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Clinical Research Article

Bone Age Maturation and Growth Outcomes in Young Children with CAH Treated with Hydrocortisone Suspension

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Abstract

Background. Young children with congenital adrenal hyperplasia (CAH) require small doses (0.1-1.25 mg) of hydrocortisone (HC) to control excess androgen production and avoid the negative effects of overtreatment. The smallest commercially available HC formulation, before the recent US Food and Drug Administration approval of HC granules, was a scored 5-mg tablet. The options to achieve small doses were limited to using a pharmacy-compounded suspension, which the CAH Clinical Practice Guidelines recommended against, or splitting tablets into quarters or eighths, or dissolving tablets into water.

Methods. Cross-sectional chart review of 130 children with classic CAH treated with tablets vs a pharmacy-compounded alcohol-free hydrocortisone suspension to compare growth, weight, skeletal maturation, total daily HC dose, and exposure over the first 4 years of life.

Results. No significant differences were found in height, weight, or body mass index *z*-scores at 4 years, and in predicted adult height, before or after adjusting for age at diagnosis and sex. Bone age *z*-scores averaged 2.8 SDs lower for patients on HC suspension compared with HC tablets ($P < 0.001$) after adjusting for age at diagnosis and sex. The suspension group received 30.4% lower ($P > 0.001$) average cumulative HC doses by their fourth birthday.

Conclusions. Our data indicate that treatment with alcohol-free HC suspension decreased androgen exposure as shown by lower bone age *z*-scores, allowed lower average and cumulative daily HC dose compared to HC tablets, and generated no significant differences in SDS in growth parameters in children with CAH at 4 years of age. Longitudinal studies of treating with smaller HC doses during childhood are needed.

Key Words: congenital adrenal hyperplasia, hydrocortisone, growth, suspension, adrenal insufficiency, bone age

Abbreviations: BMI, body mass index; CAH, congenital adrenal hyperplasia; CDC, US Centers for Disease Control and Prevention; D4A, adrenal androgen androstenedione; HC, hydrocortisone; MPH, mid-parental height; OAH, observed adult height; PAH, predicted adult height; PHV, peak height velocity; SV, simple virilizing; TargHt, target height; TO, takeoff

Patients with congenital adrenal hyperplasia (CAH) resulting from 21-hydroxylase deficiency require lifelong glucocorticoid replacement. Hydrocortisone (HC) is the preferred drug in growing children because it is associated with better linear growth outcomes than long-acting glucocorticoids [1]. The recommended total daily dose of HC is 10 to 15 mg/m^2/d divided into 3 doses [1]. This treatment is suboptimal because of HC's short half-life and because children are exposed to alternating periods of hyper- and hypocortisolemia during the day [2], incurring increased risk for the deleterious effects of both states. Hypocortisolemia triggers adrenocorticotropic hormone driven increased 17-hydroxyprogesterone and adrenal androgen androstenedione (D4A) production, which can lead to premature fusion of growth plates, genital virilization, precocious puberty, adrenal rests, polycystic ovarian syndrome, and infertility [3-7]. Hypercortisolemia also has untoward long-term effects such as osteoporosis, short stature, and increased risk for cardiovascular disease in adulthood [8-16].

The goal of treatment is to limit periods of hypocortisolemia and the resultant increased excess adrenal androgen production while using the lowest possible HC dose to avoid the effects of overtreatment. Higher rates of overweight and obesity and of hypertension have been found in children with CAH who were oversuppressed during the first 5 years of life [14, 15]. This underscores the importance of titrating incremental doses as small as 0.1 mg in infants and young children, who tend to be more glucocorticoid sensitive during this early developmental period. Before the recent US Food and Drug Administration approval of HC granules, which allows dosing increments of 0.5 mg [17], the only commercial HC formulation available for the past 20 years has been a scored 5-mg tablet.

The lack of commercially available age-appropriate formulations has led to various manipulations of the 5-mg HC

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tablet, such as pharmacy-compounded hydrocortisone suspension or capsules, splitting tablets into quarters or eighths, or dissolving tablets to an individual dose or daily batch administered over the course of the day. Adverse outcomes have been reported for all these manipulations that are done to achieve small incremental doses [18-22] except for extemporaneously compounded alcohol-free suspensions [23]. A 6-hour serial sampling cortisol pharmacokinetic and pharmacodynamic response study in children with CAH, using a dose- and body surface area-normalized area-under-the-curve analysis, found that absorption of an extemporaneously compounded alcohol-free HC suspension based on published formulations [24, 25] was comparable with commercial HC tablets [23]. The current study's aim was to compare growth, weight gain, skeletal maturation, total daily hydrocortisone dose, and total cortisol exposure over the first 4 years of life in children with CAH treated with tablets vs children treated with an extemporaneously compounded alcohol-free HC suspension that allows dosing increments of 0.1 mg.

Methods

This study was a retrospective chart review of children with classic CAH treated with alcohol-free HC suspension compared with historical controls on tablets. Study data were collected and managed using Research Electronic Data Capture tools hosted at the University of Minnesota, a secure, Health Insurance Portability and Accountability Act-protected, web-based software platform. The study was approved by the University of Minnesota institutional review board.

