched healthy reference subjects. Cameron et al.[19] and Christiansen et al.[21] described an increased fat mass in male but not in female CAH patients. However, because different parameters were used in the different studies, i.e. relative fat mass and fat mass adjusted for height by Stikkelbroeck et al.,[9] fat/lean ratio by Cameron et al.[19] and fat mass percentage by Christiansen et al.,[21] it is difficult to compare these results.

Two studies have described BMI and body composition in children with CAH. Cornean et al.[13] reported an increased BMI in 21-hydroxylase-deficient children in a retrospective study. 'Adiposity rebound', defined as the age at which the decrease in BMI reverses, was assessed in a subset of 13 patients (nine boys, four girls) in which longitudinal data were available from birth. 'Adiposity rebound' took place at a mean age of 1·74 years in the patients compared with 5·5 years for controls from the normal UK population. Early 'adiposity rebound' is of importance as it increases the risk for the development of obesity in adolescence.[22] The increment in BMI was attributed to an increase in fat mass, skinfold thickness increasing significantly between 2·5 and 5·5 years. A limitation of this study is that data were collected retrospectively and that skinfold measurements to determine body composition were used. Völkl et al.[14] evaluated BMI in children in a retrospective cross-sectional study of 89 CAH patients (aged 0·2–17·9 years). BMI SDS of the whole group was significantly elevated. In addition, a significantly higher frequency of obesity, defined as BMI SDS >2·0, was observed. Glucocorticoid dosage was positively correlated with BMI SDS, although there was no significant difference in glucocorticoid and mineralocorticoid dosage between patients with a BMI SDS of >2·0 and <2·0.

In summary, CAH is associated with an increase in BMI and an increase in body fat in both adult and paediatric patients.[9,10,12,13,19,21] Further investigations are needed to define the time of onset of obesity especially in children with CAH. The cause of the excessive increase in body weight remains unclear, but several factors may contribute. It is suspected that obesity in CAH patients is related to glucocorticoid treatment. Obesity is reported in patients treated with both 'physiological' and supraphysiological doses of glucocorticoids. Furthermore, adrenomedullary dysfunction with decreased secretion of adrenaline may play a role in the development of obesity.[23] Catecholamines, such as adrenaline, contribute to lipolysis and inhibit insulin secretion, thereby preventing an increase in fat mass.[24] The decreased secretion of adrenaline in CAH is the result of prenatal adrenomedullary maldevelopment,[23] caused by low intra-adrenal levels of glucocorticoids.[25] Hypogonadism in men and hyperandrogenism in women are also associated with the development of obesity in CAH patients.[26] Another possible explanation for the presence of obesity in CAH patients is an altered leptin axis.[17]

Leptin is known to play a role in the regulation of body weight, with an increased leptin level suppressing appetite. The fact that most obese persons exhibit high leptin concentrations is often explained by the hypothesis that obesity is a state of leptin 'resistance'.[27] Changes in the leptin axis, for example a decrease in leptin receptor levels, may play a role in the development of obesity.[28–31] Both glucocorticoids and insulin increase leptin concentrations.[32,33] In contrast, androgens are known to decrease leptin concentrations.[34,35] Therefore, in CAH patients, an altered leptin axis may play a role in the development of obesity.

A decrease in soluble leptin receptor (sOB-R) serum levels has been described in CAH patients (aged 5·6–19·6 years, *n* = 51).[17]

Table 1. Summary of studies addressing body composition in congenital adrenal hyperplasia caused by 21-hydroxylase deficiency

