Health Problems in Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency

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Introduction

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21OHD) is one of the most common inborn conditions following an autosomal recessive inheritance [1–3]. CAH is clinically classified into classic CAH, comprising the salt-wasting (SW) and the simple-virilizing (SV) forms, and non-classic CAH. The classic form has a frequency of about 1 in 10,000 to 1 in 15,000 in the general population, whereas the non-classic form is more common with an estimated incidence of about 1 in 1,000. Classic CAH due to 21OHD is characterized by a complex imbalance of adrenal steroids resulting in androgen excess, glucocorticoid deficiency and, in two thirds of affected patients, also in mineralocorticoid deficiency [1, 2]. Sixty years ago, long-term survival of CAH patients has been made possible by increasingly widespread availability of glucocorticoids. Thus, CAH has become a condition affecting almost all age groups. In recent years, increasing attention has been paid towards long-term health problems in adult life, with signs and symptoms of forerunner conditions of adult disease already emerging during the time of paediatric care. Transition of paediatric CAH patients to medical care in the adult setting is an important step to ensure optimal lifelong treatment, aiming to achieve good health and normal life expectancy and quality of life. Thus, primary and secondary prevention of health problems has to become a task of increasing importance for those involved in the care of CAH patients throughout their life.

Key Words
Congenital adrenal hyperplasia · 21-Hydroxylase deficiency · Obesity · Hypertension · Osteoporosis · Fertility
problems affect several body systems including bone, cardiovascular and metabolic health, and female and male fertility, including pregnancy management and psychosexual issues. The complexity of potential health problems emphasizes the need for care provision by multidisciplinary teams, comprising endocrinologists, geneticists, gynaecologists, urologists, psychologists, and specialist nurses plus input from other disciplines according to clinical need, which will vary by age group [2, 4].

**Corticosteroid Replacement Therapy**

Cortisol production is significantly reduced in classic CAH, whereas aldosterone production is clinically sufficient in the SV form. Thus, glucocorticoid replacement is required in all classic CAH patients, whereas the latter is only required in the SW form. However, a spectrum of salt loss in 21OHD exists, with boundaries between the SW and SV form sometimes being indistinct [5].

The goal of glucocorticoid treatment aims at replacing the missing glucocorticoids and concurrently targets the control of ACTH-driven androgen excess. Thus, in most cases higher glucocorticoid doses than for the replacement in adrenal insufficiency may be required. Treatment is monitored by the assessment of clinical signs and symptoms and also biochemical monitoring. A consensus statement from 2002, published by the European Society for Paediatric Endocrinology and the Lawson Wilkins Paediatric Endocrine Society, suggests a common hydrocortisone dose of 10–15 mg/m² during childhood [6]. The recent Endocrine Society Clinical Practice Guideline also recommends hydrocortisone as primary glucocorticoid substitution formula during childhood and adolescence, whereas in adulthood long-acting glucocorticoids such as prednisolone and dexamethasone may be used as well [7].

A dose-dependent negative effect of glucocorticoids on linear growth has been demonstrated during infancy, childhood and adolescence. Thus, the glucocorticoid dose should be kept at the possible minimum [8]. Two recent studies found negative effects on final height with hydrocortisone doses exceeding 17 mg/m² per day during puberty [9] and reduced final height outcome under treatment with prednisone, a synthetic steroid with considerably longer half-life [10]. Importantly, height velocity and bone maturation in untreated patients with mild forms of SV CAH seem to increase only after the first year of life [11]. Normal final height can be achieved by careful hydrocortisone titration avoiding ‘growth toxic’ doses [9]. This stresses the importance to meticulously monitor and adjust replacement to avoid complex, expensive and experimental treatment regimens to delay puberty with or without additional use of growth-stimulating substances.