Patients were treated using an HC regimen divided into 3 to 5 doses daily. We chose the age of 4 years to perform a cross-sectional study based on our cohort's age distribution. We were initially interested in growth over the first 10 years of life because individual HC doses of less than 2.5 mg are usually needed in this age group. The tablet group's visits were equally distributed over the ages 0 to 9 years, whereas for suspension-group patients, the vast majority (82%) of visits with data were for ages 0 to 4 years. Of the group that switched from tablets to suspension, 84% of visits with data were before 6 years of age. We chose the age of 4 years because it was the oldest age with sufficient data in all 3 groups. A total of 149 patients were being treated for CAH at the age of 4 years between 1980 and 2019 with either tablets or suspension, 19 of whom had nonclassic CAH and were excluded from this analysis.

Height, weight, and bone maturation (bone age *z*-scores) were used as key study indicators of chronic over- and under-exposure to cortisol and cumulative increased androgen exposure. Age- and sex-adjusted bone age *z*-scores were calculated using reference values obtained from Greulich and Pyle [26].

Height-for-age, weight-for-age, and body mass index (BMI)-for-age *z*-scores were generated using standard growth charts from the US Centers for Disease Control (CDC) [27] using the CDC SAS macros. Corrected height *z*-score was calculated as the height *z*-score minus target height *z*-score. Four height measurements were outliers and removed from the data.

Statistical Methods

Descriptive statistics of our study population at 4 years old are summarized by mean ± SD. Hydrocortisone dosages are summarized using 4 measures: "HC dose at 4 years," the daily HC dosage the patient was taking on their fourth birthday; "HC AUC," the cumulative HC dose since beginning of treatment and until the age of 4; and "average HC dose at 4 years," HC AUC divided by the number of days on HC. All recorded doses > 35 mg/m^2/d were excluded from the dataset. In the past (> 2 decades ago), a few providers would treat infants with HC > 35 mg/m^2/d during the first week or 2 after diagnosis. These data points were excluded from a few infants in the tablet group; their regular dose following these 2 weeks were used instead. All data were measured at standard care clinic visits, which occurred at irregular intervals that were different for each child. Therefore, standardized *z*-score measures at 4 years of age were estimated for each individual by fitting a Gaussian kernel smoother with an adaptively chosen bandwidth [28] to all available visit data for that individual ("stats" package in R) [29]. Weighted linear regression was used to assess the effect of treatment differences on *z*-score measures, with weights calculated as the inverse of the time span between the latest visit before and earliest visit after the fourth birthday to give greater weight to measures that were made closer to the fourth birthday. Adjusted models for height *z*-score, bone age *z*-score, and corrected height *z*-score accounted for age at diagnosis and sex, whereas weight *z*-score and BMI *z*-score models adjusted for age at diagnosis and height *z*-score. Predicted adult weight (PAH) measures were analyzed using linear regression models adjusted for age at diagnosis, sex, and diagnosis. All PAH measures except for corrected PAH also adjusted for target height *z*-score. Group differences in hydrocortisone dose were assessed by 2-sample *t* tests.

To analyze the effect of switching from tablets to suspension, children who switched from hydrocortisone tablet to suspension at any age, not necessarily before age 4 years, were matched on sex and age at diagnosis to children in the tablet group, with a 1:2 matching ratio. Height *z*-score, weight *z*-score, and BMI *z*-score were then estimated at the time of switching, 1 year after switching, and 2 years after switching by the same kernel smoothing method previously described. The *z*-score outcomes for HC tablet participants were calculated for the same age as their matched counterparts who switched from tablets to suspension. Change in *z*-score measures within 1 and 2 years of switching were then assessed by linear regression models. Adjusted models accounted for the same confounders as previously described *z*-score models. The sample size for these analyses was small but because no similar data have been published, we present plots of these data with smooth curves describing trends. Specifically, *z*-scores of participants who switched from tablets to suspension were smoothed using Loess applied to all available visit data for each person (using the ggplot2 package in R) [30]. Only participants who had at least 1 year of data before switching and at least 2 years of data after switching were included in the matched analysis or Loess graphs. All graphs and analyses were computed in R version 3.5.1 [29].

Auxological Analyses

We performed auxological analyses of each patient's serial longitudinal heights over the course of clinical treatment using the triple logistic model. This model uses a Bayesian technique to fit three logistic curves to each patient's height data and determine the contribution of early-childhood, mid-childhood, and adolescent growth periods to their PAH

[31, 32]. The model does not require height at maturity because this is estimated from the fit, and it can detect and locate growth velocity inflections (minima and maxima) at the linear growth milestones. Multiple growth measures can be calculated by this modelling technique such as age, height, and velocity at early-childhood minimum, at mid-childhood minimum, at pubertal "takeoff" (TO), and at peak height velocity (PHV). Adolescent height increment (linear growth between TO and PAH) and PAH can also be calculated. All patient height velocity and attained height curves were independently inspected by 3 pediatric endocrinologists relative to the raw data to further ascertain fit. For tablet patients, who had height data through 18 years and more, we ascertained the predictive accuracy of our auxological model fit. This was achieved by deriving population mean observed adult height (OAH) after age 18 years and comparing that estimate with the model PAH for the tablets-only subpopulation. A 1-way test of means was then used to compare mean PAH (cm) with OAH of patients overall and by sex.

All predicted height estimates at the each of the milestones were converted into height-for-age and percentile *z*-scores based on the CDC normative charts. For example, PAH was converted into PAH *z*-score according to the CDC 2000 height charts for age 18 years. Height-for-age and percentiles *z*-scores were also calculated for early- and mid-childhood heights. Also, for the subset that had mid-parental height (MPH), we calculated target height, TargHt (females: TargHt = MPH − 6.5 cm; MPH + 6.5 cm for males), which were then converted into internal and CDC *z*-scores (ie, TargHt *z*-score). Finally, we calculated corrected PAH-z-score = PAH z-score—TargHt z-score.

