Cardiovascular and Metabolic Outcomes in Congenital Adrenal Hyperplasia: A Systematic Review and Meta-Analysis

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Background: Individuals with congenital adrenal hyperplasia (CAH) require glucocorticoid therapy to replace cortisol and to control androgen excess. We sought to evaluate the effects of glucocorticoid therapy on cardiovascular and metabolic outcomes in individuals with CAH.

Methods: We searched bibliographical databases through January 2016 for studies evaluating cardiovascular risk factors in individuals with CAH treated with glucocorticoids compared with controls without CAH. We used a random-effects model to synthesize quantitative data.

Results: We included 20 observational studies (14 longitudinal, six cross-sectional) with a moderate to high risk of bias. The average dose of glucocorticoids (in hydrocortisone equivalents) was 9 to 26.5 mg/m^2/d. In the meta-analysis (416 patients), compared with controls without CAH, individuals with CAH had increased systolic blood pressure [weighted mean difference (WMD), 4.44 mm Hg; 95% CI, 3.26 to 5.63 mm Hg], diastolic blood pressure (WMD, 2.35 mm Hg; 95% CI, 0.49 to 4.20 mm Hg), homeostatic model assessment of insulin resistance (WMD, 0.49; 95% CI, 0.02 to 0.96), and carotid intima thickness (WMD, 0.08 mm; 95% CI, 0.01 to 0.15 mm). No statistically significant differences were noted in fasting blood glucose, insulin level, glucose, or insulin level after 2-hour glucose load or serum lipids. Data on cardiac events were sparse, and most of the literature focused on surrogate outcomes.

Conclusion: Individuals with CAH demonstrate a high prevalence of cardiovascular and metabolic risk factors. The current evidence relies on surrogate outcomes. Long-term prospective studies are warranted to assess strategies for reducing cardiovascular risk in individuals with CAH. (***J Clin Endocrinol Metab*** **103: 4097–4103, 2018)**

Congenital adrenal hyperplasia (CAH) refers to a group of autosomal recessive disorders characterized by impaired biosynthesis of cortisol affecting ~1 in every 15,000 live births (1). The most common form of CAH presenting in infancy, referred to as classic congenital adrenal hyperplasia (CCAH), is due to a mutation in CYP21A2, the gene encoding the 21-hydroxylase enzyme. CYP21A2 mutation is seen in ~95% of all CCAH

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Abbreviations: BMI, body mass index; CAH, congenital adrenal hyperplasia; CCAH, classic congenital adrenal hyperplasia; DBP, diastolic blood pressure; HTN, hypertension; NCCAH, nonclassic congenital adrenal hyperplasia; SBP, systolic blood pressure.

cases and is characterized by cortisol deficiency, with or without aldosterone deficiency and androgen excess (1, 2). Depending on the extent of enzyme impairment, CCAH is subclassified as either salt losing or simple virilizing (3). Nonclassic congenital adrenal hyperplasia (NCCAH), estimated at 0.1% to 1% or even higher depending on ethnicity and race, is usually detected in later childhood, adolescence, or adult life, and it is associated with relatively mild enzyme impairment (4, 5). Although the latter group often does not require continuous or lifelong glucocorticoid treatment, many patients with NCCAH receive glucocorticoids for durations ranging from months to many years to control androgen excess.

Early diagnosis and treatment of CCAH are essential for the prevention of morbidity and mortality. The goals of management are to provide adequate supplementation for adrenal insufficiency (glucocorticoids ± mineralocorticoids), as well as control androgen excess (glucocorticoids). The balance between the two is the main challenge in clinical practice, as control of androgen excess can require supraphysiological or subphysiological glucocorticoid replacement. Both excessive glucocorticoid and mineralocorticoid supplementation might lead to increases in cardiovascular risk factors. In contrast, poor compliance or insufficient glucocorticoid therapy can lead to androgen excess, infertility, and development of adrenal crest tumors (6, 7).

