Review

Health problems of adolescent and adult patients with 21-hydroxylase deficiency

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Abstract. Twenty-one-hydroxylase deficiency (21-OHD) is one of the most common forms of congenital adrenal hyperplasias. Since the disease requires life-long steroid hormone replacement, transition from pediatric clinical care to adolescent and adult care is necessary. Recently, several studies have shown that morbidity and quality of life in adolescent and adult patients with 21-OHD are impaired by obesity, hypertension, diabetes mellitus, impaired glucose tolerance, dyslipidemia, and osteoporosis. In addition, excess adrenal androgen impairs fertility in both females and males. This mini review discusses the current health problems in adolescent and adult patients with 21-OHD and ways to prevent them.

Key words: 21-hydroxylase deficiency, adolescent, adult, obesity, fertility

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Introduction

The most common form of congenital adrenal hyperplasia is 21-hydroxylase deficiency (21-OHD), which affects about 1 in 18,000 worldwide (1–3). This disease is classified into three subtypes according to its severity. The most severe form is the salt-wasting (SW) form caused by glucocorticoid and mineralocorticoid deficiencies. SW females express virilized external genitalia (VEG) together with low serum sodium levels. The simple virilizing (SV) form also presents with VEG in affected female neonates, but aldosterone synthesis is not impaired. Nonclassic (NC) is the mildest form and can manifest as hyperandrogenism later in life (3). These phenotypic differences are mainly due to the genotype of the 21-hydroxylase gene *(CYP21A2)* (1–5).

Patients with SW and SV forms require life-long steroid replacement. During the pediatric period, the main targets for treatment are normal physical growth, normal development of secondary sex characteristics, and the avoidance of adrenal crisis (1, 3). However, in adolescents and adults, growth is no longer a concern. Instead, the main targets for treatment are shifted to normal fertility and the prevention of metabolic health problems (6–8).

After 1950, the disease prognosis improved due to the introduction of glucocorticoid and mineralocorticoid treatments; however, current glucocorticoid replacement therapy is not ideal. Excessive androgen from the adrenal gland is sometimes difficult to suppress with glucocorticoid treatment and this results in precocious puberty and short stature in boys
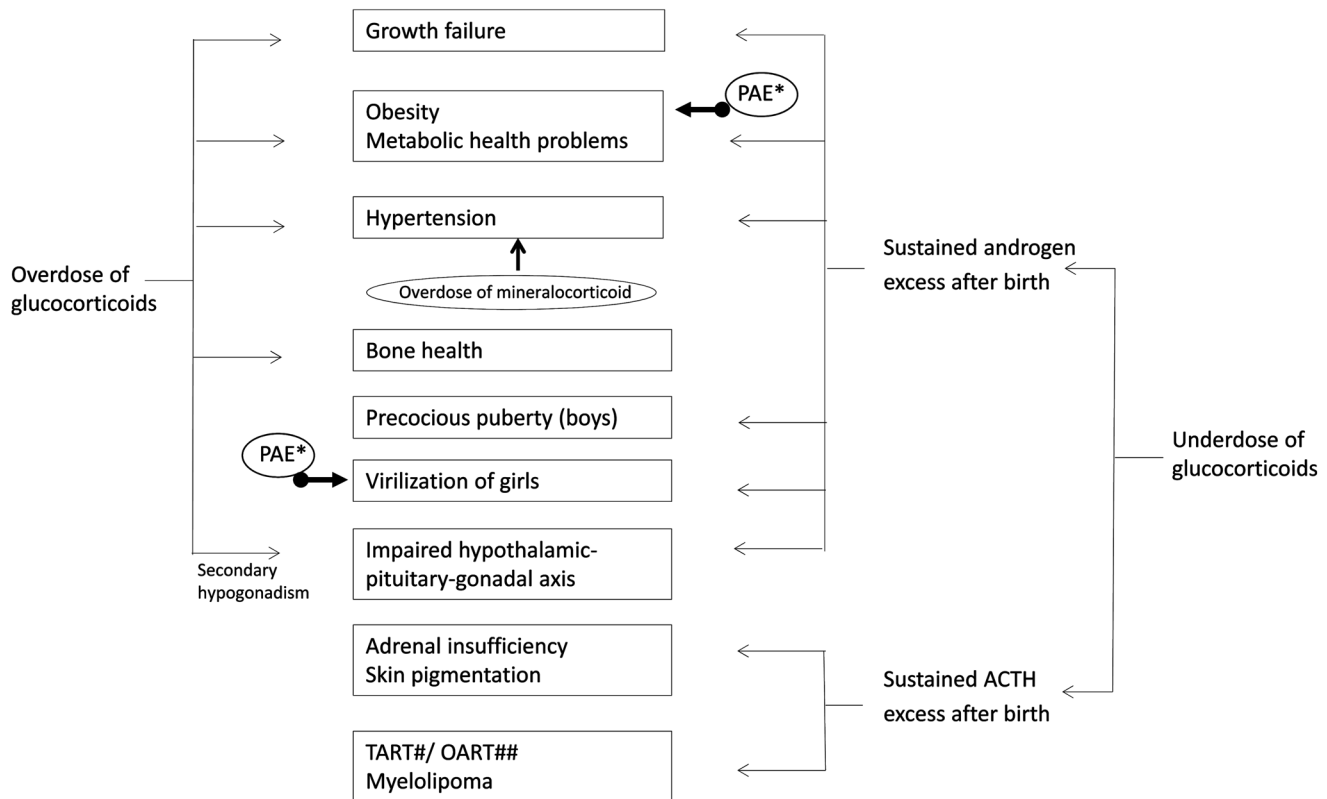
Fig. 1. Endocrine imbalances in 21-OHD. * PAE: Prenatal androgen excess. # TART: Testicular adrenal rest tumor. ## OART: Ovarian adrenal rest tumor. Prenatal androgen excess causes virilization of the female fetus. In addition to high postnatal androgen, high prenatal levels of androgen from the adrenal gland may be related to the development of obesity, insulin resistance, and metabolic problems (bold arrow).