Results

Our analysis included 130 patients (70 females) with classic CAH (Table 1), of whom 100 children had salt-wasting CAH and 30 had simple virilizing Fig. 1. At 4 years of age, 89 children were on HC tablets, 16 were on suspension, and 25 had been switched from tablets to suspension, which they did at average age 19 months (SD 13.6). Table 1 summarizes baseline characteristics, anthropometric data, bone age *z*-scores, and HC doses in the 3 groups (suspension, tablets, switched tablets to suspension) at 4 years of age. The mean age at diagnosis was 0.11 and 0.22 years in the switched and suspension groups, compared with 0.71 years in the tablet group ($P = 0.019$, 0.12 respectively). There were no statistically significant differences in the mean target height and mean target height *z*-score in children in the switched and suspension groups compared with the tablet group ($P = 0.31$, 0.53 respectively).

HC Dosing

Table 2 summarizes the differences in HC doses among children treated with tablets or suspension. Children who were treated with suspension on their fourth birthdays were receiving a significantly lower average daily HC dose (9.19 [SE 0.37]) compared with children treated with tablets (13.13 [SE 0.68], $P < 0.001$). Similarly, the cumulative HC exposure up to 4 years of age (HC AUC [mg/m^2]) was also significantly lower in children treated with the suspension (13,020 [SE 640]) compared with tablets (17,490 [SE 1270], $P = 0.002$). When this cumulative dose was averaged over the duration of treatment, the average daily HC dose was 30.4% lower in the suspension group compared with tablets ($P < 0.001$).

Attained Growth Measures (Table 3)

Height *z*-scores at 4 years did not differ significantly between children in the tablet group and either the suspension or switched groups, nor did height *z*-scores corrected to target height *z*-scores. After adjusting for age at diagnosis and sex, these differences remained nonsignificant. Weight and BMI *z*-scores at 4 years of age were similar in the 3 groups, with no significant differences before or after adjusting for age at diagnosis and height *z*-scores.

Bone Age

Mean bone age *z*-score in the tablet group was 3.0 (SD 3.5) compared with 1.2 (SD 2.1) in the suspension group and 1.4 (SD 1.6) in the switched group (Table 3). Bone age *z*-score for the group using suspension was lower than the tablets group by 7.2 SDs on average ($P < 0.001$). After adjusting for age at diagnosis and sex, the suspension group bone age *z*-scores averaged 2.78 SDs lower than tablets ($P = 0.001$). The switched group had bone age *z*-scores lower by 5.93 ($P < 0.001$) SDs before adjusting for age at diagnosis and sex, but after adjustment the difference was 1.41 ($P = 0.11$).

Subanalyses of the Group That Switched

Subanalysis on patients who were switched from tablets to suspension by the age of 4 years found no significant effect on height, weight, and BMI *z*-scores of switching compared with continued treatment with tablets, at 1 year and 2 years after switching (Table 4). Our sample size was too small to study this effect over a longer period, but we present the available data because no other data exist. Visualization of the data showed an overall trend of decreasing height *z*-scores before switching, which seems to improve upon switching from tablets to suspension (Fig. 2A). A plot of height *z*-scores corrected by target height *z*-scores showed a similar trend (Fig. 2B). Similar visualization of weight and BMI *z*-scores (Fig. 2C, 2D) suggested that both seemed to be transiently increasing in the first 2 to 3 years after switching, after which the weight *z*-score curve seemed to stabilize, whereas the BMI *z*-score curve trended down as the height *z*-scores continued to improve.

Predicted Growth Outcomes

The suspension and switched groups did not differ significantly from the tablets group in attained heights and velocities at the various pubertal milestones, or in PAH (Table 5). This remained true when the PAH models were adjusted for age at diagnosis, sex, diagnosis, and target height *z*-score (Table 6). Corrected PAH (PAH *z*-score minus TargHt *z*-score) also did not differ significantly among the 3 groups, nor did age, height, or growth velocity at different growth windows including the early and mid-childhood growth windows, takeoff points at puberty, adolescent increment, and peak height velocity (Table 5). Comparing mean predicted final adult height with mean observed adult height in the tablet group, the current auxologic model fit underestimated females' heights by 2.6 cm and overestimated males' heights by 3.4 cm but no difference (height difference = 0.45 cm, $P = 0.75$) in OAH and PAH for both males and females combined.

Discussion

Our study is the first to report growth, bone maturation, and weight outcomes in children with CAH treated with