Randomized controlled studies on different glucocorticoid replacement strategies in classic CAH do not exist. During childhood, hydrocortisone is the preferred and recommended drug. Longer-acting glucocorticoids are commonly given after finalization of linear growth in adolescents and adults. In a European-wide survey including 125 centres, hydrocortisone (92% of infants, 90% of children, 70% of adolescents) was the predominantly used steroid in paediatric care, whereas only 36% used hydrocortisone as the primary replacement in adults (14% prednisone, 13% prednisolone, 33% dexamethasone, 4% cortisone acetate). The majority of European centres administered the glucocorticoid dose following a circadian rhythm with the highest dose given in the early morning, as recommended for patients with other causes of adrenal insufficiency [12]. However, also a reverse circadian application is used with the highest dose taken before bed time or late in the evening [13]. A short-term study in 15 children comparing both treatment regimens (high morning vs. high evening hydrocortisone dose) did neither show differences in hormonal control nor sleep quality [14]. However, the short duration (2 weeks for each treatment) and small number of participants does not allow conclusions on long-term outcome. Regardless of type of glucocorticoid or time of application, current glucocorticoid replacement regimens fail to mimic the physiological circadian rhythm of cortisol secretion [15]. Studies applying hydrocortisone as a continuous infusion via subcutaneous insulin pumps showed better hormonal control and decreased exposure to hydrocortisone [16, 17]. Oral hydrocortisone preparations with delayed and extended release provide the therapeutic option for more physiological glucocorticoid replacement and might improve future pharmacological therapy in CAH [18].

Mineralocorticoid replacement is required in all patients with classic CAH at least during infancy and salt supplementation [6]. Fludrocortisone doses during the first year of life are commonly 150 µg/m² per day and higher than in later life. This is explained by physiological mineralocorticoid resistance during earlier postnatal life [19], which improves with maturation of the kidney; however, the exact mechanism underlying this phenomenon remains to be elucidated. Consequently, the relative mineralocorticoid dose in relation to body surface decreases throughout life. Fludrocortisone doses of 100 µg/m² per day are commonly sufficient after the first 2 years of life. This requirement drops further and adolescents as well as
adults are usually sufficiently supplemented with a total daily dose of 100–200 μg (50–100 μg/m² per day). Mineralocorticoid replacement is monitored by plasma renin activity or concentrations and blood pressure measurements using age, sex and height-adjusted references [20]. Suppressed plasma renin concentrations indicate overtreatment with the risk to induce iatrogenic hypertension with associated long-term complications. Considerable overlap of aldosterone concentrations and plasma renin activity has been shown between patients with traditionally termed ‘salt-wasting’ and ‘simple-virilizing’ CAH [5]. In principle, it might be worthwhile to reconsider the clinical usefulness of a subclassification into SW and SV forms and to look at mineralocorticoid deficiency as a spectrum of variable degrees rather than an arbitrary ‘yes/no’ decision. Importantly, mineralocorticoid requirement should be assessed on a regular basis and interpreted in conjunction with clinical findings throughout the lifetime, in particular as requirements may change with age, as outlined above. Adequate mineralocorticoid replacement generally facilitates hydrocortisone dose reduction, with 40 mg hydrocortisone exerting equivalent mineralocorticoid activity to 100 μg fludrocortisone. Of note, prednisolone has only reduced and dexamethasone does not possess any mineralocorticoid activity [4], which may lead to the necessity of mineralocorticoid dose adjustment when changing the glucocorticoid used for replacement in CAH.

**Bone Health**

Studies on bone mineral density in CAH, mostly including adolescents and young adults, generally show normal bone mineral density in patients with CAH [21–28] (table 1). However, data on bone mineral density in adults older than 30 years and in postmenopausal women indicate increased prevalence of osteopenia and osteoporosis in CAH compared to healthy controls [29–31]. Although no direct association with glucocorticoid dose could be shown so far, suppressed androgen concentrations may suggest some association with glucocorticoid overtreatment [29]. One study showed an increased fracture risk in women with CAH; in addition, bone mineral density values are indicative of osteopenia and osteoporosis [30]. The decreased bone mineral density in recent studies was observed despite a higher BMI in CAH [29–34]. Sufficient data on bone health in adults older than 40 years and particularly in CAH males are lacking, and at present it is therefore difficult to recommend regular monitoring of bone mineral density outside study settings.

**Cardiovascular and Metabolic Health**

Recent data demonstrate unfavourable cardiovascular changes in patients with CAH (table 2). Increased BMI and blood pressure compared to healthy controls already during childhood and adolescence represent major risk factors for potentially increased cardiovascular morbidity in CAH [35, 36]. An increased BMI and a higher frequency of obesity were found in 89 children (0.2–17.9 years) and BMI appeared to be positively correlated with the glucocorticoid dose [35]. The increase in fat mass has been described to occur in children aged between 2.5 and 5.5 years [37]. Interestingly, there might be a difference between patients with classic CAH, who have an increased fat mass, and patients with non-classic CAH, who have a higher lean body mass [38]. Increased total body fat has been described in adults with CAH using dual energy x-ray absorptiometry [21, 25, 27, 28], but no change in body fat distribution has been found [39]. It has been speculated that an increased body weight and fat mass might be due to an altered leptin axis in CAH; however, current findings are not fully conclusive [40–42].