and virilization and short stature in girls. To suppress adrenal androgen, supraphysiological doses of glucocorticoids are necessary (1, 3, 6–8); however, these induce iatrogenic Cushing features, resulting in metabolic health problems (1, 3, 6–8). Achieving a glucocorticoid balance is very difficult.

This mini review discusses the current health problems in adolescent and adult patients with 21-OHD and ways to prevent them.

Metabolic and Cardiovascular Issues

Health problems associated with patients with 21-OHD are summarized in Fig. 1. To date, several studies have shown an increased risk of obesity, hyperlipidemia, and hypertension in adolescent and adult patients with 21-OHD (9–12). Finkelstein *et al.* (9) reported the clinical features of 244 adult patients with 21-OHD in the United States. In this study, approximately 30% of patients were obese and 18% had metabolic syndrome. From a study in the United Kingdom, Arlt *et al.* (10) reported that in adults with 21-OHD, obesity was observed in 42% of patients, hypercholesterolemia in 46%, and insulin resistance in 29%. In addition, women with SW and SV 21-OHD had higher diastolic blood pressure than age- and sex-matched controls. Falhammar *et al.* (11) presented 21-OHD data from adults in Sweden. According to their study, the frequency of hypertension, hyperlipidemia, atrial fibrillation, and venous thromboembolism were higher than those of control groups. In

addition to hypertension, impaired vascular endothelial and smooth muscle function was observed in adolescents with 21-OHD (13, 14).

From Japan, Matsubara *et al.* (15) reported data on the growth and body composition of children with 21-OHD. Body mass index (BMI) both in male and female patients increased and adiposity rebound occurred earlier in patients compared with healthy Japanese children. Furthermore, the same Japanese group reported that lower body weight and BMI at birth were related to early adiposity rebound and suggested that prenatal androgen excess may affect the early adiposity rebound (16). Early adipose rebound in children with 21-OHD has also been reported by Sarafoglou *et al.* (17). It is well recognized that early adiposity rebound is associated with future obesity (18, 19); however, the mechanism of early adipose rebound in children with 21-OHD has not yet been clarified. Additionally, life style intervention for prevention of obesity in children with 21-OHD is also important.

