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Early Adiposity Rebound Predicts Obesity and Adiposity in Youth with Congenital Adrenal Hyperplasia

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Abstract

Introduction: Youth with classical congenital adrenal hyperplasia (CAH) have higher prevalence of cardiometabolic risk factors such as obesity, abdominal adiposity, and hypertension. Patients with CAH also exhibit an earlier adiposity rebound (AR) compared to normative populations. However, the predictive relationship between AR and cardiometabolic risk factors needs to be better understood.

Methods: We performed a retrospective cohort study at a U.S. tertiary pediatric center in youth with classical CAH due to 21-hydroxylase deficiency. AR was determined by cubic polynomial modeling. A subset of participants had fasting analytes, whole-body dual-energy x-ray absorptiometry, and magnetic resonance imaging as adolescents.

Results: In 42 youth with CAH (45.2% female, 54.8% Hispanic, 90.5% salt-wasting form), the average age at AR was 3.4 ± 1.3 years of age. AR differed by BMI-z, with youth with obesity having an earlier AR (2.8 ± 1.0 years) compared to lean youth (4.1 ± 1.3 years, p = 0.001). However, AR did not differ by either CAH form or sex. Earlier AR predicted higher BMI-z at 7 and 12 years of age. In addition, earlier AR predicted increased central obesity (as measured by

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Author Contributions

G.B., V.K.T., and M.S.K. conceptualized and designed the study. G.B. collected the data. D.H.H. and W.S.K. performed analysis of MRI images. M.Y.Y. performed cubic polynomial modeling. V.K.T. performed comparative and inferential statistics. G.B. and V.K.T. drafted the initial manuscript, in conjunction with M.S.K. All authors critically reviewed the manuscript and approved the final manuscript as submitted.

Statement of Ethics

The study was reviewed and approved by the Children's Hospital Los Angeles institutional review board (CCI-12–0020 Natural History Study of CAH from Infancy; CHLA-14–00191 Congenital Adrenal Hyperplasia Neuroimaging: Emotions and Appetite Testing; CCI-09–00261 Cardiovascular Disease Risk in Congenital Adrenal Hyperplasia). Participant and their parents provided informed consent and assent in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

Mitchell E. Geffner currently serves or has recently served as an advisor to Adrenas, Daiichi Sankyo, Gilead, Neurocrine Biosciences, Novo Nordisk, Nutritional Growth Solutions, Pfizer, QED, and Spruce Biosciences; on data safety monitoring boards for Ascendis, Millendo, and Tolmar; and receives royalties from McGraw-Hill and UpToDate. The other authors have no conflicts of interest to declare.

waist circumference, subcutaneous adipose tissue, and trunk fat) and total body fat in adolescence. AR was negatively correlated with bone age, and its relationships with HDL and hypertension were trending towards significance.

Conclusions: AR in youth with classical CAH could serve as a useful clinical marker to identify those patients who are at higher risk for developing cardiometabolic risk factors during childhood and adolescence.

Keywords

Congenital adrenal hyperplasia; adiposity rebound; obesity; body mass index; 21-hydroxylase deficiency

Introduction

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is characterized by impaired cortisol and aldosterone biosynthesis, and excess androgen production. One in 15,000 children have classical CAH—either the salt-wasting (SW) or simple-virilizing (SV) form—and overall, one in 200 Caucasians have the mild, non-classical form [1, 2]. A mutation in the *CYP21A2* gene is the most common cause of CAH, leading to 21-hydroxylase deficiency, and 90% of all cases of CAH [3]. Youth with classical CAH have an increased prevalence of obesity, higher total body fat, and increased subcutaneous and visceral adipose tissue compared to unaffected matched controls [4, 5]. Moreover, youth with CAH have higher rates of cardiometabolic risk factors and metabolic syndrome, with higher leptin, fasting insulin, and reduced insulin sensitivity as measured by HOMA-IR compared to unaffected youth [4, 6, 7].

