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Cardiovascular Disease Risk in Adult Women with Congenital Adrenal Hyperplasia Due to 21-hydroxylase Deficiency

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Abstract

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is a common autosomal recessive disorder characterized by impaired cortisol biosynthesis, with or without aldosterone deficiency, and androgen excess. Patients with the classic (severe) form also have epinephrine deficiency. Patients with CAH have an increased prevalence of risk factors for cardiovascular disease including obesity, hypertension and insulin resistance. Androgen excess in women appears to be an additional risk factor for cardiovascular disease. Carotid intima media thickness, a measure of subclinical atherosclerosis also has been found to be increased in adults with CAH. The multiple hormonal imbalances present in the adult woman with CAH, in combination with chronic glucocorticoid therapy, contribute to cardiovascular disease risk. Further investigation of the predisposition to cardiovascular disease in women with CAH is warranted. Longitudinal studies are needed and interventions targeting obesity, insulin resistance, hypertension and hyperandrogenism may offer improved outcome.

Keywords

cardiovascular risk; congenital adrenal hyperplasia; metabolic syndrome; hyperandrogenism

INTRODUCTION

Congenital adrenal hyperplasia (CAH) is an autosomal recessive androgen excess disorder of adrenal origin. Ninety-five percent of cases are due to deficiency of the 21-hydroxylase enzyme[1]. Classic CAH, the most severe form, is characterized by impaired cortisol and aldosterone secretion, and impaired adrenomedullary function (Figure 1). Females with classic CAH are born with ambiguous genitalia due to exposure to excess androgens *in utero*. They have adrenal insufficiency, and 75 percent have severe aldosterone deficiency resulting in salt-wasting. These women receive life-time glucocorticoid, and usually, mineralocorticoid therapy. Adult women may present with nonclassic CAH (NCAH), the mild form of the disease, with manifestations of hyperandrogenism such as hirsutism or

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infertility. The mild impairment in 21-hydroxylase enzyme allows for sufficient cortisol production, but at the expense of androgen excess. Women with NCAH are born with normal genitalia and do not have adrenal insufficiency. They may have no apparent clinical symptoms and their presentation may overlap with polycystic ovarian syndrome (PCOS). Many, but not all, women with NCAH require glucocorticoid therapy.

Little is known about the metabolic long-term consequences in adult women with CAH. However, several cardiovascular disease (CVD) risk factors have been found to be increased in patients with CAH including obesity, hypertension and insulin resistance. PCOS, a more common endocrinopathy characterized by androgen excess in women, has been associated with an unfavorable cardiovascular risk profile. Studies of patients with PCOS suggest that androgen excess in women may be an independent risk factor for CVD[2,3]. Long-term glucocorticoid therapy and the hormonal imbalances characteristic of CAH play a role in the development of adverse CVD risk in women with CAH.

CVD is a leading cause of morbidity and mortality for women in the U.S. Traditional CVD risk factors include: hypertension, dyslipidemia, age >55 years, current smoker, diabetes, and family history of premature coronary artery disease in a 1st-degree relative (men <55 years, women <65 years)[4]. Newer CVD risk factors continue to emerge, including metabolic syndrome, insulin resistance, markers of subclinical atherosclerosis, impaired endothelial function, and inflammation. Some of these CVD risk factors have been studied in patients with CAH and others have yet to be studied.

HORMONAL IMBALANCES AND CVD RISK

Hypercortisolism

Patients with CAH are at risk for iatrogenic Cushing syndrome because supraphysiological glucocorticoid doses are often needed to adequately suppress adrenal androgen production[1]. Cushing syndrome has been found to be associated with adverse risk for CVD[5,6]. In one study, 74% of patients with Cushing syndrome were overweight or obese, and >60% of patients had at least three CVD risk factors[6].

There is no standard glucocorticoid regimen for treating adults with CAH. Adults are treated with a variety of glucocorticoid regimens including short-acting hydrocortisone given twice or thrice daily, or longer-acting forms of glucocorticoid, such as dexamethasone or prednisone[7]. No form of glucocorticoid replacement is able to mimic the normal circadian rhythm of cortisol secretion[8]. This nonphysiological replacement might contribute to the development of signs and symptoms of hypercortisolism and the subsequent development of CVD risk factors.