Several hypotheses have been proposed for developing obesity; 1) glucocorticoid excess, 2) postnatal androgen excess, and 3) prenatal androgen excess (Fig. 1).

Regarding glucocorticoid excess, the current replacement therapy is not ideal. Since the current glucocorticoid regimen is usually divided into three doses (morning, daytime, and evening), it is impossible to mimic the normal circadian rhythm of the ACTH-cortisol axis thereby preventing the early morning surge of ACTH, which is the main driver of excess androgen secretion from the adrenal gland (3, 7, 8). To obtain good control, a glucocorticoid dose higher than the physiological dose is required. As a result, high serum cortisol levels lead to Cushing features and several additional health problems (Fig. 1). To solve these problems and mimic physiological cortisol secretion, a modified release formulation of hydrocortisone has recently been developed and clinical trials of this drug have been reported (20, 21). According to these studies, twice-daily administration of this drug achieved a dual rhythm of cortisol secretion, remarkably similar to physiological cortisol secretion. Furthermore, this medication can suppress 17-hydroxyprogesteron and adrenal androgen much better than the conventional glucocorticoid regimen. This finding is promising for the development of a glucocorticoid replacement regimen for 21-OHD.

Knowles *et al.* (22) reported on the clinical presentations of children with 21-OHD in the United Kingdom, aged 1–15 yr, where neonatal mass screening for congenital adrenal hyperplasia is not performed nationwide. In this study, 21% of boys and 41% of girls were obese at the time of the first diagnosis prior to glucocorticoid treatment. It has also been reported that decreased insulin sensitivity is associated with hyperandrogenism in untreated patients with NC form of 21-OHD (23, 24). In addition, insulin resistance was also found in women with polycystic ovary syndrome (PCOS) with hyperandrogenism (25). These findings indicate that excess adrenal androgen may induce insulin resistance and obesity. Furthermore, several animal studies suggest that prenatal hyperandrogenism affect fetal programming, resulting in insulin resistance, dyslipidemia, cardiovascular disease, and metabolic syndrome (26, 27). Taken together, these data suggest that patients with 21-OHD have an increased risk of obesity independent of glucocorticoid therapy, due to pre- and postnatal adrenal androgen excess.