These negative health outcomes may start early in life, as youth with CAH have an earlier age at adiposity rebound (AR) [8–10]. Typically, BMI quickly increases during the first year of life, and then decreases until it reaches a nadir in early childhood [11]. AR is defined as the second rise in body mass index (BMI) corresponding to an increase in the number and size of adipocytes [12, 13]. In normative populations across several countries, AR occurs between 5 to 7 years of age [12, 14, 15]. However, AR examined in youth with CAH has been found to be markedly younger at 1.7 years of age in the U.K., 3 years of age in Japan, and 3.3–3.8 years of age in the U.S. [8–10]. The age at AR could hold additional clinical significance as it has been found to be predictive of BMI, increased adiposity, and heightened risk for metabolic syndrome in healthy adults [12, 15–18]. In addition, earlier AR has been associated with higher BMI and fat mass, a lipoprotein phenotype associated with insulin resistance, and an increased metabolic risk score at 7 years of age in otherwise healthy children [16, 19, 20]. However, more needs to be understood about AR and cardiometabolic risk in youth with CAH.

Therefore, the purpose of this study was to determine the predictive relationship between age at AR in youth with classical CAH and markers of CAH severity, body composition in adolescence, and cardiometabolic risk factors.

Materials and Methods

Study Population

This was a retrospective cohort study of 42 youth with CAH followed at the Children's Hospital Los Angeles (CHLA) CAH Comprehensive Care Center. The cohort was 45.2% female and 54.8% Hispanic. All participants had classical CAH due to 21-hydroxylase deficiency, with 90.5% SW and 9.5% SV.

Inclusion criteria were a biochemical diagnosis of classical CAH (SW or SV) due to 21-hydroxylase deficiency and medical records documenting height and weight from at least 2–7 years of age. All participants were on hydrocortisone treatment, and they were not on any anti-obesity pharmacotherapy. Forty-one of 42 patients were treated with fludrocortisone. Participants were excluded from this study if they were diagnosed with non-classical CAH, the mildest form of CAH. This study was approved by the CHLA Institutional Review Board. Written consent was obtained from all parents and/or participants, and all minors up to 14 years of age gave assent.

Age at Adiposity Rebound

From 2 years, and approximately every 6 months thereafter until 7–9 years of age, participant ages and clinical heights, weights, and BMIs were recorded retrospectively from the medical record. BMI Z-Score (BMI-z) was calculated using U.S. reference population mean and standard deviations for BMI-for-age measurements from the National Center for Health Statistics of the Centers for Disease Control [21]. Additionally, if participants had available data, weight-for-length percentiles were calculated from clinical length and weight measurements during the first 1–2 years of age. For the purposes of modeling, all participants had at least five data points for BMI percentile or weight-for-length versus age with an average of 12.6 ± 2.4 data points per participant.

The cubic polynomial model, a widely used method thought to reflect natural BMI trajectory, was used to determine age at AR as previously described [22]. From 1–9 years of age, all available BMI and weight-for-length measurements were used to create a cubic polynomial model for each participant's BMI trajectory. AR was located at the age corresponding to the local minimum of the polynomial fitted curve. Estimates of age at AR were included in the analyses if the R^2 (coefficient of determination) for the cubic model was greater than 0.65. The cubic polynomial equation was as follows where Y was BMI (kg/m^2), X was the age (years), and ε was the error term.

$$\log(Y) = \beta_0 + \beta_1 X + \beta_2 X^2 + \beta_3 X^3 + \varepsilon$$

We calculated the age at the local minimum of the cubic polynomial to find the age at AR.

Disease-specific Factors: Markers of CAH Severity

We recorded 17-hydroxyprogesterone (17-OHP) levels from the newborn screen and/or the confirmatory venous draw at the time of diagnosis and used the highest value for analysis.

Bone age radiographs were read by one of three pediatric endocrinologists (including M.S.K., M.E.G.), using the Greulich-Pyle method. The standard deviation (SD) of bone age for all clinically available x-rays using the Greulich-Pyle method was recorded and averaged, with a mean number of 9.5 radiographs per participant. Doses of hydrocortisone (mg/m^2/day) and fludrocortisone (mg/day) were collected from all visit notes 1 year prior to the age at AR for each participant, and the average doses were calculated.

Weight Status and Body Composition

In all 42 participants, BMI-z was collected retrospectively for clinic visits in closest proximity to ages 7 years (7.5 ± 0.5), 12 years (12.4 ± 0.5), and 18 years (18.2 ± 0.4), and at the latest or most recent clinic visit (13.1 ± 3.8 years). A subset of 23 participants included in this cohort also participated in another prospective study [23]. In these participants, additional measurements have been taken thus far at a single time point in adolescence (12.3 ± 2.9 years). Anthropometric measurements were taken, including hip and waist circumferences. Whole-body dual-energy x-ray absorptiometry (DXA; Hologic, Marlborough, MA) was used to measure total body fat mass, total percent fat, total trunk fat mass, and total lean body mass. MRI was performed (Achieva 3-Tesla, Philips Healthcare, Cleveland, OH) to assess abdominal subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) volume.

