The impact of higher glucocorticoid dose on clinical outcomes in congenital adrenal hyperplasia: A systematic literature review

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INTRODUCTION

- Classic congenital adrenal hyperplasia (CAH) is a rare condition most often caused by 21-hydroxylase deficiency (21-OHD), leading to impaired cortisol and often aldosterone biosynthesis[1]
- High-dose or supraphysiologic glucocorticoids (GC) alone (ie, higher doses than needed for cortisol replacement) have been used to treat patients with CAH to manage excess adrenocorticotropic hormone (ACTH) and adrenal androgen production[1,2]
- Long-term exposure to supraphysiologic doses of GCs leads to increased risk of GC-associated complications across cardiometabolic, bone, growth, and other domains[2]

OBJECTIVE

- As the relationship between higher GC dose and clinical outcomes in CAH has not been fully synthesized in prior literature, the purpose of this systematic literature review (SLR) was to comprehensively characterize the relationship between higher GC dose and clinical outcomes at exposures relevant to CAH

METHODS

Search strategy and screening

- PubMed (via PubMed.com) and Embase (via Embase.com) were searched from database inception to April 1, 2024. Search algorithms were built using free text and Boolean syntax and included terms related to endocrine disease, mild autonomous cortisol secretion (MACS), GCs/steroids and dose, and clinical or safety outcomes. There was no restriction on timeframe; results were restricted to English language human studies with abstracts
- The SLR followed PRISMA guidelines with scope defined using PICOS criteria (population, intervention, comparators, outcomes, study design; **Table 1**)
- Literature screening at the title/abstract and full-text screening phases was performed by 2 independent reviewers. Conflicts were resolved by a third independent reviewer and/or mutual discussion

Outcomes

- Relationships between GC dose and clinical outcomes were summarized into categories including bone outcomes, cardiometabolic outcomes, height/growth outcomes, and other outcomes (ie, quality of life, mortality, adverse events, hospitalizations, fertility, etc)
- Key publications of interest were defined based on their quality and relevance to our objective: patient population included CAH, primary objective included evaluation of the effect of GC dose, included statistical analyses, and overall risk of bias was better than high based on the Cochrane Collaboration's Tool for Assessing Risk of Bias

Table 1. Systematic literature review inclusion and exclusion criteria

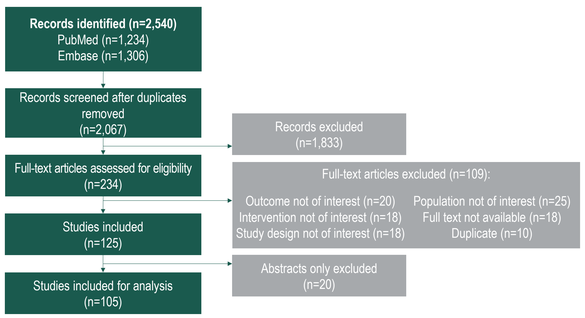
	Inclusion criteria	Exclusion criteria
Population	Patients with MACS or those receiving long-term, oral GCs diagnosed with any of the following: congenital adrenal hyperplasia, adrenal insufficiency, hypoadrenalism, adrenal gland hypofunction, hypopituitarism, Addison's disease, or polymyalgia rheumatica	Healthy volunteers or patients without a diagnosis of included conditions
Interventions	Oral GCs	Oral GCs not used or used for <90 days (excluding patients with MACS)
Comparators	No restrictions	None
Outcomes	Relationship of higher GC dose with clinical outcome	No clinical outcome reported
Study design	Randomized, controlled trials, observational or cross-sectional studies, or systematic reviews (reviewed for primary sources)	Case reports, *in vitro* or animal studies, letters, comments, editorials, or news articles

Key: GC, glucocorticoid; MACS, mild autonomous cortisol secretion.

RESULTS

- Of 2,540 records identified, 105 met the protocol-defined selection criteria for inclusion and included 541 outcomes (**Figure 1**)

Figure 1. PRISMA flow diagram



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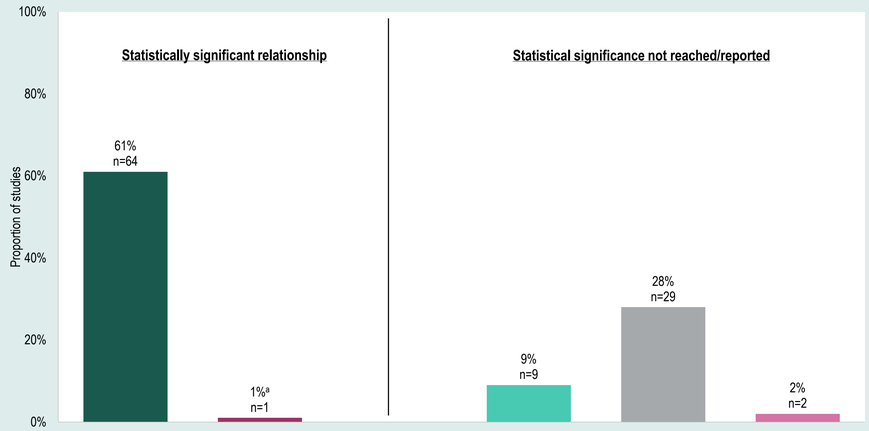
Please contact medinfo@neurocrine.com with any questions.**