Study (ref.)	Study population (n)	Gender	Age (years), mean ± SD	Therapy CAH group	Methods	Outcome
Stikkelbroeck et al.[9]	Salt-wasting (24) Simple virilizing (3) Nonclassic (3) Controls (30)	12♀;12♂ 3♂ 3♂ 15♀;15♂	♂:22 ± 2 ♀:21 ± 3 ♂:22 ± 2 ♀:21 ± 2	Cumulative hydrocortisone dose 5 yr • Anti-inflammatory (g/m²) ♂ 24 ± 5 ♀ 17 ± 5 • Growth retarding (g/m²) ♂ 26 ± 6 ♀ 18 ± 5	DXA	↑Fat mass (adjusted for height) ↑Relative fat mass
Falhammar et al.[10]	Salt-wasting (27) Simple virilizing (28) Nonclassic (6) Age-matched controls (61)	61♀ 61♀	18–63 (range) 18–63 (range)	All patients: glucocorticoids (±50% prednisolone, mean dosage 6·3 ± 0·32 mg/day, ± 33% hydrocortisone 33·3 ± 2·1 mg/day, others cortisone acetate, dexamethasone or combination. 82% fludrocortisone (0·09 ± 0·01 mg/day)	DXA	Similar percentage body fat and total and regional fat mass in patients and controls Higher total and regional fat mass in patients older than 30 years compared to younger patients
Hagenfeldt et al.[12]	Salt-wasting (12) Simple virilizing (1) Controls (12)	13♀ 12♀	24 ± 3 22 ± 1	5: dexamethasone 0·5–0·75 mg/day 5: prednisolone 5·6–12·5 mg/day 1: cortisone acetate 37·5 mg/day 1: triamcinolone 8 mg/day 1: cortisone acetate 15 mg and prednisolone 3·75 mg/day 12: fludrocortisone 0·075–0·15 mg/day	DXA	↑Body fat
Cameron et al.[19]	Salt-wasting (18) Simple virilizing (3) Age-matched controls (21)	8♀;10♂ 3♂ 10♀;11♂	8 – 32 (range) n.m.	Mean hydrocortisone dose: 32·7 mg/day* Mean fludrocortisone dose: 0·17 mg/day*	DXA	↑Fat/lean ratio in ♂♂
Christiansen et al.[21]	Salt-wasting (17) Simple virilizing or nonclassic (1) Age-matched controls (120)	8♀;10♂ 80♀;40♂	18 –33 (range) n.m.	All patients: glucocorticoids 17: mineralocorticoids Dose unknown	DXA	↑Fat mass percentage in ♂♂
Cornean et al.[13]	Salt-wasting (19) Simple virilizing or nonclassic (3) Controls: normal UK population	14♀;8♂	12·6 (range 7·1–204)	Mean hydrocortisone dose: 18·9 mg/m²/day Mean fludrocortisone dose: 0·13 mg/m²/day	Skinfold measurement	↑Fat mass

*Calculated from Table 1 in Cameron et al.[19] using anti-inflammatory hydrocortisone equivalents for glucocorticoid doses[60] ref, reference; SD, standard deviation; CAH, congenital adrenal hyperplasia; DXA, dual X-ray absorptiometry. n.m., not mentioned.

This observation suggests that also membrane leptin receptors are decreased leading to a state of 'leptin resistance'. In this study, sOB-R:leptin ratios and serum leptin levels were significantly correlated with insulin levels and insulin sensitivity. Serum leptin levels were not different in CAH patients compared with matched controls. In other studies, serum leptin levels have been described to be elevated[36] or normal[37] in CAH patients. Leptin levels are known to be correlated with fat mass. Two studies showed a positive correlation between BMI and serum leptin levels.[17,37] A positive correlation between the percentage of body fat and leptin levels was noted by Saygili et al.[37]