Cardiometabolic Risk Factors

In the same subset of 23 participants, a fasting comprehensive metabolic panel and lipid panel were obtained early in the morning at a single time point in adolescence, prior to participants taking their CAH medications (HPLC, Quest Diagnostics Nichols Institute, San Juan Capistrano, CA). HDL cholesterol, triglycerides, and glucose levels were analyzed. Blood pressure was also measured in participants at this time. High blood pressure was classified as having either a systolic or diastolic blood pressure greater than the 90^{th} percentile based on age, sex, and height [24].

Statistical Analysis

SAS 9.3 software (SAS Institute, Cary, North Carolina) was used to generate cubic models for each participant. R Studio Version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for descriptive, comparative, and bivariate analyses. For parametric data, two-tailed *t*-tests were used to test for associations and, for non-parametric data, the two-tailed Mann-Whitney *U* test was used to test for associations. Pearson correlations were used to determine the direction and strength of associations. Simple linear regressions were used to determine the size of effects. P values ≤ 0.05 were deemed statistically significant and p values ≤ 0.1 as trending towards significance.

Results

Age at Adiposity Rebound

In our CAH cohort, the mean age at AR was estimated to be 3.4 ± 1.3 years old. The corresponding BMI for this age was 16.6 ± 1.6 kg/m^2, and the BMI percentile or weight-for-length percentile was 62.0 ± 29.4%. Age at AR did not statistically differ by sex or CAH

phenotype (Table 1). Stratifying by BMI-z at the last clinic visit, youth with obesity had a significantly earlier AR (2.8 ± 1.0 years) as compared to those youth classified as lean (4.1 ± 1.3 years; p = 0.001).

Disease-specific Factors: Markers of CAH Severity

Among youth with CAH, age at AR was significantly correlated with average bone age SD (r = −0.39, p = 0.01) (Table 2). AR was not correlated with 17-OHP at diagnosis, or with average hydrocortisone dose (p = 0.4 for both). However, AR was positively correlated with the average fludrocortisone dose (r = 0.31, p = 0.04).

Weight Status and Body Composition

Age at AR was significantly correlated with BMI-z at 7 years (r = −0.78, p < 0.001), 12 years (r = −0.65, p < 0.001), and latest available measurements (r = −0.47, p = 0.002), but not at 18 years (r = −0.29, p = 0.4) (Table 3). For each year earlier that AR occurred, regression analysis predicted that BMI-z at 7 years would increase by 0.70 SD, BMI-z at 12 years by 0.37 SD, and the latest BMI-z by 0.32 SD. Of the 23 youth who also participated in a prospective study of body composition, 22 youth had completed whole-body DXA scans and 16 completed MRI scans at 12.3 ± 2.9 years old. Controlling for age at the time of the scans, we found AR to be negatively correlated with total body fat (r = −0.49 p = 0.03), lean body mass (r = −0.48, p = 0.03), trunk fat (r = −0.51, p = 0.02), and SAT volume (r = −0.56, p = 0.03; Table 3). For each earlier year that AR occurred, the total body fat mass increased by 4.17 kg, total body lean mass increased by 3.32 kg, trunk fat mass increased by 1.86 kg, and SAT volume increased by 1.29 L. The relationship with percentage body fat (r = −0.37, p = 0.09) trended towards significance.

Cardiometabolic Risk Factors

The age at AR was negatively correlated with waist circumference percentile (r = −0.47, p = 0.02), and for each earlier year that AR occurred, the waist circumference percentile increased by 10.14% (Table 4). The predictive relationships with HDL cholesterol (r = 0.39, p = 0.07) and high blood pressure (β = 0.17, p = 0.06) trended towards significance, but there was no relationship with glucose or triglycerides.

Discussion

The main finding of our study was that an earlier age at AR in youth with classical CAH due to 21-hydroxylase deficiency predicted an increased BMI-z at 7 and 12 years of age, as well as increased central obesity and total body fat in adolescence. We found the age at AR to be 3 years of age in youth with classical CAH at our center, supporting other studies that have shown AR to be 2–4 years earlier in CAH youth compared to the general population [9, 10]. We also observed that this early age at AR occurs in youth with CAH independent of weight status, with AR occurring at 2.8 years in obese youth and 4.1 years in lean youth with CAH. These findings suggest that disease-specific factors that promote accelerated development and premature adrenarche could underlie the biological basis of AR in CAH.