Hyperandrogenism

Androgen excess appears to be a risk factor for CVD in women based on the unfavorable CVD risk profile found in women with hyperandrogenism. Obese women are characterized by functional hyperandrogenism, with elevated free testosterone likely playing a role in the development of the metabolic syndrome. In PCOS, elevated free testosterone has been associated with increased systolic blood pressure (SBP) and diastolic blood pressure (DBP),

independent of other factors such as age, insulin resistance and dyslipidemia[9]. In 280 young healthy women, elevated DHEAS levels were found to have an independent association with blood pressure (BP) levels[10].

Androgen excess may be an independent contributor to the development of dyslipidemia, with one study of 21 women with hyperandrogenism showing independent effects of hyperandrogenism and hyperinsulinism on dyslipidemia[11]. Women with PCOS are predisposed to developing abnormal, atherogenic lipid profiles, with increased total cholesterol, LDL-C and triglyceride levels, and decreased HDL-C levels closely associated with insulin resistance [12].

Hyperandrogenism may itself lead to hyperinsulinism, as studied in adolescent girls and women[13,14]. Interestingly, antiandrogen (flutamide) treatment results in partial reversal of insulin resistance in hyperandrogenic women[15]. In PCOS, a primarily ovarian androgen excess disorder, patients have insulin resistance, irregular menses and infertility, often combined with obesity. High insulin levels act on the ovary, with luteinizing hormone (LH), to increase thecal cell production of testosterone[16] (Figure 1). Many of the findings in PCOS may be applicable to the adult female with CAH. However, much is unknown regarding the clinical implications of hyperandrogenism in relation to CVD risk in the adult female with CAH.

Insulin Resistance

Insulin resistance is a main component of the metabolic syndrome and a risk factor for coronary artery disease. In patients with CAH, insulin resistance has been noted in several studies, by different indices including fasting insulin, homeostasis model assessment-insulin resistance (HOMA) and frequently sampled IV glucose tolerance test (FSIVGTT). Higher insulin levels and HOMA have been noted in mixed cohorts of male and female patients with CAH, compared to body mass index (BMI) matched controls[17,18], and in adult women >30 years old with classic CAH or NCAH[19]. In women with untreated NCAH, insulin resistance has been noted by FSIVGTT or HOMA method[20,21]. In a long-term follow-up study of adults with CAH, HOMA was found to increase with increasing BMI[22].

Patients with classic CAH have impaired adrenomedullary function, and epinephrine deficiency in classic CAH has been associated with elevated insulin and leptin levels[17,23–25]. Leptin, secreted by adipose tissue, modulates energy homeostasis by acting centrally, and is in turn regulated by multiple factors including the adrenal medulla and insulin (Figure 1).

Adrenomedullary function has not been evaluated in NCAH, but is expected to be normal or near-normal. Interestingly, in a study of 18 untreated NCAH women, hyperinsulinism, but not hyperleptinemia was found[21]. The relationship between insulin and leptin is complex, as they indirectly influence each other through their action on the central nervous system, with evidence of a possible direct effect of leptin on the β cell[26] (Figure 1).

Insulin has also been shown to increase adrenal steroidogenesis, by increasing 17,20 lyase and 17 α-hydroxylase activity, key catalytic enzymes in androgen production [15,27]. Insulin resistance may contribute to irregular menses in women with CAH[19], similar to patients with

PCOS. There is an increased incidence of polycystic ovaries on ultrasonography in females with CAH[28], with an overall prevalence of 76% in postmenarchal women with CAH found in one study[29].

Obesity

Obesity is reaching epidemic proportions in the U.S.[30,31] with a concomitant increase in the prevalence of cardiovascular disease, type 2 diabetes and the metabolic syndrome[32]. Several measurements of obesity exist including BMI, waist circumference, and measurements of percent total body fat such as skin-fold thickness, whole body dual-energy x-ray absorption (DXA) scan, or bioelectrical impedance analysis[33]. Using these measures, obesity in U.S. women is defined as a BMI ≥30 kg/m2, waist circumference ≥88 cm, or percent total body fat ≥35%[33]. Abdominal obesity has been associated with an increased CVD risk and the development of type 2 diabetes[34], with a higher visceral-to-subcutaneous fat ratio leading to worsened insulin sensitivity[35,36].