Dyslipidaemia

Only five studies have reported on lipid profiles in CAH patients.[10,11,38–40] Bayraktar et al.[38] studied untreated adult female nonclassic CAH patients (n = 50, aged 22 ± 2·91 years) and found that lipid profiles were not different from controls (i.e. total cholesterol, 4·6 ± 0·83 vs. 4·7 ± 0·77 mmol/l; HDL-cholesterol, 1·50 ± 0·28 vs. 1·55 ± 0·26 mmol/l; LDL-cholesterol, 2·56 ± 0·56 vs. 2·58 ± 0·58 mmol/l; and triglycerides, 1·14 ± 0·13 vs. 1·01 ± 0·12 mmol/l). Sartorato et al.[39] found similar results in male and female adult patients with the classic form of CAH caused by 21-hydroxylase deficiency, all treated with glucocorticoids (n = 19, aged 28 ± 3·5 years). Lipid profiles were not significantly different compared with healthy controls (total cholesterol, 168 ± 49 vs. 189 ± 36 mg/dl; HDL-cholesterol, 65 ± 15 vs. 61 ± 32 mg/dl; and triglycerides, 83 ± 37 vs. 84 ± 56 mg/dl). Falhammar et al.[10] evaluated serum lipids in treated adult females with classic and nonclassic CAH caused by 21-hydroxylase deficiency (n = 61). Patients were divided into two groups: patients younger than 30 years and patients 30 years or older. All patients received treatment with prednisolone or hydrocortisone. Most patients (50 of 61) also received fludrocortisone. Total cholesterol, HDL-cholesterol, LDL-cholesterol, HDL to LDL ratio and triglycerides did not differ between younger patients and controls. Patients of 30 years of age or older had higher HDL to LDL ratios (P = 0·03) and a tendency towards higher HDL-cholesterol (P = 0·074) compared with healthy controls. This change in lipid profile is considered to be protective for cardiovascular disease. Falhammar et al.[10] did not show any unfavourable changes in the lipid profile of adult female CAH patients. Bachelot et al.[11] found normal total cholesterol, triglycerides and LDL-cholesterol levels in adult patients with classic CAH, both with a BMI < 25 (n = 24) and with a BMI > 25 (n = 21).

Only one study evaluated lipid profiles in children with CAH. Botero et al.[40] determined serum lipid profiles in 14 prepubertal children with CAH caused by 21-hydroxylase deficiency (four boys and 10 girls; aged 13 months–10 years) and in 14 healthy prepubertal children (eight boys and six girls; aged 21 months–9 years). All CAH patients were on glucocorticoid treatment with prednisone (dosage equivalent to 10–20 mg/m^2/day hydrocortisone). The study provided no information about the type of CAH and no matched control group was used. A statistically significant larger percentage of patients in the CAH group had serum triglycerides above 1·0 mmol/l compared with the control group (64·3% vs.

14·3%). Mean serum levels of triglycerides were also significantly elevated compared with the control group (1·32 ± 0·15 vs. 0·75 ± 0·07 mmol/l; P = 0·04). These findings were attributed to the use of glucocorticoids, especially prednisone. Furthermore, insulin resistance may also have contributed to the elevated levels of triglycerides. Mean serum levels of total cholesterol, LDL-cholesterol and HDL-cholesterol were not significantly different compared with controls.

In summary, studies evaluating the lipid profile in adult CAH patients[10,11,38,39] did not show unfavourable changes. Therefore, an altered lipid profile does not seem to be an important cardiovascular risk factor in adult CAH patients. Because obesity and insulin resistance (see further), both observed in CAH patients, are known to be associated with dyslipidaemia[41], it is surprising that lipid profiles in CAH patients are normal. A possible explanation for this finding is that lipid profiles were mainly evaluated in younger CAH patients. Evaluation of dyslipidaemia in older CAH patients, especially those older than 50 years of age, is needed.

Hypertension

Seven studies have evaluated blood pressure in CAH patients[10,39,42–46] as summarized in Table 2. Two studies[10,39] have evaluated blood pressure only in adult CAH patients, four studies[42–45] in both paediatric and young adult patients and one study[46] reports on blood pressure in paediatric CAH patients only.

Falhammar et al.[10] found supine and upright blood pressure values mostly within the normal range, both in female CAH patients younger than 30 years (n = 27) and 30 years or older (n = 34). No differences in supine and upright blood pressures were observed in female CAH patients and healthy controls. Three CAH patients older than 30 years received antihypertensive therapy, whereas controls did not receive antihypertensive medication. Defining hypertension as a supine blood pressure >140/90 mmHg, three CAH patients and four controls older than 30 years showed hypertension. Sartorato et al.[39] found blood pressure values within the normal range in both male and female classic CAH patients receiving glucocorticoid replacement therapy with hydrocortisone or dexamethasone. In both male (n = 9) and female (n = 10) CAH patients, systolic and diastolic blood pressures did not differ from healthy controls.