Table 1. Descriptive statistics of the study population at 4 years of age

Covariate	Switched (25)	Suspension (16)	Tablet (89)
	12 F, 14 SW	7 F, 12 SW	51 F, 73 SW
Age at diagnosis, y	0.11 ± 0.28 (24)	0.22 ± 0.75 (16)	0.71 ± 1.9 (62)
Age at diagnosis, SW, y	0.01 [0.00, 0.20]	0.01 [0.01, 0.40]	0.02 [0.00, 0.50]
Age at diagnosis, SV, y	0.46 [0.01, 1.10]	1.51 [0.01, 3.00]	0.98 [0.01, 8.00]
Age switched to suspension, y	1.58 (SD: 1.13)	---	---
Target height, cm	172 ± 7.5 (24)	171 ± 8.7 (16)	169 ± 16.9 (54)
Target height z-score	0.13 ± 0.55 (24)	0.07 ± 0.64 (16)	-0.08 ± 1.2 (54)
PAH, cm[a]	165 ± 10.2 (18))	169 ± 7.9 (12))	169 ± 11.8 (69)
PAH *z*-score[a]	-0.55 ± 0.79 (18)	-0.19 ± 0.44 (12)	0.0 ± 1.1 (69)
Corrected PAH *z*-score[a]	-0.69 ± 0.71 (17)	-0.29 ± 0.6 (12)	0.15 ± 1.5 (47)
HC dose at 4 y, mg/m^2/d	9.2 ± 2.4 (25)	9.2 ± 2.4 (16)	13.1 ± 4.8 (51)
HC AUC, mg/m^2	13309 ± 4038.5 (25)	12565 ± 4289.2 (16)	17493 ± 9065.6 (51)
Avg HC dose, mg/m^2/d on HC	10.3 ± 1.9 (25)	10.0 ± 2.3 (16)	14.7 ± 4.9 (51)
Height *z*-score	0.11 ± 1.2 (16)	-0.07 ± 0.99 (10)	0.04 ± 1.4 (38)
Corrected height *z*-score	0.02 ± 1.2 (15)	-0.15 ± 1.3 (10)	0.27 ± 2.1 (29)
Bone age *z*-score	1.4 ± 1.6 (12)	1.2 ± 2.1 (8)	3.0 ± 3.5 (26)
Weight *z*-score	0.42 ± 1.1 (16)	0.68 ± 1.2(10)	0.49 ± 1.2 (38)
BMI *z*-score	0.66 ± 0.86 (16)	1.1 ± 1.2 (10)	0.81 ± 1.0 (38)

All values are presented as mean ± SD (median). Each of the *z*-score values was estimated at 4 years using a Gaussian kernel smoother.
Abbreviations: BMI, body mass index; AUC, area under the curve; HC, hydrocortisone; PAH, predicted adult height; SV, simple virilizing; SW, salt wasting.
[a]The model used to determine PAH does not incorporate bone age and may underestimate differences because of skeletal maturity. Lack of available height data after age 10 years in the suspension group may impact estimation of PAH.

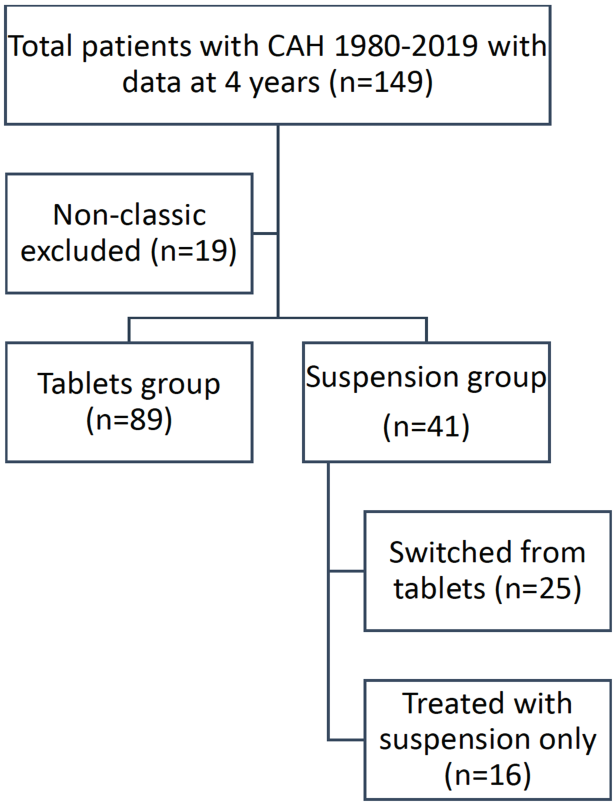

Figure 1. Flow chart of our study population and their distribution among the 3 groups: tablets, suspension, switched from tablets to suspension.

an alcohol-free pharmacy-compounded HC suspension, which differs chemically from the last commercially available HC suspension (cypionate), which was withdrawn from the market 20 years ago [33]. The HC cypionate suspension was found to require higher daily doses, caused higher 17-hydroxyprogesterone and androstenedione levels, increased weight gain, and cushingoid features compared with HC tablets [33]. Since then, the CAH consensus guidelines have recommended against use of any formulation of HC suspension [1]. The consequence was fewer options to achieve small and incremental doses (0.1-0.5 mg) of HC needed to treat young children with CAH, including splitting tablets into quarters or eighths, diluting tablets in water, or using a commercially available long-acting glucocorticoid suspension.

We found that alcohol-free HC suspension allowed smaller doses and incremental dosing changes so that at 4 years of age, average daily HC dose was 30% lower compared with children treated with tablets. Similarly, the cumulative HC exposure (HC AUC, mg/m^2) was on average 4470 mg less than the tablet group up to the age of 4 years. Both these statistically and clinically significant results demonstrate that the flexibility of smaller doses (0.1-1.2 mg) with suspension compared to tablets can lead to reduced total glucocorticoid exposure in young children during the important early years of growth and development.