In a long-term follow-up study of 45 adult females and males with classic and nonclassic forms of CAH, 47% were overweight based on BMI[22]. Falhammar *et al.* found a higher BMI and higher waist-to-hip ratio, compared to controls, in women 30 years or older with classic CAH and NCAH[19]. Higher body fat mass has also been reported in studies of young female and male adults with CAH, compared to controls[37,38]. In 13 women with classic CAH, increased body fat percentage was attributed to over-treatment with glucocorticoid[39], although a positive correlation between glucocorticoid dose and measurements of obesity has not always been found[38]. In young adult patients with CAH treated with relatively low glucocorticoid doses, increased fat mass was found in CAH patients, compared to controls[37]. In children with CAH, a correlation between BMI and age, as well as a progressive increase in fat mass during childhood, has been reported[40,41]. In female children with CAH, bioelectrical impedance analysis of body fat mass showed an increased body fat ratio in CAH patients, compared to controls[42].

Although functional hyperandrogenism is associated with increased abdominal adiposity in women[43], the relationship between hyperandrogenism and abdominal adiposity in CAH has not been studied.

Hypertension

There is minimal data on hypertension in adult patients with CAH. In adult females with CAH, women ≥30 years old had a higher standing DBP compared to younger patients[19].

Children with classic 21-hydroxylase deficiency have a higher prevalence of hypertension in several studies. On 24-hour ambulatory monitoring, children with salt-wasting CAH exhibited elevated blood pressures during the daytime, with an absent physiologic nocturnal nadir in SBP, which could have implications for future CVD risk[44]. The alterations in BP in these children were associated with BMI, particularly in female patients, and were not affected by mineralocorticoid or glucocorticoid replacement dose. In another study of children and adolescents with classic CAH, elevated SBP correlated with BMI and skin-fold thickness measures, along with leptin and insulin levels[45]. There was no correlation between elevated BP and hormone replacement dosages. Essential hypertension (hypertension of

unknown etiology) was noted in 5 of 91 children with classic 21-hydroxylase deficiency[46] possibly due to dysregulation inherent to CAH.

Dyslipidemia

Patients with CAH might be at risk for dyslipidemia due to chronic glucocorticoid therapy. A case-control study examining the effect of glucocorticoid treatment on prepubertal Hispanic children with CAH, versus controls, showed abnormalities primarily in triglyceride levels of CAH patients on prednisone treatment[47]. Patients on glucocorticoid therapy for other conditions have been noted to have dyslipidemia. Patients with Cushing syndrome can have abnormal lipids, and may also exhibit insulin resistance and hyperandrogenism[6]. Risk for dyslipidemia in CAH is an area that requires further study.

Subclinical Atherosclerosis

Increased intima media thickness (IMT) is a leading modality to measure subclinical atherosclerosis. Increased carotid IMT has been noted in adult female and male patients with different forms of CAH due to 21-hydroxylase deficiency[18]. In these patients, IMT was independent of glucocorticoid doses and androgen concentrations. Long-term follow-up study, including the relationship between IMT and hormonal imbalances, is needed to understand the significance of these findings.

Markers of chronic inflammation

Atherosclerosis is a process that is in part due to local inflammation. Markers of inflammation that have been shown to predict CVD risk include: high sensitivity C-reactive protein, plasminogen activator inhibitor-1, and increased lymphocytes and monocytes. Both obesity and insulin resistance have been linked to inflammation[48]. Obesity is associated with chronic low-grade inflammation, with a higher prevalence of macrophages in adipose tissue of obese individuals[49], and release of cytokines (IL-6, TNF-alpha) and adipokines from the adipose tissue which can lead to inflammation and stimulate the hypothalamic-pituitary-adrenal (HPA) axis[50]. This area has yet to be studied in patients with CAH.

CONCLUSIONS

Several CVD risk factors have been identified in patients with CAH, including obesity, hypertension and insulin resistance. These risk factors are inter-related, and androgen excess in women may play an important role. Alterations in the HPA axis, chronic glucocorticoid therapy, and adrenomedullary dysfunction also likely contribute to the development of CVD risk factors. The interplay between metabolic abnormalities and hormonal imbalances, especially excess androgen in women, in both classic and nonclassic forms of CAH requires further study.