Increased BMI correlates with elevated systolic blood pressure and CAH patients with normal weight presented with a tendency to diastolic hypotension, but preserved nocturnal dip of blood pressure [36]. Daytime systolic blood pressure in children and adolescents with CAH was found elevated in one study and the physiological nocturnal dip in blood pressure was absent [43], also described in another small cohort of paediatric CAH patients [44]. Recently, normal systolic blood pressure has been found in children with classic CAH, but slightly elevated blood pressure in non-classic CAH compared with controls [38]. In adult Swedish women with CAH, hypertension (defined as blood pressure above 140/90 mmHg) was observed in 3 patients (4.9%) older than 30 years, but also in 4 controls (6.6%) [39]. A retrospective analysis of blood pressure data from patient notes in the first year of life did not reveal elevated values [45]. A large cross-sectional study in adult CAH patients from the UK showed a blood pressure within the normal range, with significantly higher diastolic blood pressure in women with classic CAH as compared to age- and sex-matched controls [31]. Current data suggest a risk towards the development of higher blood pressures in CAH patients and possibly hypertension. No strong correlation of blood pressure with either glucocorticoid or mineralocorticoid dose or renin levels has been demonstrated [36, 44]. It remains unclear whether altered blood pressure is caused by iatrogenic intervention; therefore, mineralocorticoid
replacement should be carefully monitored including regular plasma renin measurements. Possible metabolic consequences of increased body fat include dyslipidaemia and insulin resistance. Only one study in CAH children treated with prednisone showed elevated triglycerides [46], whereas other studies performed in adults and children demonstrated normal cholesterol, triglycerides as well as LDL and HDL cholesterol [38, 39, 47]. Normal lipid profiles were also found in 50 untreated females with non-classic CAH [48]. Overweight and obese adults with classic CAH had similar lipid profiles to patients with normal BMI [33]. Decreased HDL levels and increased small-dense LDL were found in 27 children and young adults [49]. A larger and more homogeneous cohort of 61 females showed an even higher HDL/LDL ratio in CAH women older than 30 years (n = 34) compared to controls [39]. A recent UK study showed hypercholesterinaemia in a significant percentage of adult CAH patients; however, a significant percentage of patients was overweight with a median BMI of 27.2 kg/m² in males and 32.9 kg/m² in females with the classic form and 29.4 kg/m² in females with the non-classic form [31]. Thus, most studies show normal lipid profiles and there is little evidence for general dyslipidaemia in CAH. Therefore, a regular control of the lipid profile in all younger patients might not be necessary in clinical routine. However, it remains unclear if dyslipidaemia becomes a problem in later life with only little data on patients older than 50 years available.

Several studies found decreased insulin sensitivity in CAH patients using various methods such as oral glucose tolerance test [33, 47], the homeostasis model assessment method (HOMA-IR) [33, 40–42, 47, 48], or forearm model combined with local indirect calorimetry [50]. Decreased insulin sensitivity has already been documented in children with CAH [40, 42]. Unfavourable changes in HOMA-IR were found in CAH children compared to healthy controls, mainly relating to higher fasting insulin concentrations [40]. Treatment with pioglitazone in 12 CAH patients showed improvement of insulin sensitivity as well as blood pressure [51]. The recently published UK adult CAH cohort found insulin resistance according to HOMA-IR in one third of the patients [31]. Overall, altered insulin sensitivity seems to be therapy-associated. Both over- and undertreatment can potentially lead to insulin resistance in CAH. Undertreatment causes hyperandrogenism, which is associated with insulin resistance, whereas overtreatment can induce increased insulin resistance due to glucocorticoid excess (Fig. 1).

Increased carotid intima media thickness, a surrogate marker of atherosclerosis, was found in 19 young adults (28 ± 3.5 years) with CAH [47]. This was independent of hormonal control, glucocorticoid dose or metabolic parameters such as lipid status or glucose and insulin concentration. Onset, progression and prognostic implications of these structural changes are currently unclear.