De Silva et al.[42] performed 24-h ambulatory blood pressure monitoring in 11 treated CAH patients (M:F = 4:7) with a mean age of 14·5 years. Nine patients were 21-hydroxylase deficient (five salt losers), one patient had 11β-hydroxylase deficiency and one had lipoid adrenal hyperplasia. None of the patients had hypertension defined as a mean systolic and diastolic blood pressure >95th percentile. However, five patients had a high mean blood pressure (90th percentile) with elevated mean systolic and diastolic pressures during the awake period. Limitations of this study are the small sample size of the study population and the heterogeneity of patients, with inclusion of both children and adults, two of them not being 21-hydroxylase deficient. In addition, two different blood pressure references were used: 24-h ambulatory blood pressure specific references and office blood pressure references. When using specific ambulatory reference data, one patient showed both

Table 2. Summary of studies addressing blood pressure in congenital adrenal hyperplasia

Study (ref.)	Study population (n)	Gender	Age (years), mean ± SD	Therapy CAH group	Methods	Blood pressure (mmHg) (±SD)
Falhammar et al.[10]	Salt-wasting (27) Simple virilizing (28) Nonclassic (6) Age-matched controls (61)	61♀ 61♀	18–63 (range) 18–63 (range)	All patients: glucocorticoids (±50% prednisolone, ± 33% hydrocortisone, others cortisone acetate, dexamethasone or combination 82% fludrocortisone	BP was registered supine and standing	♀<30 years: 110/71 (supine) ♀<30 years: 120/75 (upright) ♀>30 years: 110/75 (supine) ♀>30 years: 115/79 (upright)
Sartorato et al.[39]	Classic 21-OH deficiency (19) • Salt-wasting (12) • Simple virilizing (7) Controls (19)	10♀; 9♂ 10♀; 9♂	28 ± 3·5	All patients: glucocorticoid replacement with hydrocortisone or dexamethasone 12 patients mineralocorticoid therapy	Average of three BP measurements with a sphygmomanometer on separate occasions	♂: SBP 123·3 ± 13·2 ♂: DBP 83·3 ± 8·7 ♀: SBP 126·5 ± 7·5 ♀: DBP 83·9 ± 4·9
De Silva et al.[42]	Classic 21-OH deficiency (9) • Salt-wasting (5) 11β-hydroxylase deficiency (1) Lipoid adrenal hyperplasia (1)	7♀; 4♂	14·5, range: 8·5–27·2	All patients were on glucocorticoid replacement at supraphysiological doses	24-h ABPM	SBP: 115·1 ± 10·3 DBP: 68·3 ± 7·2
Roche et al.[43]	Classic 21-OH deficiency (38) • Salt-wasting (38)	23♀; 15♂	11·2, range: 6·1–18·2	All patients received replacement therapy in the form of oral hydrocortisone and fludrocortisone	24-h ABPM	Mean 24-h BP: SBP: 124·9 ± 11·7 DBP: 76·2 ± 14·9
Völkl et al.[44]	Classic 21-OH-deficiency (55) • Salt-wasting (45) • Simple virilizing (10)	32♀; 23♂	5·3–19·0 (range)	All patients received replacement therapy with glucocorticoids: hydrocortisone (40), prednisone (12) or dexamethasone (3) 53 patients received fludrocortisone	24-h ABPM	24-h BP in SDS for age: ♂: SBP 0·23 ♂: DBP -0·65 ♀: SBP 0·47 ♀: DBP -0·65
Hoepffner et al.[45]	Classic 21-OH deficiency (34) • Salt-wasting (28) • Simple virilizing (6)	21♀; 13♂	6–17 years (n = 23) 18–26 years (n = 11)	All patients received glucocorticoid treatment with hydrocortisone	In outpatient clinic: oscillometric device (n = 34), under hospitalization: 24-h BP measurement with portable oscillometric device (n = 34) and 24-h ABPM (n = 11)	BP values in 11 children and adolescents who participated in all three measurements: Day-mean SBP in hospital:125·9 ± 9·6 Day-mean DBP in hospital:78·5 ± 7·0 SBP in outpatient clinic:117·1 ± 11·8 DBP in outpatient clinic:72·6 ± 6·3 Day-mean SBP of ABPM:114·8 ± 5·7 Day-mean DBP of ABPM:68·7 ± 4·6
Nebesio et al.[46]	Classic 21-OH deficiency (91)	49♀; 42♂	Unknown	All patients with hypertension were treated with both hydrocortisone and fludrocortisone (n = 5)	Retrospective chart review, methods of BP measurement unknown	Peak recorded SBP for each patient with hypertension (n = 4): 115/146/300/146

Ref, reference; SD, standard deviation; OH, hydroxylase; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; ABPM, ambulatory blood pressure monitoring.

daytime and nocturnal hypertension, six patients (54%) had nocturnal hypertension and eight patients (73%) had nocturnal blood pressures above the 90th percentile.