Hypertension can be caused by an overdose of glucocorticoids which can also involve mineralocorticoids. Mineralocorticoids are used in the treatment of SW 21-OHD. In the SV form, there may be a subclinical aldosterone deficiency, and mineralocorticoids may be beneficial in maintaining serum sodium and decreasing ACTH and vasopressin, resulting in a lower glucocorticoid dosage (3). An Endocrine Society Clinical Practice Guideline recommends that mineralocorticoids should be used in all patients with 21-OHD during early infancy (3). Bonfig *et al.* (28) reported that 45% of these
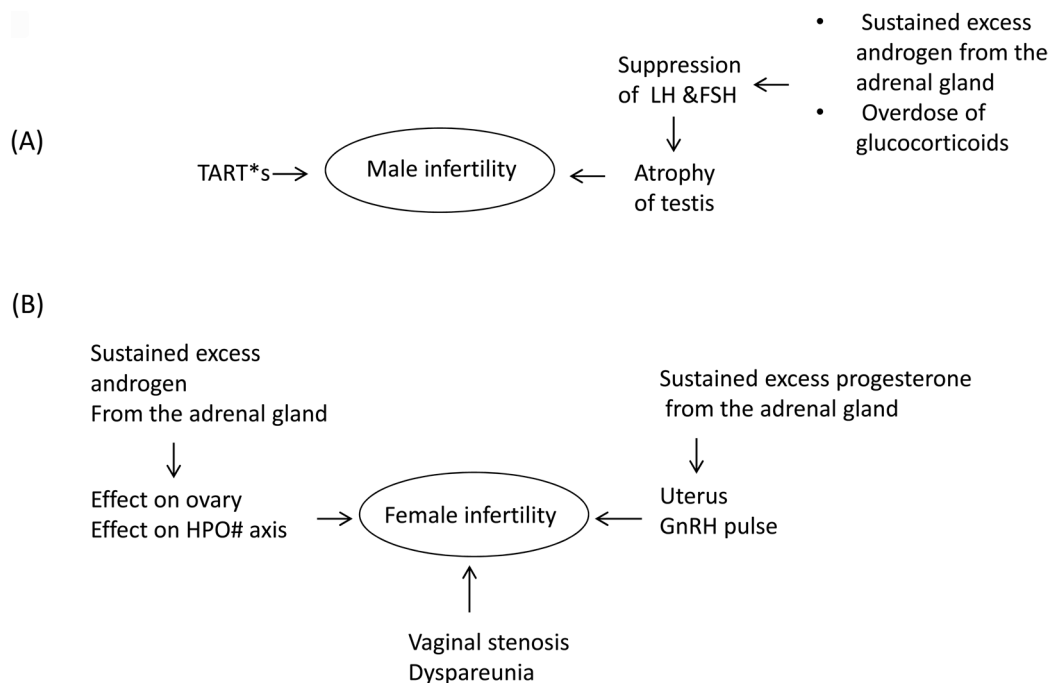
Fig. 2. (A) Factors affecting male infertility. In adult males with 21-OHD, TARTs are frequently observed, affecting male fertility. (B) Factors affecting female infertility. In females, excess androgen and progesterone from the adrenal gland affects the ovaries, hypothalamic-pituitary-ovarian axis, and the uterus, resulting in infertility. In addition, vaginal insufficiency with dyspareunia after surgery is related to a low fertility rate. * TART: Testicular adrenal rest tumor. # HPO: Hypothalamic-pituitary-ovary.

patients had increased systolic blood pressure during the first year of life and 15% were still hypertensive at 2 yr of age. They suggested that hypertension in these children is probably caused by mineralocorticoid excess (28, 29). Therefore, to avoid mineralocorticoid excess, close monitoring of blood pressure and plasma renin activity are mandatory not only in adolescent and adult patients, but also from infancy to childhood.

Fertility in Male Patients

Male fertility in patients with 21-OHD is impaired when disease control is poor. A recent French study reported that severe oligospermia or azospermia was found in 42% of male patients. There are several reasons for male infertility (Fig. 2A). First, excess androgen from the adrenal gland impairs testicular function, suppressing LH and FSH, resulting in testicular atrophy. Second, testicular adrenal rest tumors (TARTs) may be involved. TARTs have been found in 20% to 50% of male patients with classical 21-OHD (12, 30–32). The pathogenesis of TART is considered to involve adrenocortical primordial cells, which aberrantly move into the testis or reprogram Leydig cell precursors (30–32). TARTs destroy normal testicular tissue and cause compression of the seminiferous tubules leading to obstructive azospermia.

Fertility in Female Patients

Adult females with 21-OHD are at risk of oligomenorrhea, chronic anovulation, and infertility (33–35). These symptoms are caused by multiple factors (Fig. 2B) (33–35), one being the direct effect of adrenal androgen on the ovaries.

Androgens induce enlarged multicystic ovaries and theca interstitial hyperplasia in 21-OHD (34). Female-to-male trans-sexual individuals with testosterone administration also develop polycystic ovaries (36). Secondly, a high serum androgen level is thought to impair the normal hypothalamic-pituitary-ovarian (HPO) axis. A study of females with NC 21-OHD showed an increase in LH release (37), resulting in ovarian dysfunction, similar to that observed in polycystic ovary syndrome (33–35). Thirdly, excess progesterone from the adrenal gland also affects reproductive function. It has been reported that high levels of progesterone impair endometrial receptivity and decidualization (38). In addition, gender dysphoria and vaginal insufficiency with dyspareunia after surgery, have been related to a low fertility rate (39, 40). Finally, overdoses of glucocorticoids also induce hypogonadotropic hypogonadism due to the inhibitory effect on the hypothalamic control of gonadotropin secretion (41).