Average bone age *z*-scores were significantly higher in children treated with tablets compared with the suspension group. As a result, children on tablets would be expected to have accelerated linear growth that results in higher average height *z*-scores compared with the suspension group at 4 years of age. However, the difference in average height *z*-scores was not statistically significant, thereby suggesting that higher cumulative HC exposure in the tablet group possibly had a negative impact on growth of children treated with tablets. The significantly lower bone age *z*-scores in the suspension group suggests that androgen production was not excessive, even though they received lower total daily doses of HC and had lower cumulative HC exposure. Lower bone age *z*-score is

Table 2. Results of independent 2-sample *t* tests comparing the HC dose at 4 years

Variable	Mean (SE) in tablet group	Mean (SE) in suspension group	*P* value
HC dose, mg/m²/d	13.13 (0.68)	9.19 (0.37)	<0.001
HC AUC, mg/m²	17 490 (1270)	13 020 (640)	0.002
Average HC dose, mg/m²/d on HC)	14.67 (0.69)	10.21 (0.32)	<0.001

"HC dose" is the HC dosage (mg/m²/d) the patient was taking on their fourth birthday. "Average HC dose" is the average dosage per day the patient has taken since being prescribed HC, before their fourth birthday. HC AUC is the total cumulative dose the patient has taken before their fourth birthday.
Abbreviations: AUC, area under the curve; HC, hydrocortisone.

Table 3. Results of unadjusted and adjusted weighted linear regression models to assess the effect of hydrocortisone suspension only and switched-to-suspension compared to tablet at 4 years of age

Unadjusted			Adjusted		
Outcome	Predictor	Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value
Height *z*-score	Switched (vs tablet)	-0.05 (-0.79 to 0.69)	0.90	-0.10 (-0.82 to 0.62)	0.79
	Suspension (vs tablet)	-0.04 (-1.03 to 0.94)	0.93	-0.32 (-1.27 to 0.64)	0.52
Corrected height *z*-score	Switched (vs tablet)	-0.51 (-1.75 to 0.73)	0.42	-0.77 (-1.98 to 0.44)	0.22
	Suspension (vs tablet)	-0.45 (-2.03 to 1.13)	0.58	-0.52 (-2.04 to 1.00)	0.51
Bone age *z*-score	Switched (vs tablet)	-5.93 (-8.64 to -3.23)	<0.001	-1.41 (-3.11 to 0.30)	0.11
	Suspensions (vs tablet)	-7.20 (-9.31 to -5.10)	<0.001	-2.78 (-4.24 to -1.31)	0.001
Weight *z*-score	Switched (vs tablet)	-0.20 (-0.93 to 0.52)	0.58	-0.18 (-0.57 to 0.21)	0.37
	Suspension (vs tablet)	0.20 (-0.77 to 1.17)	0.69	0.26 (-0.25 to 0.77)	0.32
BMI *z*-score	Switched (vs tablet)	-0.21 (-0.81 to 0.39)	0.49	-0.29 (-0.86 to 0.29)	0.33
	Suspension (vs tablet)	0.26 (-0.54 to 1.05)	0.53	0.23 (-0.53 to 0.99)	0.55

Outcome measures at 4 years were estimated by Gaussian kernel smoothers. Height *z*-score, bone age *z*-score, and corrected height *z*-score model was adjusted for age at diagnosis, and sex. Weight *z*-score and BMI *z*-score models were adjusted for age at diagnosis and height *z*-score.
Abbreviation: BMI, body mass index.

a favorable outcome because it should translate into a longer growth period, leading to better final adult height outcomes.

Patients who were switched from HC tablets to suspension showed improvement in their height *z*-scores upon switching, illustrated in Figs. 2A and 2B. However, the difference in height *z*-scores at 1 year and at 2 years after switching compared with the time of switching were not statistically significant, likely because of the small sample size and variable duration of follow-up. Also, some of these switched patients had been referred to our clinic because of poor growth and oversuppression of the HPA axis while on tablets, as evident by undetectable D4A, 17-OHP, and ACTH levels before their morning hydrocortisone dose [34]. Recovery of the HPA axis may take time depending on the duration of high cortisol exposure [35, 36]. GH axis recovery may lag even further, masking the growth response to the decreased total daily dose and cortisol exposure. In the switched group, this could explain why the PAH *z*-score was significantly lower than the population mean represented by 0 SD score on CDC reference curve.

Although our suspension-treated cohort were still in early or mid-childhood at the time of this report, triple logistic modeling allowed us to study their predicted growth patterns at early-childhood minimum, mid-childhood minimum, TO, PHV, and PAH, none of which differed significantly from children treated with tablets. As described previously, the lack of differences in these growth milestones, despite lower bone age *z*-scores and lower glucocorticoid dosing in the suspension group, may occur because the auxological model assumes normal growth in the absence of data in these later growth periods. Our model seemed to fit well with the available observed growth data in the tablet group, where we had height measures during the early childhood (0-5 years), mid-childhood (5-10 years), and adolescent years (10-15 years). Our auxological model, however, is not without limitations. First, it does not incorporate bone age measurements and may therefore have underestimated the PAH of children on suspension who had significantly lower bone age advancement and were clinically expected to have better final adult height outcomes. Also, the lack of available height data after age 10 years in children on suspension might have impacted estimation of PAH because the auxological model assumes typical growth in periods where data are not available. For the same reasons, estimation of age, height, and velocity at PHV may be less accurate in children on suspension.