RESULTS

- More than half of studies were in adult patient populations (55%; n=58; **Table 2**), and most were in patients with CAH (65%; n=68; **Table 2**)
- Of 65 articles reporting statistically significant results, the most reported relationship with higher GC doses was with adverse clinical outcomes (n=64; 61%). In the 40 articles that reported non-significant results, 9 (9%) reported adverse clinical outcomes trends, 29 (28%) reported no trend, and 2 (2%) reported improved clinical outcomes trends (**Figure 2**). These trends were consistent when considering specific clinical outcomes categories (**Figure 3**)
- Eleven articles were identified as key publications of interest based on their relevance to our objective (**Table 3**)

Figure 2. Type of relationship between higher GC dose and clinical outcomes (N=105)



[a]This represented 1 study that assessed pain and quality of life in 10 weeks. A positive statistically significant relationship is clinically reasonable with higher GC dose in this short follow-up period. Key: GC, glucocorticoid.

Table 3. Key studies of interest

Author year *Study design, N*	GC dose[a]	Outcome(s)	Results
Pediatric studies (GC dose reported as mean dose in mg/m²/d)			
Bonfig 2009[3] *Retrospective, N=92*	Females: 17.2 Males: 17.9		Significant negative correlation between mean daily hydrocortisone dose and final height in a logistic regression model (*P*<0.01). No correlation was found if the dose was given by 2 years of age (*P*>0.05)
Cordeiro 2013[4] *Retrospective, N=31*	High dose: 22.6 Low dose: 13.1		Final height was negatively correlated with hydrocortisone dose in a simple regression analysis (r=-0.48; r²=0.23; *P*<0.05). Significant height loss was observed during the growth period; mean z-score for final height was -2.05±0.98 after a mean follow-up time of 12.5±1.76 years, compared to pretreatment height z-score of 0.60±2.35 (*P*=0.014)
Elnecave 2008[5] *Retrospective, N=16*	Group 1: 17.39 Group 2: 13.06		Significant inverse relationship between BMD of lumbar spine and mean GC dose was found by cortical and trabecular quantitative computed tomography in a linear regression (r=-0.55; p=0.03, r=-0.52; *P*=0.04, respectively)
Merke 2000[6] *Prospective, N=28*	Group 1: 13.3 Group 2: 8.6		After two years, pediatric patients taking mean HCe of 13.3mg/m2/d showed a growth velocity of 0.1±0.5 SD units compared to 1.58±0.6 SD units in children taking mean HCe of 8.6mg/m2/d (*P*≤0.01).
Sarafoglou 2014[7] *Retrospective, N=104*	18.9		An adjusted mixed linear regression model showed that a predicted adult height would decrease by 0.37cm for every 1mg/m2/d dose of hydrocortisone (β=-0.37; *P*<0.005)
Silva 1997[8] *Prospective crossover, N=26*	Group 1: 15 Group 2: 25		A height for age Z-score (mean, SE) for children was greater while using 15mg/m2 HCe (0.28 [0.11]) compared to 25mg/m2 HCe (-0.06 [0.12]) (*P*=0.02). No significant difference was detected in weight
Wada 2023[9] *Retrospective, N=56*	Median, 1Y: 24.3 Median, 3Y: 18.6		Multivariate regression analysis showed changes in BMI-SDS and percent BMI positively correlated with hydrocortisone dose at 1 year old (β=0.59, *P*=0.011; β=0.57, *P*=0.013, respectively). This was consistent during late infancy (β=0.56, *P*=0.027; β=0.53, *P*=0.034, respectively). No significant findings were observed with height
Mixed pediatric and adult studies (GC dose reported as mean dose in mg/m²/d)			
Schnaider-Rezek 2011[10] *Retrospective, N=18*	18.3		No association between GC dose and weight, waist circumference, blood pressure, insulin resistance, and HOMA-IR (*P*>0.05 for all)
Adult studies (GC dose reported as mean dose in mg/d[b])			
Ceccato 2016[11] *Retrospective, N=38*	Cumulative GC: 17.3 mg		A linear regression did not reveal any relationship between total cumulative GC dose and BMD or bone metabolism
Han 2013[12] *Retrospective, N=196*	Not Reported		Prednisone equivalent dose was positively correlated with systolic blood pressure, diastolic blood pressure, HDL, and HOMAR-IR in an adjusted partial correlation analysis (*P*<0.05 for all)
Riehl 2020[13] *Retrospective, N=244*	SW: 34.1 SV: 35.5 NC: 23.0		BMD of lumbar spine was negatively correlated with hydrocortisone dose in females with CAH in a multivariate linear regression analysis (r²=0.695; *P*<0.001). No significant correlation in males with CAH