Tumors in Adults with 21-OHD

While TARTs are frequently observed in adult male patients, ovarian adrenal rest tumors (OARTs) are rare in comparison (6–8). In one small study, 15 female adult patients were evaluated by ultrasonography and magnetic resonance imaging and no cases of OARTs were found (42). These female patients were regularly followed while hospitalized and good control of the disease was achieved. OARTs were usually found when 21-OHD disease management was very poor and an adrenalectomy was performed (43, 44).

Adrenal myelolipoma has also been reported in patients with 21-OHD (45–48). Myelolipoma is a benign tumor composed of myeloid tissue and it is thought that sustained high ACTH levels may play a role in the growth of this tumor. In one study, 6% of adult patients with 21-OHD had myelolipomas, but none had malignant tumors (47). Since myelolipomas are benign, resection

is not necessary, but in cases of very large or bilateral tumors they may be surgically removed (45, 46, 48).

Bone Problems

Glucocorticoids are used therapeutically for several diseases such as autoimmune, rheumatic, kidney, gastrointestinal, and endocrine disorders. Since excess glucocorticoids cause osteopenia and osteoporosis, patients with 21-OHD have an increased risk for these conditions (49). Currently, controversies exist concerning bone health in adolescent and adult patients with 21-OHD. A study from the United States showed that 37% of adult patients had low bone mineral density (BMD) (9). In a study of adult patients with 21-OHD from the United Kingdom, 40% of patients exhibited osteopenia while 7% had osteoporosis (10). On the other hand, Koetz *et al.* (50) reported normal lumbar spine BMDs in patients with 21-OHD. Ceccato *et al.* (51) also reported that lumbar spine BMDs was similar to that of age-matched controls. Furthermore, they showed there was no relationship between glucocorticoid dosage and lumbar spine BMDs.

These contradictory results may be due to heterogeneous populations, disease types, age, and glucocorticoid treatment regimens. While it has not been possible to draw a definitive conclusion regarding bone loss in patients with 21-OHD, it is important to keep in mind that osteopenia and osteoporosis may occur due to their lifelong treatment with glucocorticoids.

Hormonal Evaluation of Adolescents and Adults

Seventeen-hydroxyprogesterone (17-OHP) is a standard marker of glucocorticoid dose and presumably androgen excess in children and adults, but the correlation between 17-OHP and adrenal androgen is thought to be variable in adults (6–8). In both male and female children and adults, normal and suppressed 17-OHP

levels indicate glucocorticoid overdose. Merke *et al.* (6, 8) suggest that adult target levels for 17-OHP should be 400–1200 ng/dL. However, in young adult females interested in maintaining fertility, 17-OHP should be administered at a lower level (< 800 ng/dL) (6, 8). As previously stated, progesterone from the adrenal gland impairs fertility in females. Casteras *et al.* (52) reported that in their patients, they maintained a low serum progesterone level (< 0.6 ng/mL) during the follicular phase, yet their patient pregnancy rate was 91% which is similar to that of the normal population. Therefore, this level of progesterone in the follicular phase may be recommended to adult females who want to become pregnant.

In adult males without TARTs, rather high levels of serum 17-OHP (< 2,500 ng/dL) are acceptable. When very high testosterone levels are produced by the adrenal gland, adrenal androgen suppresses LH and FSH, resulting in testicular atrophy and infertility in adult males. Auchus (7) suggested that the measurement of androstenedione may be useful in determining whether testosterone in an adult male is derived from the testes (normal function) or the adrenal gland (compensatory and/or abnormal function). According to this study, if the androstenedione to testosterone ratio is > 0.5, testosterone is mainly derived from the adrenal gland, while if this ratio is < 0.2, the testosterone is mainly derived from the testes. In addition, serum levels of LH and FSH also affect fertility in adult males. King *et al.* (53) reported that an elevated FSH level is associated with TARTs and a suppressed LH level is a marker for oligospermia, therefore routine measurement of LH and FSH levels should be carried out in male patients.