**Female Fertility and Pregnancy Rate**

Several studies indicate reduced fecundity and fertility in women with classic CAH [52] (Table 3). Childbirth rates are low, but pregnancies are commonly normal and uneventful [53]. Another study reported nine births in 6 women seeking pregnancy and a benefit of additional mineralocorticoid medication also in patients with SV CAH [54]. A Finnish study observed a significantly lower child rate in women with classic CAH compared to the general population [55]. The prognosis for successful fertility and child rate in the SW group was very poor [55]; however, the number of patients seeking fertility and attempting to conceive was not reported in this study [55]. When differentiating between fecundity and fertility, in a UK study, only 23 of 106 women had actively tried to conceive, of whom 21 (91.3%) were successful [56]. Interestingly, pregnancy rates in patients with SW CAH and SV form were similar in this study [56]. Thus, nowadays

**Fig. 1.** Schematic overview of the hypothalamus-pituitary-adrenal axis and the hypothalamus-pituitary-gonadal axis in the situation of undertreatment (left side) and overtreatment (right side) in classic CAH. In situations of glucocorticoid undertreatment, secreted adrenal androgens are aromatized to oestrogens suppressing the hypothalamus-pituitary-gonadal axis. However, glucocorticoid overtreatment inhibits the GnRH secretion axis leading to hypogonadotropic hypogonadism. High ACTH concentrations, even if only intermittently, stimulate the growth of benign TART in the testes. Glucocorticoids are responsible for a number of metabolic side effects on the cardiovascular system, liver, bone, adipose tissue and muscle. Undertreatment leads to low blood pressure and potentially hypoglycaemia due to reduced gluconeogenesis in the liver. Underreplacement leads to elevated adrenal androgens causing early epiphyseal closure and thus reduced final height. Low glucocorticoids also cause muscle weakness, myalgia and weight loss. Overtreatment results in volume retention with oedema and high blood pressure. Patients tend to have increased blood sugars and lipids due to increased gluconeogenesis and lipolysis, respectively. Glucocorticoid-induced osteopenia and osteoporosis are mainly caused by inhibition of osteoblast function, leading to a decrease in bone formation. Furthermore, glucocorticoid overexposure can cause muscle atrophy and myopathy.

DHEA = Dehydroepiandrosterone.
Comorbidities in CAH

<table>
<thead>
<tr>
<th>Undertreatment</th>
<th>Overtreatment</th>
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<tbody>
<tr>
<td>Low blood pressure, hyponatraemia, hyperkalaemia</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>Hypoglycaemia (gluconeogenesis)</td>
<td>Liver</td>
</tr>
<tr>
<td>Reduced final height due to early epiphyseal closure as a result of increased adrenal androgens, Increased bone mass</td>
<td>Bone</td>
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<tr>
<td>Weight loss</td>
<td>Adipose tissue</td>
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<tr>
<td>Muscle weakness, myalgia</td>
<td>Muscle</td>
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Cardiovascular: High blood pressure, volume retention, oedema, hypernatraemia, hypokalaemia
Liver: Hyperglycaemia, hypertriglyceridaemia (gluconeogenesis, lipolysis?)
Bone: Osteopenia, osteoporosis (inhibition of osteoblast function, vitamin D antagonism)
Adipose tissue: Redistribution of fat mass (adrenocortical obesity), hyperlipidaemia (lipolysis?)
Muscle: Muscle atrophy, myopathy
overall fertility but not pregnancy rates seem to be reduced compared to the general population.

CAH results not only in exaggerated levels of 17-hydroxyprogesterone but also of progesterone, which may interfere with implantation when excessively elevated. Suppression of progesterone levels is sometimes very difficult to achieve. In some cases, even suppressing 17-hydroxyprogesterone concentrations did not affect elevated progesterone concentrations [57]. Adrenalectomy has been successfully used in single cases to normalize progesterone concentrations and resulted in spontaneous conception [58]. However, this procedure bears also a number of risks, including surgical and anaesthetic complications and leaves the patient completely adrenal insufficient. Moreover, adrenal rest tissue may become hyperplastic and overproduce androgens postoperatively due to even increased ACTH drive after bilateral adrenalectomy. In contrast to reduced fertility in classic CAH, fertility is only mildly reduced in non-classic CAH, but without glucocorticoid treatment an increased miscarriage rate has been reported [59, 60].