Roche et al.[43] performed 24-h ambulatory blood pressure monitoring in 38 salt-wasting 21-hydroxylase-deficient patients (15 males, 23 females) with a mean age of 11·2 years. Using task force references for office blood pressure measurements[47] instead of 24-h ambulatory specific references, which would have been more appropriate, they found that 58% of the patients had systolic hypertension and 24% had diastolic hypertension. Mean daytime systolic blood pressure was significantly higher than in the reference population and 84% had no physiological nocturnal systolic dip. Mean systolic and diastolic blood pressures were not significantly different between males and females. In CAH patients, there was a positive relationship between systolic blood pressure and BMI, which was most marked in females.

Völkl et al.[44] performed 24-h ambulatory blood pressure monitoring in 55 treated patients with proven 21-hydroxylase deficiency (32 females, 23 males) aged between 5 and 19 years. Measured blood pressure values were transformed into SDS matched for age, height, sex and the same oscillometric method respectively. Their data showed a significantly elevated systolic blood pressure during both day- and night-time (daytime 0·67 SDS, nighttime 0·63 SDS). Surprisingly, diastolic blood pressure was significantly decreased during the day with normal values during the night. A normal nocturnal drop of systolic blood pressure was found. Blood pressure parameters positively correlated with BMI and skinfold thickness.

Hoepffner et al.[45] focused on differences in blood pressure measured in the outpatient clinic and in the ward in 23 children and adolescents and 11 adult CAH patients. All patients received glucocorticoid treatment with hydrocortisone. Blood pressure measured during hospital admission was significantly elevated in children and adolescents compared with that measured in the outpatient clinic. All blood pressures measured were within the normal range. Measurement of 24-h ambulatory blood pressure showed blood pressure values in the normal range in all patients. No correlations were found between blood pressure on one hand, and sex, BMI or dosage of mineralocorticoids on the other hand.

Nebesio et al.[46] performed a retrospective chart review of children with 21-hydroxylase deficiency to evaluate the prevalence of hypertension, defined as blood pressure >95th percentile for age and gender, using published reference values. Six of 91 patients showed hypertension (6·6%). Patients were aged 58 days – 12·6 years at the time of hypertension diagnosis. No relation between blood pressure and BMI or dosage of hydrocortisone was found. Nebesio et al.[46] concluded that children with 21-hydroxylase deficiency have a higher prevalence of hypertension compared with historical reports on hypertension in a paediatric population.

In conclusion, in most studies performed in young CAH patients, there is a tendency towards an increased prevalence of hypertension. Further studies are required to investigate this relation in older CAH patients. It is well known that mineralocorticoid excess, like in primary aldosteronism or in forms of CAH with elevated levels of adrenal steroids with mineralocorticoid effect such as 11-hydroxylase deficiency, results in high blood pressure.[48] Therefore, treatment with too high doses of mineralocorticoids or unjustified treatment with mineralocorticoids in patients with the SV type of CAH with suppressed renin levels may cause high blood pressure. However, in the reviewed papers, no correlations between renin levels and blood pressure values were observed in CAH patients.[42–46] Glucocorticoid excess, as in Cushing's syndrome, is also known to result in high blood pressure.[49] Therefore, treatment with relatively high doses of glucocorticoids may also play a role in the development of high blood pressure in CAH patients.[50]