Height/Growth outcomes · Bone outcomes · Cardiometabolic outcomes
Statistically significant adverse clinical outcomes · Not statistically significant

[a]GC doses varied by study; studies with multiple doses does not imply comparison between doses. [b]A body surface area of 1.73 m² was utilized to convert GC dose to mg/day. [c]Adverse clinical outcomes include articles that had ≥1 statistically significant adverse clinical outcome and no significant improved outcomes
Key: BMD, bone mineral density; BMI, body mass index; BMI-SDS, body mass index standard deviation score; CAH, congenital adrenal hyperplasia; GC, glucocorticoid; HCe, hydrocortisone equivalent; HOMA-IR, homeostatic model assessment for insulin resistance; NC, non-classic; SE, standard error; SW, salt wasting; SV, simple virilizing.

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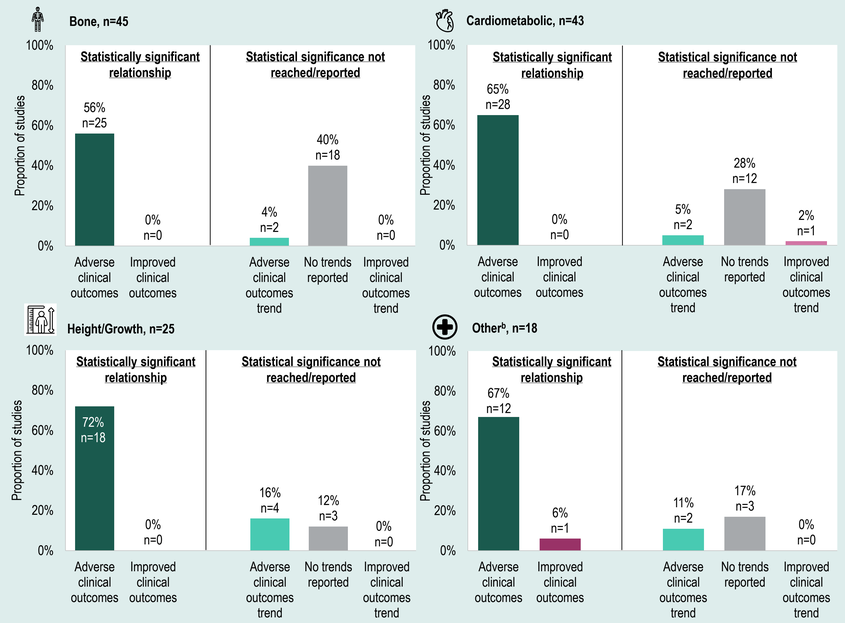
Table 2. Study characteristics

Characteristic	Included studies (N=105), N (%)
Age group	
Pediatrics	38 (36)
Adults	58 (55)
Mixed	9 (9)
Patient population[a]	
CAH	68 (65)
Adrenal insufficiency	12 (11)
Addison's disease	10 (10)
Hypopituitarism	10 (10)
PMR	7 (7)
MACS	1 (1)
Pituitary adenoma	1 (1)

[a]Some studies included multiple disease states; therefore, the sum will be greater than 105 studies.
Key: CAH, congenital adrenal hyperplasia; MACS, mild autonomous cortisol secretion; PMR, polymyalgia rheumatica.

Figure 3. Relationship between higher GC dose and different clinical outcomes[a]



[a]Some studies included multiple outcomes; therefore, the sum will be greater than 105 studies.
[b]Other outcomes include quality of life, mortality, fertility, hospitalizations, and stroke.
Key: GC, glucocorticoid.

CONCLUSIONS

- **This SLR underscores the abundance of literature that shows a profound clinical burden associated with higher exposures to GCs, even in the range relevant to CAH. This clinical burden also manifests as a humanistic burden on patients**
- **Novel non-GC treatment options for CAH, the first of which (crinecerfont) was approved December 2024, enable patients to lower their GC dose while maintaining or improving their disease control, which may reduce the incidence and/or severity of associated complications**

LIMITATIONS

- Our focus on endocrine disorders does not address much higher doses of GC that are used for anti-inflammatory purposes across a broad range of rheumatologic and other conditions
- For some endpoints in CAH, both excess androgens and excess GC can independently impact the outcome (eg, growth), which may confound findings
- Sparse literature on MACS may be due to its relatively recent recognition as a distinct disease
- Many of the studies were not designed to measure GCs vs clinical outcomes, which may account for the trends seen as opposed to statistically significant differences. Additionally, many studies had short-term follow-up periods, small sample sizes, or lacked control for confounding factors
- Statistical significance does not always equate to clinical significance; hence, the results of each study need to be carefully assessed by clinicians

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