There are multiple causes for reduced fertility in females with classic CAH, including unsatisfactory intercourse due to inadequate vaginal introitus, chronic anovulation due to poorly controlled androgen excess, failure of implantation due to elevated progesterone concentration and psychological factors including differences in psychological orientation [61]. Importantly, glucocorticoid undertreatment will cause androgen excess and anovulation, while glucocorticoid overtreatment results in the suppression of the hypothalamic-pituitary-gonadal axis, in both instances resulting in compromised fertility (fig. 1).

**Male Fertility**

Fertility in men with classic CAH appears to be significantly reduced (table 3). Finnish CAH males had 80% less fatherhoods than observed in the general population [62]. Recent data from the UK showed that 37% (24/65) of males had sought fertility and 67% (16/24) had been successful [31]. Few studies have investigated fecundity in men with classic CAH but all observed significantly impaired fecundity [63–65]. A major underlying cause is testicular adrenal rest tumours (TART). The incidence of TART in male patients with 21OHD has been reported in up to 94% of cases [64, 65]. TART can already be detected in prepubertal children [66, 67]. In contrast, ovarian adrenal rest tumours are very rare [68, 69]. TARTs are thought to originate from aberrant adrenal cells descending during embryogenesis with testicular cells. ACTH-suppressive glucocorticoid treatment is widely believed to result in TART shrinkage [70]. However, in cross-sectional studies, ACTH concentrations and TART size did not correlate and TARTs even occurred in overtreated patients as indicated by suppressed ACTH concentrations [64, 65, 67]. Neither incidence nor morphology of TART correlated with hormonal profiles [71]. Dexamethasone-suppressive therapy has the potential to reduce tumour size and to restore sperm counts and fertility [72]. However, efficient treatment required therapeutic doses of 0.75 mg dexamethasone per day and more, resulting in significant side effects including major weight gain; thus, dexamethasone is an option for short-term treatment only, e.g. to achieve fertility.

Another commonly overlooked reason for reduced fecundity in males is secondary hypogonadism due to glucocorticoid overtreatment [65]. A third mechanism causing hypogonadotrophic hypogonadism is poor hormonal control with increased adrenal androgens, resulting in a negative feedback on the HPG axis mainly via aromatization to oestrogens (androstenedione to oestrone and testosterone to oestradiol) (fig. 1). In such situations, inhibin B might be a better marker of testicular function than LH and FSH [65, 73].