Insulin resistance

Nine studies have investigated insulin sensitivity in CAH patients, as summarized in Table 3.[11,17,27,36–39,51–53] Most studies have used the homeostasis model assessment method (HOMA-IR) or the oral glucose tolerance test (OGTT) to assess insulin sensitivity. Only the study of Paula et al.[51] has applied the forearm model combined with local indirect calorimetry, and showed that insulin sensitivity was decreased in adult females with CAH, compared with female controls. Thirty minutes after glucose ingestion, the serum insulin levels in their group of patients were significantly higher than in healthy controls. In a study by Speiser et al.,[52] using OGTT, insulin sensitivity was significantly lower than expected for BMI in patients compared with controls ($4·1 \pm 0·6$ *vs.* $9·7 \pm 1·2$ [min/µU/ml]; $P < 0·05$). Saygili et al.[37] measured insulin sensitivity by HOMA-IR in untreated nonclassic 21-hydroxylase-deficient adult women, and found insulin resistance and hyperinsulinaemia. HOMA-IR was $3·2 \pm 0·8$ in patients and $1·8 \pm 0·6$ in controls. Serum fasting and nonfasting insulin levels in patients were significantly higher than in controls ($14·6 \pm 10·3$ *vs.* $4·2 \pm 0·5$ IU/l, $P < 0·001$ and $85·4 \pm 20·5$ *vs.* $30·2 \pm 3·5$ IU/l, $P < 0·001$, respectively). Insulin resistance and hyperinsulinaemia were associated with hyperandrogenism. Serum leptin levels did not differ between patients and controls.

Sartorato et al.[39] studied insulin sensitivity in 19 adult patients with CAH caused by 21-hydroxylase deficiency, using OGTT and HOMA-IR. Significantly elevated fasting plasma insulin levels ($11·6 \pm 3·20$ µU/ml *vs.* $5·18 \pm 2·4$ µU/ml, $P < 0·0001$) and HOMA-IR ($2·46 \pm 1·9$ *vs.* $1·12 \pm 0·58$, $P = 0·0033$) were found in CAH patients compared with controls.

An OGTT was also performed in adult CAH patients by Bachelot et al.[11] HOMA-IR was used to calculate insulin sensitivity. No control subjects were used in this study. During OGTT, two of 45 CAH-patients were identified with glucose intolerance. HOMA-IR was calculated in 40 patients: $1·58 \pm 0·26$ in salt wasting patients, $2·01 \pm 0·91$ in simple virilizing patients and $1·39 \pm 0·19$ in patients with the nonclassical form of CAH. HOMA-IR was significantly correlated with BMI and 17-OHP levels. Bachelot et al.[11] concluded, based on HOMA-IR, that insulin sensitivity tends to decrease when BMI and androgen levels increase.

In contrast to the studies discussed earlier, Bayraktar et al.,[38] using HOMA-IR, did not find a decrease in insulin sensitivity in CAH patients. HOMA-IR was $2·18 \pm 0·11$ for CAH patients and $2·16 \pm 0·09$ in controls. In addition, Buffington et al.[53] found no insulin resistance in CAH patients. Fasting and glucose-challenged insulin levels, glucose disappearance rates after insulin injection and *in vitro* insulin binding were similar to lean controls. However,

Table 3. Summary of studies addressing insulin resistance in congenital adrenal hyperplasia