The detrimental effect of supraphysiologic glucocorticoid treatment on childhood growth is well known and has been described in children treated with steroids for autoimmune conditions [37] or inflammatory conditions such as asthma [38]. Adult height in CAH has been an outcome of interest in clinical studies over the years because it reflects the effect of cumulative exposure to both androgens and glucocorticoids. Historically, individuals with CAH have grown to a height less than healthy controls. A meta-analysis summarizing 18 studies up to 1998 found a mean final height SD score of -1.37 in 561 patients. A second meta-analysis combining 35 studies published between 1966 and 2007 showed average final height SD score of -1.38 and corrected final height SD score of -1.03 [39, 40]. Although excessive androgen levels from inadequate HC replacement can cause premature growth

Table 4. Results of unadjusted and adjusted linear regression models to assess the effect of switching from tablet to suspension

Outcome	Unadjusted	*P* value	Adjusted	*P* value
	Estimate (95% CI) for switching vs not switching		Estimate (95% CI) for switching vs not switching	
1-y change in:				
Height *z*-score	-0.04 (-0.11 to 0.03)	0.28	-0.04 (-0.12 to 0.05)	0.40
Weight *z*-score	-0.03 (-0.09 to 0.02)	0.27	-0.04 (-0.10 to 0.03)	0.25
BMI *z*-score	0.00 (-0.04 to 0.03)	0.80	-0.01 (-0.05 to 0.03)	0.59
2-y change in:				
Height *z*-score	-0.09 (-0.22 to 0.03)	0.15	-0.08 (-0.22 to 0.06)	0.25
Weight *z*-score	-0.06 (-0.17 to 0.04)	0.25	-0.07 (-0.19 to 0.05)	0.24
BMI *z*-score	0.00 (-0.07 to 0.06)	0.89	-0.02 (-0.09 to 0.06)	0.68

Abbreviation: BMI, body mass index.
[a]Height *z*-score model was adjusted for age at diagnosis and sex. Weight *z*-score and BMI *z*-score models were adjusted for age at diagnosis and height *z*-score at the time of switching.

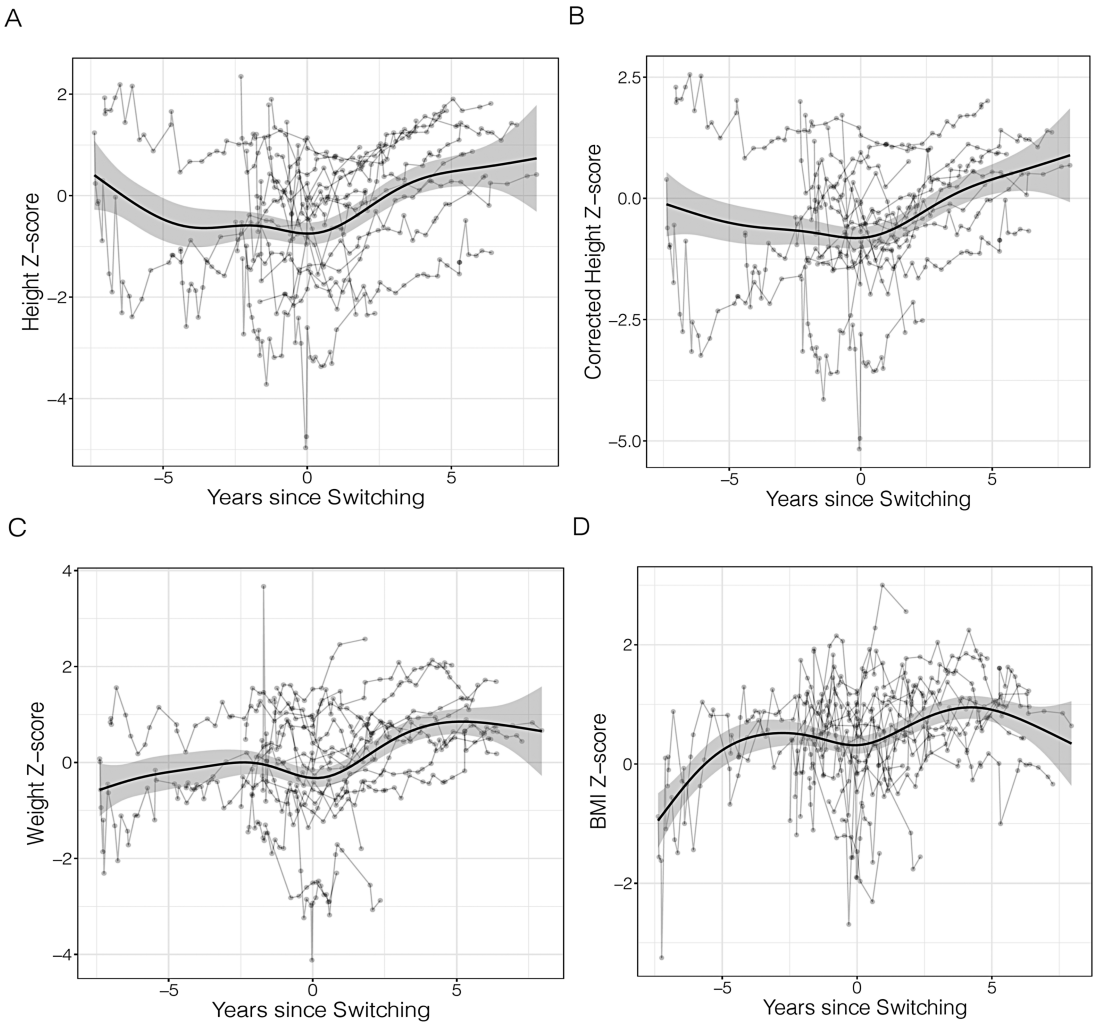

Figure 2. Panels A, B, C, D represent *z*-scores of height, corrected height, weight, and BMI, respectively, for patients who were switched from tablets to suspension.