Clinical practice varies in terms of the steroid type and regimen chosen. However, many patients may be receiving supraphysiological amounts of glucocorticoids. Cardiovascular outcomes related to steroid therapy in patients with CAH are unclear. We conducted a systematic review of the published literature to appraise and summarize the evidence regarding cardiovascular and metabolic outcomes in terms of hypertension, hyperlipidemia, glucose intolerance, and carotid intima thickness in patients with CAH treated with glucocorticoid and mineralocorticoid replacement therapy compared with controls without CAH.

Methods

This systematic review is reported following the standards set in the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement (8).

Eligibility criteria

We searched for randomized clinical trials and comparative nonrandomized studies evaluating outcomes related to hypertension, hyperlipidemia, glucose intolerance, and cardiac events in patients receiving replacement therapy with glucocorticoids and/or mineralocorticoids compared with individuals without CAH or to published population data. There was no language restriction. Studies with missing data despite contact with the authors were excluded.

Study identification

We conducted a comprehensive search of the Medline In-Process & Other Non-Indexed Citations, EMBASE, Web of Science, and Scopus databases from each database's inception through January 2016. The search strategy was designed by a medical librarian (L.J.P.) with input from some of the study investigators. Controlled vocabulary supplemented with keywords was used to search for studies evaluating selected outcomes in patients with CAH. We consulted experts in the field and reviewed references from the included studies to identify additional references.

Study selection

Reviewers working independently and in duplicate reviewed all of the abstracts and selected full-text manuscripts for eligibility. Disagreements on full-text screening were resolved by consensus.

Data collection and management

Working independently and in duplicate, the reviewers used a standardized web-based form to collect information from each eligible study. For each study, we recorded baseline clinical features of the included population, such as age; sex; serum androgen levels; body mass index (BMI); genotype; total daily dose of glucocorticoids; duration of steroid use and lifetime glucocorticoid exposure if known; total daily dose of mineralocorticoids; numbers of salt-wasting, simple virilizing, and nonclassic cases; and salt-wasting episodes. The outcomes of interest were hypertension, hyperlipidemia, glucose intolerance, and cardiac events.

Risk of bias

The risk of bias was assessed by the reviewers working independently and in duplicate using a modified Newcastle-Ottawa instrument (9). The parameters assessed were cohort selection (adequacy of case definition, representativeness of CAH cases, selection and definition of controls), comparability (comparability of CAH cases and controls based on the design or analysis), and exposure (ascertainment of exposure to glucocorticoids and/or mineralocorticoids). Disagreements were resolved by consensus.

Summary measures and synthesis of results

We performed a meta-analysis for each of the outcomes of interest using a random-effects model (10). We used the I^2 statistic to assess heterogeneity in the results. I^2 >50% indicated large inconsistency across studies (heterogeneity) not explained by chance. Meta-analysis was conducted using STATA software, version 14 (StataCorp LP, College Station, TX). The quality of evidence was assessed using the GRADE approach (grading of recommendations, assessment, development and evaluation) (11).

Supplemental material to this systematic review is publicly available online (12).

Results

We included 20 studies (Fig. 1). Fourteen studies contributed data to the meta-analysis. Study characteristics are presented in Table 1, with more details in the online repository (12). All of the studies were observational (14 longitudinal, six cross-sectional) with moderate to high risk of bias. Several other large observational studies of individuals with CAH did not provide detailed data to be included in the meta-analysis. Studies with more than 50 individuals (27–34) are summarized qualitatively.

Meta-analysis

The 14 included studies (12 longitudinal, two cross-sectional) reported data for 437 patients (300 children/adolescents and 137 adults, aged 14 months to 63 years). The average dose of glucocorticoid was 9 to 26.5 mg/m^2/d of hydrocortisone equivalent. Glucocorticoid types and regimens varied between studies and within individual studies. Most of the studies did not report on the fludrocortisone dose. Biochemical assessment in relation to hyperandrogenemia and CAH control (*e.g.*, concentrations of androstenedione and 17-hydroxyprogesterone) was reported in only four of 14 studies. Control populations consisted of healthy individuals without CAH mostly matched for age, sex, and BMI.