Study (ref.)	Study population (n)	Gender	Age (years), mean ± SD	Therapy CAH group	Methods	Insulin-resistant? (CAH patients *vs.* controls)
Paula *et al.*[51]	Classic 21-OH deficiency (4) Nonclassic 21-OH deficiency (3) Controls (9)	7 ♀ 9 ♀	28 ± 3 27 ± 2	Discontinuation of dexamethasone in classic 21-OH deficiency for 2–3 weeks prior to the study	Forearm model and local indirect calorimetry	Yes: Forearm glucose uptake (100·9 ± 10·0 *vs.* 132·5 ± 21·2 mg/100 ml forearm), insulin response (98·6 ± 194 *vs.* 59 ± 6·5 µU.ml-1/mg.100ml forearm) (*P* < 0·05)
Speiser *et al.*[52]	Nonclassic 21-OH deficiency (6) Controls (12)	6 ♀ 12 ♀	27 27	None	iv GTT	Yes: Si: 4·1 ± 0·6 *vs.* 9·7 ± 1·2 (*P* < 0·05)
Saygili *et al.*[37]	Nonclassic 21-OH deficiency (18) Controls (26)	18 ♀ 26 ♀	26 ± 9 29 ± 5	None	HOMA	Yes: HOMA: 3·2 ± 0·8 *vs.* 1·8 ± 0·6 (*P* < 0·05)
Sartorato *et al.*[39]	Classic 21-OH deficiency (19) • Salt-wasting (12) • Simple virilizing (7) Controls (19)	10♀;9♂ 10♀;9♂	28 ± 3·5	All patients: glucocorticoid replacement with hydrocortisone or dexamethasone. 12 patients: mineralocorticoid therapy	OGTT HOMA	Yes: HOMA: 2·46 ± 1·92 *vs.* 1·12 ± 0·58 (*P* = 0·00)
Bachelot *et al.*[11]	Classic 21-OH-deficiency (45) • Salt-wasting (23) • Simple virilizing (12) • Nonclassical form (10)	36♀;9♂	18–47 (range)	All patients: long term glucocorticoids	OGTT HOMA	Yes: BMI < 25: HOMA 1·31 ± 0·23 BMI > 25: HOMA 2·05 ± 0·49
Bayraktar *et al.*[38]	Nonclassic 21-OH deficiency (50) Controls (25)	50 ♀ 25 ♀	22 ± 3 22 ± 3	None	HOMA	No
Buffington *et al.*[53]	Nonclassic 21-OH deficiency (3) 3β-HSD deficiency (5) Controls (14)	8 ♀ 14 ♀	n.m. n.m.	None Hydrocortisone	OGTT ITT	No
Charmandari *et al.*[36]	Classic 21-OH deficiency (16) • Salt-wasting (12) • Simple virilizing (4) 11β-OH deficiency (2) Controls (14) • Lean (6) • Obese (8)	6♀;12♂	7 ± 3	All patients: Hydrocortisone and Fludrocortisone; 6 GnRH agonists	HOMA	Yes: HOMA: 2·2 ± 0·3 *vs.* 0·7 ± 0·04 (*P* < 0·001)
Völkl 2009 *et al.*[17]	Classic 21-OH-deficiency (51) • Salt wasting (42) • Simple virilizing (9) Controls (28)	30♀;21♂ 12♀;16♂	5–19 (range) 9 ± 2	All patients: glucocorticoid substitution with hydrocortisone or dexamethasone	HOMA	Yes: HOMA: 2·7

Ref, reference; SD, standard deviation; OH, hydroxylase; 3β-HSD, 3β-hydroxysteroiddehydrogenase; GnRH, gonadotrophin-releasing hormone; iv GTT, intravenous glucose tolerance test; HOMA, homeostasis model assessment; OGTT, oral glucose tolerance test; ITT, intravenous insulin tolerance test; Si, insulin sensitivity. n.m., not mentioned.

the inclusion of both nonclassic 21-hydroxylase-deficient patients and 3β-hydroxysteroid dehydrogenase-deficient patients results in difficulty to arrive at solid conclusions. Furthermore, no data were provided about the age of the participating patients and controls.

Two studies have evaluated insulin sensitivity in paediatric CAH patients.[17,36] Charmandari et al.[36] found that HOMA-IR was significantly elevated in children with classic CAH, compared to healthy children ($2·2 \pm 0·3$ vs. $0·7 \pm 0·04$, $P < 0·001$). CAH patients had significantly higher fasting serum insulin concentrations and significantly lower serum adrenaline and metanephrine levels. Völkl et al.[17] measured HOMA-IR in 51 patients, aged 5·1–19·6 years, with CAH caused by 21-hydroxylase deficiency. No control subjects were investigated. A HOMA-IR of 2·7 was found and the authors concluded that CAH patients were characterized by insulin resistance.

In summary, nine studies have explored insulin sensitivity either in adult or in paediatric CAH patients. Different methods were used to assess insulin sensitivity. Most studies suggest that CAH patients tend to develop insulin resistance, but studies using the gold standard technique to measure insulin sensitivity (euglyacemic hyperinsulinaemic clamp method) are lacking. In female CAH patients, hyperandrogenism may induce insulin resistance. In males, hypogonadism is associated with insulin resistance. Most studies assessing insulin sensitivity in CAH patients contained only female patients.[37,38,51–53] Studies evaluating insulin sensitivity in a selected population with male CAH patients are lacking and a possible association between hypogonadism and insulin sensitivity has not been studied. No differences in insulin sensitivity between males and females were discussed in the studies containing both male *and* female CAH patients.[11,17,36,39] Unfortunately, glucocorticoids used to treat hyperandrogenism also induce insulin resistance.[3] Therefore, both treated and untreated CAH patients seem to be at risk to develop insulin resistance. In children, reference data are lacking for most parameters used to diagnose insulin resistance. Therefore, it is difficult to diagnose insulin resistance in children and predict future disease risk.[54]