**Psychosocial Health and Well-Being**

Psychosocial and subjective health-related well-being has mainly been studied in females with CAH showing variable outcomes (table 4). A Swedish study applying semi-structured interviews found impaired quality of life (QoL) in 62 women with 21OHD. QoL was affected by genotype and surgical procedure [74]. Reduced QoL was also shown in another cohort of 40 (33 with classic CAH) females with 21OHD [53]. Trauma from distressing diagnostic procedures, chronic illness and psychological consequences were thought to be the underlying causes of impaired QoL in these women [53]. Psychosexual identification was impaired in 45 females compared to healthy controls matched for age, marital status, school education and professional background. Patients reported higher anxiety about sexual contacts and partnerships as well as an impaired body image. However, once these women had established a partnership, they perceived their partnership as more stable and satisfying compared to the healthy control population. The authors concluded that overall QoL was not affected [75]. Even a higher QoL was reported for adult CAH patients (16 females, 16 males) com-
### Table 1. Summary of studies on bone health in CAH patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>CAH form</th>
<th>Summary of key findings</th>
</tr>
</thead>
</table>
| Cameron et al., 1995 [21] | 13/8 | 8–32 SW, SV | Normal BMD in females, reduced BMD in males  
Increased fat mass                                                                 |
| Mora et al., 1996 [22]     | 11/19 | 17 ± 2 SW, SV, NC | Normal BMD  
No relation to therapy duration  
No difference in BMD between classic and non-classic CAH                        |
| Jääskelainen et al., 1996 [23] | 16/16 | 16–52 SW, SV, NC | Normal BMD in hydrocortisone-treated patients  
Low BMD in group with high-dose steroids                                             |
Reduced bone formation and bone turnover markers                                    |
| Girgis and Winter 1997 [81] | 12/16 | 4–22 SW, SV in 21OHD and 17OHD | Normal BMD, normal bone formation and resorption markers                             |
| Gussinyé et al., 1997 [82] | 10/23 | 1.5–28 SW | Normal BMD compared to sex- and age-matched controls                                      |
| Hagenfeldt et al., 2000 [25] | 0/13 | 20–29 SW, SV | Normal total BMD  
Reduced spine BMD, increased fat mass, GC effect                                         |
| Paganini et al., 2000 [26]  | 23/27 | 1–28 SW, SV, NC | Reduced BMD  
Normal bone formation and bone turnover markers                                        |
| De Almeida Freire et al., 2003 [83] | 17/28 | 5–16 SW, SV | Effect of sex (lower in females), duration of treatment, weight, BMI, and bone age on BMD |
| Stikkelbroeck et al., 2003 [27] | 15/15 | 17–25 SW, SV, NC | Normal BMD in males and females; reduced BMC in males only  
Increased fat mass, GC dose no effect on BMD                                            |
| Christiansen et al., 2004 [28] | 10/8  | 18–33 SW, SV | Normal BMD and BMC  
Increased fat mass                                                                    |
| King et al., 2006 [29]     | 0/26 | 21–71 SW, SV | Lower BMD of patients vs. controls (healthy sisters), lower DHEA in CAH vs. controls, no correlation of BMD and BMI, negative correlation between BMD and DHEA and DHEAS concentrations |
| Sciannamblo et al., 2006 [32] | 15/15 | 16–29 SW, SV | Decreased BMD compared to controls                                                       |
| Bachelot et al., 2007 [33]  | 9/36 | 18–47 SW, SV, NC | 55% of patients lower BMD                                                                |
| Falhammar et al., 2007 [30] | 0/61  | 18–63 SW, SV | Osteopenia in 48% of patients under 30 and in 73% in patients above 30 years, increased fracture risk |
| Elneceave et al., 2008 [84] | 0/16  | 4–19 SW, SV | Normal BMD compared to matched controls, but negative correlation of BMD and glucocorticoid dose |
| Chakhtoura et al., 2008 [34] | 10/28 | 16–39 SW, SV, NC | 45% had osteopenia, higher BMD in women than in men, negative correlation of BMD and cumulative GC dose, protective effect of BMI on BMD |
| Arlt et al., 2010 [31]     | 77   | 18–69 SW, SV, NC | 39.2% osteopenia at the lumbar spine, 6.8% osteoporosis at the lumbar spine, 28.8% osteopenia at the femoral neck, 1.4% osteoporosis at the femoral neck |

NC = Non-classic; BMD = bone mineral density; 11OHD = 11β-hydroxylase deficiency; 17OHD = 17-hydroxylase deficiency; GC = glucocorticoid; BMI = body mass index; BMC = bone mineral content; DHEA(S) = dehydroepiandrosterone (sulphate).
<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>CAH form</th>
<th>Summary of key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>male/ female</td>
<td>years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Speiser et al., 1992 [85]</td>
<td>0/6</td>
<td>27</td>
<td>NC</td>
</tr>
<tr>
<td>Paula et al., 1994 [50]</td>
<td>0/7</td>
<td>28 ± 3</td>
<td>Classic 21OHD, NC</td>
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<tr>
<td>Charmandari et al., 2002 [40]</td>
<td>12/6</td>
<td>7 ± 3</td>
<td>21OHD: SW, SV</td>
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<td>Roche et al., 2003 [43]</td>
<td>15/23</td>
<td>6.1–18.2</td>
<td>SW, SV</td>
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<tr>
<td>De Silva et al., 2004 [44]</td>
<td>4/7</td>
<td>8.5–27.2</td>
<td>21-OHD (SW, SV), 11OHD, CLAH</td>
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<tr>
<td>Bayraktar et al., 2004 [48]</td>
<td>0/50</td>
<td>22 ± 3</td>
<td>NC</td>
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<td>Saygili et al., 2005 [41]</td>
<td>0/18</td>
<td>26 ± 9</td>
<td>NC</td>
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<td>Völkl et al., 2006 [35]</td>
<td>41/48</td>
<td>0.2–17.9</td>
<td>SW, SV</td>
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<td>Völkl et al., 2006 [36]</td>
<td>23/32</td>
<td>5.3–19</td>
<td>SW, SV</td>
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<tr>
<td>Hoepfner et al., 2006 [86]</td>
<td>13/21</td>
<td>6–26</td>
<td>SW, SV</td>
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<tr>
<td>Nebesio et al., 2006 [87]</td>
<td>42/49</td>
<td>SW, SV</td>
<td>Children with 21OHD appear to have a higher prevalence of HTN when compared to historical reports of paediatric populations</td>
</tr>
<tr>
<td>Falhammar et al., 2007 [39]</td>
<td>0/61</td>
<td>18–63</td>
<td>SW, SV, NC</td>
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<tr>
<td>Sartorato et al., 2007 [47]</td>
<td>9/10</td>
<td>28 ± 3.5</td>
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<td>Bachelot et al., 2007 [33]</td>
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<td>Völkl et al., 2009 [42]</td>
<td>21/30</td>
<td>5–19</td>
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<tr>
<td>Völkl et al., 2009 [88]</td>
<td>21/30</td>
<td>5.6–19.6</td>
<td>SW, SV</td>
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<td>Arlt et al., 2010 [31]</td>
<td>61/132</td>
<td>18–69</td>
<td>SW, SV, NC</td>
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</tbody>
</table>