The results of meta-analyses are summarized in Table 2. Patients with CAH on glucocorticoid replacement had higher systolic blood pressure (SBP) and diastolic blood pressure (DBP) than controls. Patients with CAH had no significant differences in fasting blood glucose, blood glucose after 2-hour glucose tolerance testing, fasting insulin, or 2-hour insulin concentration after glucose load. Patients with CAH had higher homeostatic model assessment of insulin resistance than the controls. Patients with CAH and controls had similar concentrations of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. Patients with CAH had higher carotid intima thickness than the controls.

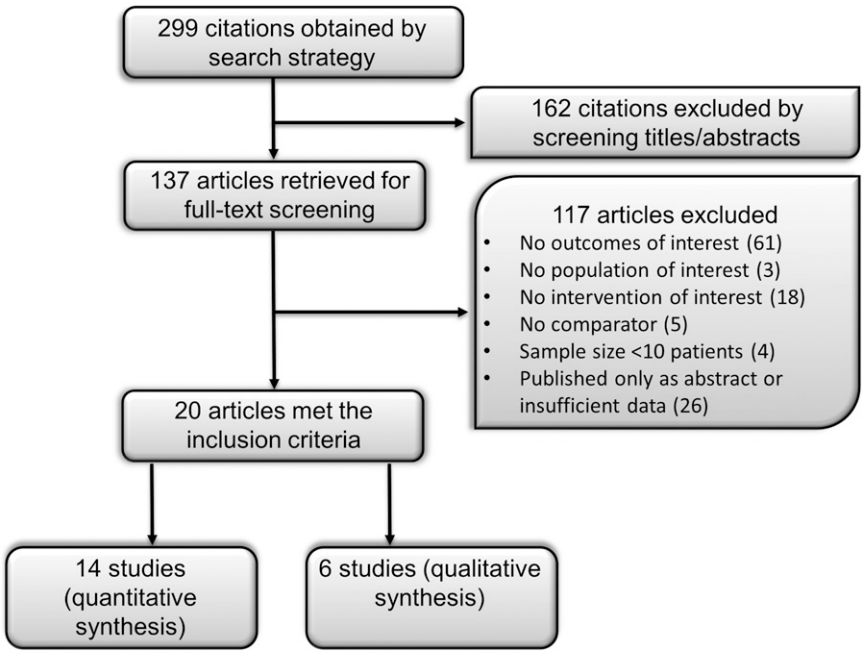

Figure 1. The process of study selection.

Subgroup analyses

Subgroup analyses were feasible for only a few comparisons. Subgroup analysis by age showed that the patients with CAH had higher SBP than the controls only in children and adolescents (results in adults were nonsignificant), whereas patients' DBP was significantly higher than that of the controls only in adults (results in children were nonsignificant).

Other subgroup analyses by age suggested that children and adolescents with CAH had lower fasting glucose and higher total cholesterol than the controls. The increase in carotid intima thickness was more pronounced in adults than in children and adolescents.

Data were unavailable for other planned subgroup analyses based on variables such as age at diagnosis, sex, genotype, dose of steroid, type of steroid, duration of treatment, method of measuring blood pressure, and CCAH vs NCCAH.

Other observational studies

Other observational studies with >50 individuals (27–34) that did not provide detailed data for inclusion in the meta-analysis are summarized qualitatively. In a cross-sectional analysis of 199 adults with CAH in the UK CAH Adult Study (27, 29, 30), higher rates of hypertension (HTN) were observed in patients with CAH diagnosed late (after 1 year) than in those diagnosed early, and HTN rates were also higher in women treated with glucocorticoids only than in those treated with both glucocorticoids and mineralocorticoids. Blood pressure was not different between the groups with different genetic mutations, and women with classic CAH had increased DBP. In a Swedish population-based study (31) studying 558 patients with CAH compared with 58,800 controls matched for sex, age, and birthplace, CAH was associated with an increased frequency of HTN. In a cross-sectional study (28) of 244 patients with CAH