Glucocorticoid and Mineralocorticoid Treatment in Adolescents and Adults

In children, hydrocortisone (HC) is used because long-acting glucocorticoids have stronger growth-suppressive effects compared with HC.

If patients with 21-OHD are well controlled, the HC regimen from childhood should be continued into adolescence and adulthood. However, disease control becomes difficult during puberty. During puberty, secretion of sex steroids, growth hormone, and insulin-like growth factor-1 increase. The increase of these hormones inhibits 11β hydroxysteroid dehydrogenase type 1 activity (54, 55) which mainly metabolizes inactive cortisone to active cortisol. Secondly, high levels of growth hormone and insulin like growth factor-1 at puberty increase the glomerular filtration rate, leading to cortisol clearance from kidney (54, 56). These findings indicate that during puberty, the dose of HC may need to be increased. According to the opinion of an expert (1), guidelines from Japan suggest that levels of HC alone can sometimes be difficult to control during puberty and thus long-acting glucocorticoids may be used in pubertal patients who have almost attained adult height. Auchus (7) proposed a stepped-up therapy for adults with 21-OHD. HC is the first step of the therapy and administration three times a day is recommended. However, HC has a short half-life, such that a bedtime dose is not sufficient to suppress the early morning rise in ACTH and subsequent excess androgen secretion. If control of the disease is difficult using only HC, a second long-acting glucocorticoid such as dexamethasone or predonisolone can be added before sleep at night. If, despite this regimen, control is poor, a third twice-daily dose of predonisolone should be considered. Once or twice daily dexamethasone is the final choice, since dexamethasone is prone to induce iatrogenic Cushing features. However, dexamethasone should be avoided in young adult women who hope to become pregnant, because placental 11β hydroxysteroid dehydrogenase type 2 is unable to inactivate dexamethasone, thus allowing transfer from the mother to the fetus (3, 7).

It has been recognized that glucocorticoid metabolism differs greatly between individuals. Consequently, dexamethasone and prednisolone

Table 1. Dose and regimen of glucocorticoids in adolescents and adults

Glucocorticoids	Times	Total doses of per day
HC	Three times a day	15–30 mg
HC + Pred*	Morning and evening HC** Bedtime Pred	15–25 mg 1–2.5 mg
HC + Dex#	Morning and evening HC** Bedtime Dex	15–25 mg 0.1–0.3 mg
Pred	Twice a day	5–10 mg/day (start 5 mg a day)
Dex	Once a day or twice a day	0.5–1 mg (start 0.1–0.15 mg a day)

*Pred: predonisolone. **HC may be used in the morning and evening when given twice as a divided dose. The evening dose of HC may alternatively be given in the early afternoon. #Dex: dexamethasone. Metabolism of dexamethasone is variable in individuals, so dexamethasone must be administered once or twice daily. Because dexamethasone can transfer to the fetus, dexamethasone should not be used in women who may become pregnant. When Pred or Dex are used, begin with a low dose. Adjust dose after 4 wk after evaluating clinical features and biochemical parameters.

treatments should begin at a low dose, and dose adjustment should be performed at 4 wk after evaluating symptoms and biochemical parameters (7, 8). Based on several reports, current commonly-used treatment regimens in adolescents and adults are summarized in Table 1.

Most patients diagnosed during childhood are treated with mineralocorticoids in combination with glucocorticoids. As mentioned previously, an excess of mineralocorticoids causes hypertension; thus, blood pressure, serum potassium, and plasma renin activity should be closely monitored. There are some reports stating that the mineralocorticoid dosage in some adult patients with SW could be gradually decreased or no longer be needed (1, 3).

Conclusion

Management targets change as a patient passes from childhood to adolescence and adulthood. In adolescents and adults, long-term side-effects of glucocorticoids should be minimized and androgen excess should be adequately suppressed to maintain fertility and to prevent metabolic consequences. Tumor prevention is also a concern.

To date, there has not been a definitive protocol covering the transition from childhood to adolescence and adult care. The best approach includes the involvement of pediatric and adult endocrinologists, health care staff, patients, and their families.

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