NC = Non-classic; 11OHD = 11β-hydroxylase deficiency; 17OHD = 17-hydroxylase deficiency; GC = glucocorticoid; ivGTT = intravenous glucose tolerance test; BP = blood pressure; CLAH = congenital lipoid adrenal hyperplasia; SDS = standard deviation score; HTN = hypertension; oGTT = oral glucose tolerance test; sOB-R = soluble leptin receptor; DHEAS = dehydroepiandrosterone sulphate.
Comorbidities in CAH

Table 3. Summary of studies on fecundity and fertility in CAH patients

<table>
<thead>
<tr>
<th>Patients male/female</th>
<th>Age years</th>
<th>CAH form</th>
<th>Summary of key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urban et al., 1978 [91]</td>
<td>20/0</td>
<td>18–37</td>
<td>SW, SV, 11OHD (n = 1)</td>
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<td>0/80</td>
<td>18–69</td>
<td>SW, SV</td>
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<td>Jääskelainen et al., 2000 [62]</td>
<td>16/0</td>
<td>16–36</td>
<td>SW, SV</td>
</tr>
<tr>
<td>Jääskelainen et al., 2000 [55]</td>
<td>0/29</td>
<td>16–53</td>
<td>SW, SV</td>
</tr>
<tr>
<td>Cabrera et al., 2001 [63]</td>
<td>30/0</td>
<td>17–43</td>
<td>SW, SV</td>
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<tr>
<td>Stikkelbroeck et al., 2001 [64]</td>
<td>17/0</td>
<td>16.6–40.8</td>
<td>SW, SV</td>
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<tr>
<td>Krone et al., 2001 [53]</td>
<td>0/18</td>
<td>18.3–36.0</td>
<td>SW, SV, NC</td>
</tr>
<tr>
<td>Hoepfner et al., 2004 [54]</td>
<td>0/7</td>
<td>22–33</td>
<td>SW, SV</td>
</tr>
<tr>
<td>Moran et al., 2006 [59]</td>
<td>0/101</td>
<td>29.7 ± 9.7</td>
<td>NC</td>
</tr>
<tr>
<td>Hagenfeldt et al., 2008 [89]</td>
<td>0/62</td>
<td>18–63</td>
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</tr>
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<td>Reich et al., 2009 [65]</td>
<td>22/0</td>
<td>18–48</td>
<td>SW, SV</td>
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<tr>
<td>Casteras et al., 2009 [56]</td>
<td>0/106</td>
<td>18–68</td>
<td>SW, SV</td>
</tr>
<tr>
<td>Bidet et al., 2010 [60]</td>
<td>0/190</td>
<td>13–52</td>
<td>NC</td>
</tr>
<tr>
<td>Arlt et al., 2010 [31]</td>
<td>65/47</td>
<td>18–69</td>
<td>SW, SV, NC</td>
</tr>
</tbody>
</table>

NC = Non-classic; 11OHD = 11β-hydroxylase deficiency; HPG axis = hypothalamus-pituitary-gonadal axis.

pared to the general Finnish population [76]. A study including only children and young adults showed normal psychological adjustment [77]. A recent Swedish study described impairment of several QoL-associated factors, but assessing QoL and sexual function by validated instruments did not identify large differences between CAH females and controls [78]. A population-based study in Norway found impaired subjective health status in adult CAH patients using the Short Form 36 (SF-36) [79]. A cross-sectional study of adult CAH patients under surveillance at 17 UK endocrine centres also showed significantly impaired subjective health status assessed by SF-36. Furthermore, the same study demonstrated increased anxiety scores in all CAH patients and increased depression scores in patients with classic CAH [31]. Comparing the subjective health status in adults with CAH from two large German specialist centres revealed impaired vitality scores measured using the SF-36; however, otherwise normal subjective health-related QoL [80]. Thus, the overall situation in CAH with regard to psychosocial health and well-
being remains unclear. Different findings are not directly comparable, as different domains of QoL and well-being have been assessed with different tools. There also remains the possibility that observed differences in QoL represent mixed results from CAH-specific factors and health care delivery. The probable onset and progression of impaired QoL or subjective health status during childhood and adolescence remain to be elucidated.