Intima-media thickness

An increased intima-media thickness (IMT) has been described as a surrogate marker of atherosclerosis and consequently a higher cardiovascular risk.[55,56] Sartorato et al.[39] used the echo-Doppler method for evaluation of IMT of the abdominal aorta, right and left common carotid arteries, carotid bulbs and common femoral arteries in adult CAH patients, all treated with glucocorticoids (aged $28 \pm 3·5$ years, $n = 19$). Significantly increased values for IMT in all arteries were found compared with healthy controls. No correlation was found between IMT on the one hand and fasting glucose, insulin levels, cumulative doses of glucocorticoids, 17-OHP or androstenedione levels on the other hand. As increased IMT is an independent predictor of vascular events, Sartorato et al.[39] concluded that CAH patients might be at risk of developing coronary, cerebrovascular and peripheral vascular disease.

Conclusion

We have reviewed the current evidence regarding the presence of conventional cardiovascular risk factors, more specifically obesity, insulin resistance, high blood pressure and elevated lipid concentrations in CAH patients. Overall, these studies demonstrate the existence of an increased fat mass, insulin resistance and an elevated blood pressure but a normal lipid profile in CAH patients. Taken together, these findings suggest that adult CAH patients seem to have a high risk to cluster a number of risk factors, fitting within the metabolic syndrome. The finding of an increased IMT in these patients suggests that these risk factors may indeed translate to cardiovascular disease.

It has been suggested that CAH patients develop an unfavourable cardiovascular risk profile either because the existence of hyperandrogenism in untreated or undertreated patients or because of the (supra)physiological doses of glucocorticoids used to suppress androgen levels to normal values (graphically shown in Fig. 1). Many other metabolic abnormalities, such as an altered leptin axis, may contribute to the development of cardiovascular disease. Further studies providing comprehensive information regarding cardiovascular risk profile are warranted, especially in older patients. Whether these risks are of a magnitude that justifies pharmacological intervention and at what age this should be started are further issues that need to be solved.

Competing interests/financial disclosure

Nothing to declare.
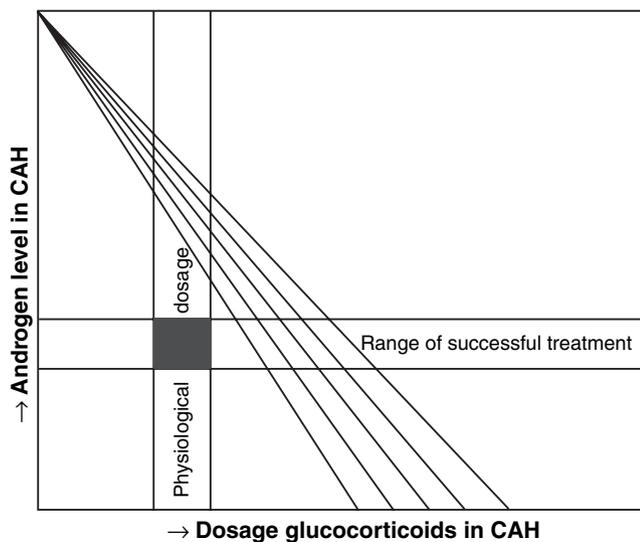
Fig. 1 Hypothetical curves, showing the relation between androgen levels and glucocorticoid dosages in CAH patients. Untreated CAH patients have high androgen levels. Supraphysiological doses of glucocorticoids are needed to normalize androgen levels. Interindividual differences in glucocorticoid sensitivity (shown by the different curves), caused by different mechanisms,[57–59] may explain differences in glucocorticoid dosage between individual patients. Patients with impaired glucocorticoid sensitivity need higher glucocorticoid dosage to suppress androgen levels and these patients might have a higher chance to develop an unfavourable cardiovascular risk.

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