acceleration and bone maturation, leading to decreased adult height potential, excessive HC exposure remains a principal reason for treatment-related growth failure in CAH. Recent studies in CAH found that higher HC doses are associated with reduced adult height. The HC effect on PAH was first quantified by Sarafoglou et al, who showed that each mg/m^2/d increase in the average HC dose during the growth period was associated with a 0.37 cm average decrease in the PAH in children with CAH [8]. Pijnenburg-Kleizen et al found that each additional mg/m^2/d of HC was associated with a

Table 5. Predicted growth variables determined by triple logistic modeling at the various linear growth milestones for patients with classic CAH to assess the effect of hydrocortisone suspension only and switched-to-suspension compared with tablets

Parameter	Tablets	Suspension only	*P* value	Switched to suspension	*P* value
PAH[a], (cm) mean (SD), median	169.0 (12.01), 166.6	169.4 (7.97), 171.5	0.88	165.1 (9.56), 162.5	0.12
PAH *z*-score[a], mean (SD), median[b]	0.00 (1.00), -0.20	0.00 (1.00), 0.26	0.99	0.00 (1.00), -0.27	0.99
z-score to CDC	-0.03 (1.11), -0.19	-0.20 (0.44), -0.25	0.61	-0.48 (0.83), -0.44	0.0478
Age at ECM age (y), mean (SD), median	4.16 (0.59), 4.24	4.37 (0.43), 4.49	0.15	3.94 (0.57), 4.03	0.99
Height at ECM (cm), mean (SD), median	101.26 (6.64), 103.2	102.94 (5.58), 102.9	0.18	99.4 (8.06), 98.7	0.90
z-score to CDC	-0.37 (1.03), -0.34	-0.37 (0.82), -0.38	0.99	-0.53 (1.39), -0.1	0.73
Percentile	40.1 (29.3), 36.7	38.5 (27.1), 35.45	1	40.7 (34.6), 46	1
Velocity at ECM (cm/y), mean (SD), median	6.84 (0.96), 6.66	6.76 (0.61), 6.63	0.18	7.24 (1.12), 7.06	0.85
Age at MCM age (y), mean (SD), median	5.9 (0.97), 6	6.05 (0.83), 6.24	0.18	5.79 (0.91), 5.95	0.90
Height at MCM (cm), mean (SD), median	113.4 (8.76), 115.39	114.2 (5.75), 116.39	0.19	112.73 (7.67), 113.13	0.87
CDC *z*-score	-0.18 (1.11), -0.37	-0.24 (0.79), -0.25	0.86	-0.18 (1.36), 0.21	0.99
Percentile	44 (31.1), 35.1	42.1 (26.7), 40.8	1	49.5 (34.3), 58.25	1
Velocity at MCM (cm/y), mean (SD), median	7.11 (1.06), 6.91	6.93 (0.52), 6.91	0.18	7.55 (1.11), 7.44	0.85
Age at TO (y), mean (SD), median	9.37 (1.42), 9.2	9.63 (0.92), 9.8	0.41	8.94 (1.64), 8.84	0.29
Height at TO (cm), mean (SD), median	137.7 (14.52), 134.25	137 (7.3), 135.58	0.86	132.7 (14.37), 132.83	0.16
CDC *z*-score	0.37 (1.30), 0.16	0.21 (0.32), 0.05	0.43	0.24 (0.95), 0.51	0.22
Percentile	56.56 (30.93), 56.19	58.00 (12.06), 52.05	0.99	56.95 (30.61), 69.31	>0.99
Velocity at TO (cm/y), mean (SD), median[a]	5.14 (1.00),5.21	5.17 (0.40), 5.20	0.99	5.29 (0.94), 5.26	0.62
Age at PHV (y), mean (SD), median[a]	12.06 (1.39),12.11	12.36 (0.99), 12.81	0.39	11.67 (1.38), 11.41	0.25
Height at PHV (cm), mean (SD), median[a]	154.2 (12.54),150.2	154.1 (7.40), 153.8	0.97	150.0 (10.60), 149.6	0.14
CDC *z*-score	0.45 (1.10),0.43	0.06 (0.59), 0.01	0.47	-0.03 (1.29),0.43	0.41
Percentile	61.11 (27.52),66.51	52.09 (20.64), 50.43	0.53	51.04 (36.01), 66.46	>0.99
Velocity at PHV (cm/y), mean (SD), median[a]	7.44 (1.30),7.42	7.82 (0.94), 7.46	0.99	7.74 (1.16), 7.68	0.33

P values for medians were assessed with Kruskal-Wallis test, and that of means by *t* test or ANOVA.
Abbreviations: CAH, congenital adrenal hyperplasia; CDC, US Centers for Disease Control and Prevention; ECM, early childhood minima; MCM, mid-childhood minima; PAH, predicted adult height; PHV, peak height velocity; TO, takeoff.
[a]The model used to determine growth milestones does not incorporate bone age and may underestimate differences because of skeletal maturity for ages where height data are not available (ie, suspension group after 10 years). Lack of available height data after age 10 years in the suspension group may impact estimation of age, height, and velocity at PHV as well as PAH.
[b]*z*-score compared with the Nordic population.