Table 1. Description of Included Studies

Study ID	Country	Study Design	Age Group	Sample Size	Overall Methodological Quality
Studies included in quantitative synthesis					
Botero *et al.*, 2000 (13)	Colombia	Case-control	Children	14	Low
Charmandari *et al.*, 2002 (14)	Germany	Case-control	Children	18	Moderate
Sartorato *et al.*, 2007 (15)	Italy	Case-control	Adults	19	Moderate
Falhammar *et al.*, 2007 (16)	Sweden	Case-control	Adults	61	Moderate
Zimmermann *et al.*, 2010 (17)	Romania	Case-control	Children and adolescents	27	Low
Williams *et al.*, 2010 (18)	United Kingdom	Case-control	Children	25	Moderate
Mooij *et al.*, 2011 (19)	Netherlands	Case-control	Adults	27	Low
Falhammar *et al.*, 2011 (20)	Sweden	Case-control	Adults	30	Moderate
Harrington *et al.*, 2012 (21)	Australia	Case-control	Children	14	Low
Wasniewska *et al.*, 2013 (22)	Italy	Cross-sectional	Adolescents	18	Moderate
Amr *et al.*, 2014 (23)	Egypt	Case-control	Children	32	Moderate
Subbarayan *et al.*, 2014 (24)	United Kingdom	Case-control	Children and adolescents	107	Low
Marra *et al.*, 2015 (25)	Italy	Cross-sectional	Adolescents	20	Moderate
Akyürek *et al.*, 2015 (26)	Turkey	Case-control	Children and adolescents	25	Low
Studies included in qualitative synthesis					
Arlt *et al.*, 2010 (27)	United Kingdom	Cross-sectional	Adults	203	NA
Finkelstain *et al.*, 2012 (28)	United States	Cross-sectional	All	244	NA
Krone *et al.*, 2013 (29)	United Kingdom	Cross-sectional	Adults	153	NA
Han *et al.*, 2014 (30)	United Kingdom	Cross-sectional	Adults	199	NA
Falhammar *et al.*, 2015 (31)	Sweden	Case-control	All	588	NA
Bonfig *et al.*, 2016 (32)	Germany	Case-control	Children and adolescents	716	NA

NA, not assessed.

conducted at the National Institutes of Health, elevated blood pressure was more common in patients with CCAH than in patients with NCCAH. In a German cohort of 716 children and adolescents (32), the prevalence of HTN was 12.5%, was higher in younger children than in adolescents (18.5% vs 4.9%), and was higher in salt-wasting CAH than in simple virilizing CAH. Until 8 years of age, fludrocortisone dose but not hydrocortisone dose was correlated significantly with blood pressure. In a Brazilian case-control study (34), HTN was found in 12% of patients, and heterozygotes for the *BclI* polymorphism within intron 2 of the glucocorticoid receptor (*NR3C1*) gene exhibited higher SBP than wild-type subjects. Völkl *et al.* (33) showed that daytime and nighttime SBP were also significantly elevated, whereas daytime DBP was significantly lowered and was normal during the night, and overall, there was a normal nocturnal drop in SBP but not in DBP. Other findings from the Swedish cohort (31) were that patients with CAH had higher prevalence rates of HTN, hyperlipidemia, atrial fibrillation, venous thromboembolism, obesity, and diabetes.

Quality of evidence

The quality of evidence (*i.e.*, certainty in these estimates) was low due to the observational nature of the evidence, the moderate to high risk of bias, and the high degree of heterogeneity. Overall, the studies relied on

Table 2. Meta-Analysis Results

Outcome	WMD	95% CI
SBP, mm Hg[a]	4.4	3.3 to 5.6
DBP, mm Hg[a]	2.4	0.5 to 4.2
Fasting blood glucose, mg/dL	−2.35	−5.21 to 0.51
2-h blood glucose (GTT), mg/dL	10.24	−0.07 to 20.55
Fasting insulin, mU/L	1.17	−0.32 to 2.267
2-h insulin, mU/L	5.96	−8.37 to 20.34
HOMA-IR[a]	0.49	0.02 to 0.96
Total cholesterol, mg/dL	2.70	−1.55 to 6.96
LDL cholesterol, mg/dL	0.43	−2.70 to 3.56
HDL cholesterol, mg/dL	3.43	−0.67 to 7.52
Triglycerides, mg/dL	3.33	−3.40 to 10.06
Carotid intima thickness, mm[a]	0.08	0.01 to 0.15

Positive numbers indicate higher values in individuals with CAH.