A multifactorial intervention approach, including behavior modification and targeted pharmacologic therapy, should be considered in women with CAH who have major CVD risk factors. Future prospective, longitudinal studies of women with CAH to assess cardiovascular events, morbidity and mortality, and long-term outcomes in relation to hormonal imbalances are needed. Greater knowledge in the pathophysiology of CAH and

the relationship to CVD risk will lead to therapeutic strategies that aim to treat and prevent adverse CVD outcomes.

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Abbreviations Key

CAH	congenital adrenal hyperplasia
NCAH	nonclassic congenital adrenal hyperplasia
PCOS	polycystic ovarian syndrome
CVD	cardiovascular disease
SBP	systolic blood pressure
DBP	diastolic blood pressure
BP	blood pressure
LH	luteinizing hormone
HOMA	homeostasis model assessment-insulin resistance
FSIVGTT	frequently sampled IV glucose tolerance test
BMI	body mass index
DXA	dual-energy x-ray absorption
IMT	intima media thickness
HPA	hypothalamic-pituitary-adrenal

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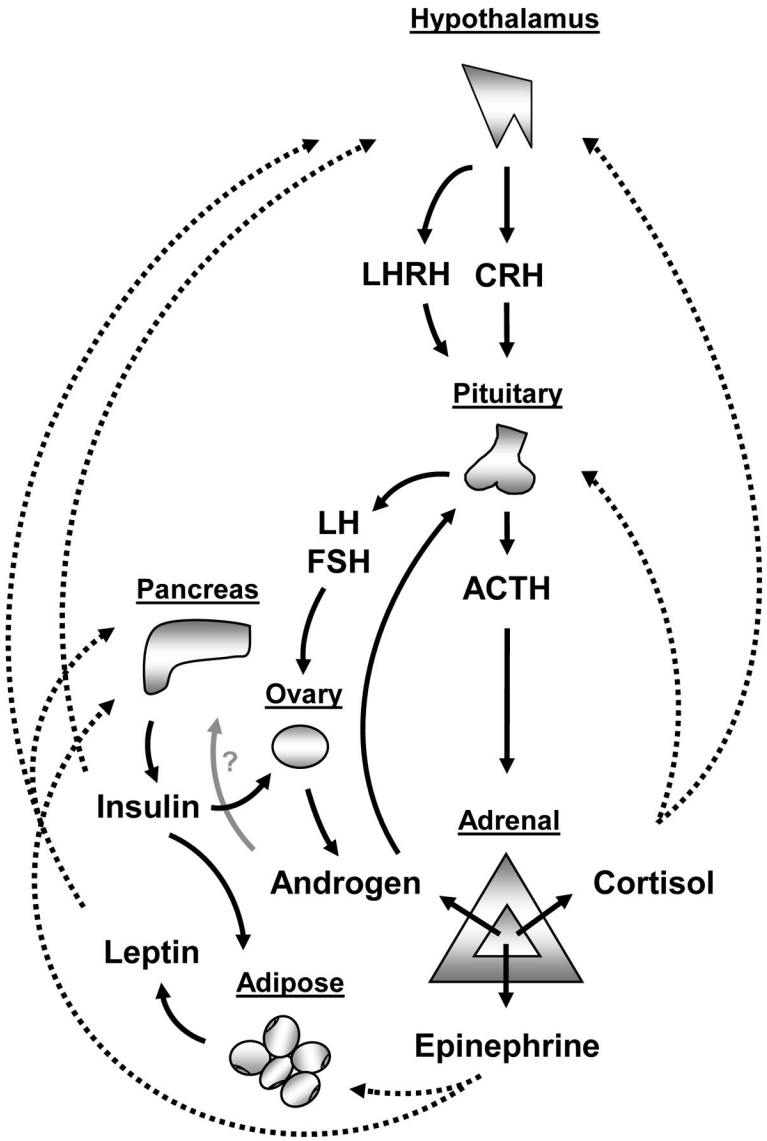

Figure 1.

Schematic representation of the complex interplay between: the hypothalamic-pituitary-adrenal axis, the hypothalamic-pituitary-ovarian axis, the adrenal production of cortisol, epinephrine and androgen, and the regulation of leptin and insulin. These pathways are altered in congenital adrenal hyperplasia.