**Conclusion**

Management of CAH patients is complex with an increasing number of challenges requiring multidisciplinary expert care. Individualized glucocorticoid and mineralocorticoid replacement therapy should aim for appropriate replacement avoiding under- or overtreatment. Currently, the degree of the iatrogenic component in observed comorbidities during later life is unclear. Therefore, early forerunners of recognized health problems in later life require early identification, life-long assessment and individualized therapy adjustment. A smooth transition process between paediatric and adult care and continuous communication between paediatric and adult endocrinologists, and other specialists involved in the multidisciplinary team is essential to improve care for patients suffering from this complex condition.

**Acknowledgments**

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**Table 4. Summary of studies on QoL in CAH patients**

<table>
<thead>
<tr>
<th>Patients male/female</th>
<th>Age, years</th>
<th>CAH form</th>
<th>Summary of key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuhnle et al., 1995 [75]</td>
<td>0/45</td>
<td>27 ± 6.6</td>
<td>SW, SV, NC</td>
</tr>
<tr>
<td>Jääskelainen et al., 2000 [76]</td>
<td>16/16</td>
<td>27.4 ± 8.5</td>
<td>SW, SV</td>
</tr>
<tr>
<td>Berenbaum et al., 2004 [77]</td>
<td>42/72</td>
<td>3–31</td>
<td>SW, SV, NC</td>
</tr>
<tr>
<td>Johannsen et al., 2006 [90]</td>
<td>0/40</td>
<td>17.9–51.8</td>
<td>21OHD: SW, SV, NC; CLAH, 17OHD; ORD</td>
</tr>
<tr>
<td>Nordenskjold et al., 2008 [74]</td>
<td>0/62</td>
<td>18–63</td>
<td>SW, SV, NC</td>
</tr>
<tr>
<td>Frisen et al., 2009 [78]</td>
<td>0/62</td>
<td>18–63</td>
<td>SW, SV, NC</td>
</tr>
<tr>
<td>Nermoen et al., 2010 [79]</td>
<td>25/47</td>
<td>18–72</td>
<td>SW, SV</td>
</tr>
<tr>
<td>Arlt et al., 2010 [31]</td>
<td>47/101</td>
<td>16–64</td>
<td>SW, SV, NC</td>
</tr>
<tr>
<td>Reisch et al., 2010 [80]</td>
<td>39/65</td>
<td>18–80</td>
<td>SW, SV</td>
</tr>
</tbody>
</table>

NC = Non-classic; 17OHD = 17-hydroxylase deficiency; EDLQ = Every Day Life Questionnaire; MLDL = Munich List of Quality of Life Dimensions; POMS = Profile of Mood States; PGWB = Psychological General Well-Being; CBCL = Child Behaviour Checklist; SIQYA = Self-Image Questionnaire for Young Adolescents; MPQ = Multidimensional Personality Questionnaire; QoL-AGHDA = Quality of Life Assessment of Growth Hormone Deficiency in Adults; SCL-90-R = Symptom Checklist 90 Revised; PGWBI = Psychological General Well-Being Index; QoLS = Quality of Life Scale; HADS = Hospital Anxiety and Depression Scale; GBB24 = Giessener Beschwerdebogen 24 (Giessen Complaint List); ORD = P450 oxidoreductase deficiency.
41 Saygili F, Oge A, Yilmaz C: Hyperinsu-
46 boteiro D, Arango A, Danon M, Lifshitz F:

38 Williams RM, Deeb A, Ong KK, Bich W,
44 de Silva KS, Kanumakala S, Brown JJ, Jones
40 Charmandari E, Weise M, Bornstein SR,
45 Mooij CF, Kapusta L, Otten BJ, Claahsen-
36 Völkl TMK, Simm D, Dotsch J, Rascher W ,
37 Cornean RE, Hindmarsh PC, Brook CG:

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