Abbreviations: GTT, glucose tolerance test; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein; WMD, weighted mean difference.

[a]Denotes a statistically significant difference ($P < 0.05$).

surrogate outcomes, with minimal data on hard end points.

Discussion

Main findings

This systematic review and meta-analysis suggested that, compared with controls without CAH, individuals with CAH had increased SBP, DBP, insulin resistance, and carotid intima thickness. No statistically significant difference was noted in fasting blood glucose or lipids. We were unable to draw conclusions regarding the effects of several important variables such as sex, glucocorticoid type and dose, fludrocortisone dose, and genotype. Data on cardiac events were sparse. However, ample evidence suggests that these surrogate cardiometabolic risk factors are associated with increased future cardiac events. For example, in the Framingham Heart Study cohort, a stepwise increase in cardiovascular event rates was noted in adult men with higher baseline blood pressure categories (35). Other epidemiological studies (36–40) have also demonstrated that, in men and women in different age groups, SBP and DBP had a continuous and graded positive association with cardiovascular disease outcomes. However, no such conclusions could be drawn based on isolated measurements of blood pressure in children.

Limitations and strengths

There were several limitations to this systematic review and meta-analysis. The quality of evidence (*i.e.*, certainty in these estimates) was low due to the observational nature of the evidence, the high risk of bias, the reliance on surrogate outcomes, and the heterogeneity of the included studies. The age at which the steroid therapy was initiated and the duration of follow-up were not specified in most studies. Data were not available to perform several important planned subgroup analyses comparing outcomes by sex, BMI, or weight *z* score; number of salt-wasting episodes; CAH genotype; type and dose of steroid used; duration of steroid therapy; and method of blood pressure measurement. Notably, blood pressure was measured by different methods (supine, upright, and 24-hour ambulatory measurements) in these studies. Data were not available separately for patients with NCCAH.

The strengths of this review were related to the comprehensive literature search, *a priori* established protocol, and duplicate process of study selection and appraisal.

Implications

On the basis of the results of this systematic review and meta-analysis, we conclude that patients with CAH might demonstrate increased cardiovascular and metabolic risk compared with reference population controls. Potential contributing factors include excessive therapy with glucocorticoids or mineralocorticoids and uncontrolled androgen excess. Therefore, efforts should be exerted to minimize these possible contributors (41). Administering close to physiological doses of glucocorticoids and using the lowest needed doses of mineralocorticoids are essential. Additional attention should be paid to maintaining a healthy body weight and BMI, both of which are known correlates of higher blood pressure. Promising approaches with new modified-release and pediatric-specific low-dose glucocorticoid formulations might be additional tools that could help in achieving these goals (42). Careful monitoring of symptoms and signs of excessive glucocorticoid dosing is important. Increased dosing of glucocorticoids is appropriate in patients with febrile illness, major surgery, or trauma; however, it should not be implemented in the presence of other types of mental and emotional stress or minor illnesses or before routine physical exercise. Adolescents and adults should be monitored as per standard guidelines for the development of metabolic syndrome, hyperlipidemia, and hypertension. Preemptive lifestyle counseling to reduce cardiovascular risk is paramount. Studies evaluating strategies to reduce the risk of metabolic and cardiovascular outcomes in patients with CAH are needed.

Conclusion

Individuals with CAH demonstrate a high prevalence of cardiovascular and metabolic risk factors; however, we found no evidence of actual morbidity or mortality due to

cardiac events. Long-term prospective studies are warranted to assess strategies for reducing cardiovascular risk in individuals with CAH.

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