Table 6. Results of adjusted linear regression models to assess the effect of hydrocortisone suspension only and switched-to-suspension compared with tablet on PAH

Outcome	Predictor	Estimate (95% CI)	*P* value
[a] PAH	Suspension (vs tablet)	-1.27 (-4.36 to 1.82)	0.42
	Switched (vs tablet)	-0.23 (-4.27 to 3.80)	0.91
[a] PAH *z*-score	Suspension (vs tablet)	-0.18 (-0.63 to 0.27)	0.43
	Switched (vs tablet)	-0.03 (-0.62 to 0.56)	0.93
[a] PAH *z*-score – target height *z*-score	Suspension (vs tablet)	-0.44 (-1.19 to 0.31)	0.26
	Switched (vs tablet)	-0.08 (-1.00 to 0.84)	0.87

Target height z-score is adjusted for age and diagnosis, sex, and diagnosis. PAH and PAH *z*-score models are adjusted for age at diagnosis, sex, diagnosis, and target height *z*-score.
Abbreviation: PAH, predicted adult height.
[a]The model used to determine PAH does not incorporate bone age and may underestimate differences from skeletal maturity. Lack of available height data after age 10 years in the suspension group may impact estimation of PAH.

reduction in near adult height of 0.13 SD score [41], which is equivalent to 0.78 cm in females and 0.89 cm in males [42].

Although higher HC doses were previously used for initial treatment of infants, accumulating evidence suggests that this is not necessary and is probably disadvantageous. Absent any treatment, boys with a late diagnosis of simple-virilizing CAH did not display growth acceleration in the first 6 months of life [43], indicating relative androgen insensitivity early in life and that lower HC doses could be sufficient. Height velocity and bone age were not accelerated up to 1 year of age in another untreated simple-virilizing cohort [44]. On the other side, treatment with higher doses of HC in the first few years of life was shown to negatively affect growth. Grigorescu-Sido et al found that higher doses of glucocorticoids (15-25 mg/m^2/d) between 1 and 5 years of age negatively affected growth velocity during that interval and were also associated

with impaired adult height compared with children receiving lower doses of glucocorticoids (10-15 mg/m²/d) [45]. Manoli et al demonstrated that adult height in their salt-wasting group was strongly associated with height achieved at 2 years of age, which was negatively related to HC dose in the period from birth to 2 years [46]. Treatment with doses between 9 and 15 mg/m²/d in the first 3 years of life resulted in normal bone age and growth velocity at the age of 3 years [43]. In addition to higher doses, increased cumulative HC exposure during early years may have a detrimental effect on growth. Bomberg et al reported that children with simple-virilizing-CAH fared the same as or better than their salt-wasting-CAH counterparts in final adult height, despite their later age of diagnosis and more advanced bone age [9].

Children with CAH are at higher risk for earlier adiposity rebound and increased early-onset obesity and overweight; 35% to 40% percent of children with CAH are reported to be obese [3, 15], which contributes to their unfavorable cardiovascular profile [47, 48]. Children with CAH tend to experience adiposity rebound 2 to 4 years earlier than the general population [49]. Avoiding oversuppression and increasing BMI over the first 5 years of life is especially important because chronic exposure to glucocorticoids may increase the risk of earlier adiposity rebound and increased risk of obesity during adulthood [50]. In our suspension-treated cohort, neither mean BMI nor weight-for-age *z*-score at 4 years differed significantly from patients treated with tablets. In the switched group, although the sample size was too small to detect a difference, the weight *z*-scores curve seemed to be transiently increasing after the time of switching to suspension (Figs. 2C, 2D), which corresponds to the increase in height *z*-scores. The initial uptrend in BMI *z*-scores was followed by decreasing BMI *z*-scores as the weight *z*-score curve seemed to stabilize and the height *z*-scores continued to improve. The improvement in BMI could also possibly be due to accretion of lean muscle with less adiposity.

A limitation of our study, which is also a limitation of current monitoring of children with CAH, is that adrenal steroid (17-OHP and D4A) concentrations are measured only 3 to 4 times a year during clinic visits. At each visit androgen levels are measured at different times in relation to morning or afternoon HC dosing depending on clinic openings and patient availability. Because both 17-OHP and D4A are in a state of dynamic equilibrium in response to the HC dosing regimen and because they are measured during clinic visits at different times after a dose, their concentrations are widely variable and only provide assessment of exposure at a single point in time. Further, 17-OHP and D4A concentrations have been shown to have significant intra-individual and inter-individual variability and significant between-subject variability [2].

Another limitation of our study is the young age of patients on suspension, which limits our ability to assess their full growth period requiring reliance on our predictive model, which has its own limitations, as previously discussed. Our sample size is relatively small, especially for the suspension and switched groups, which affected statistical power, and the analyses were complicated further by the irregular spacing of repeat measurements on individual children.

In conclusion, alcohol-free HC suspension along with the commercially available HC granules are viable alternatives to HC tablets in treating young children with CAH because they can provide increments as low as 0.1 mg and 0.5 mg, respectively, allowing lower HC doses. There are pros and cons to both formulations. Hydrocortisone granules are available in 4 predefined strengths (0.5 mg, 1 mg, 2 mg, and 5 mg), whereas HC suspension can be dosed from 0.1 to 1 mg in 0.1-mg increments. Infants tend to be more sensitive to HC because they have high biologically active cortisol from decreased cortisol binding globulin during the first 2 years of life; therefore, having the option of < 0.5 mg is an advantage. Another difference is seen in the youngest children where it is generally easier to administer, for example, 1.5 mg of suspension (1.5 m/L) through a syringe than opening 2 capsules (0.5 mg and 1 mg) and dropping that volume of granules containing 1.5 mg of HC into the back of the child's mouth followed by water to ensure granules were swallowed. The most significant difference, however, is that granules have gone through US Food and Drug Administration approval and are commercially available. Quality control for compounded medications is not as rigorous as for commercial medications, which can lead to concerning inconsistency between different preparations. Therefore, if prescribing an alcohol-free suspension, providers should recommend the use of a quality compounding pharmacy.

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Data Availability

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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