In the general population, earlier AR is associated with more advanced bone age in males only. This is in contrast to youth with CAH in our cohort, where there was a significant association between AR and bone age in both males and females, suggesting that youth with CAH may have more male-typical patterns of body development and AR [22, 25]. The age at AR was nearly identical in both males and females with CAH (3.4 years, $p = 1.0$), in contrast to numerous studies in the general population that have confirmed that AR occurs earlier in females [22, 26–28]. Youth with CAH are exposed to excess androgens, with females sometimes exhibiting male secondary sex characteristics and behaviors [29, 30]. Our findings suggest that females with CAH could also have more male-typical patterns of body composition development. Both adipose tissue and lean mass were negatively correlated with age at AR suggesting a disease-specific influence on both compartments via overall growth. Excess androgens in youth with classical CAH could promote increased lean mass, thereby also affecting age at AR. When we examined various markers of body composition in adolescents with CAH, patterns of sexual dimorphism did not differ from those seen in the general population (Supplementary Table 1); females had significantly higher % total body fat than males, but sex differences in waist-to-hip circumference ratios, total body fat mass, trunk fat, lean mass, SAT, and VAT were not statistically significant, likely due to small sample size [31]. To truly understand the effect of hyperandrogenism in females with CAH on body composition development, these measurements can be repeated in a larger sample.

Because of its predictive value, AR could be a useful tool for clinicians to identify youth with CAH who are at increased risk of future obesity. However, more studies are needed to fully understand the relationship between AR and metabolic syndrome. In our cohort, AR was strongly correlated with waist circumference, a strong predictor of VAT, and exhibited correlations trending towards significance with HDL cholesterol and high blood pressure, but none of the participants met diagnostic criteria for metabolic syndrome in children (International Diabetes Foundation) [32–34]. Given that metabolic syndrome incidence increases with age, this work should be repeated in an older and larger cohort to determine if AR is a predictor for metabolic syndrome among youth with CAH. While this work used cubic polynomial modeling, AR can also be estimated through a visual inspection method that would be practical for clinicians. Age at AR by visual inspection is located at the age corresponding to the lowest BMI between 1–9 years of age (Supplementary Figure 1) [12]. We found that estimates of AR by cubic polynomial modeling (3.4 ± 1.3 years) and visual inspection (3.6 ± 1.6 years) were strongly correlated in our cohort ($r = 0.79$, $p < 0.001$). Interestingly, we found that age at AR by visual inspection was significantly correlated to BMI-z during adolescence, but not metrics of central obesity. This discordance could be a result of a well-documented overestimate of AR using visual inspection that comes from choosing the later BMI as the point of AR given a plateau (defined as two or more consecutive BMI values that were less than 0.1 kg/m^2 apart) [35]. Therefore, clinicians using visual inspection should be aware that AR may be occurring even earlier in patients who have a plateau in their growth curves before AR.

There are some limitations to our study. First, due to the retrospective nature of data collection, our sample size was limited by the number of medical records with BMI documented from 2–7 years of age. As a result of this qualifying criterion, our sample had a

higher proportion of youth with SW CAH as compared to SV CAH than expected for a typical CAH patient population. Prior to newborn screening being instituted in California in 2005, male youth with SV CAH at our center were diagnosed with CAH later in early childhood and often did not have BMI documented between 2–7 years of age. Data for BMI, bone age, and medication doses could not be consistently recorded at standard time intervals, and BMI-z at 18 years was only available for 11 participants, limiting the strength of our predictive model. Second, because the metrics of abdominal adiposity and additional cardiometabolic risk factors were only attained through participation in a different, prospective study, the age at which these measurements were taken was not standardized. Third, AR has been criticized as a predictor for earlier BMI percentile crossing rather a true biological phenomenon [36]. However, by measuring body composition through DXA and MRI, we were better able to understand the relationship between AR and adiposity specifically. Fourth, edge effects may negatively impact the estimation of AR using a cubic polynomial method [36]. To limit these effects and to improve the overall fit of the model, we restricted our data to an upper limit of 9 years of age. Finally, we were unable to capture the potential impact of glucocorticoid and mineralocorticoid replacement therapy on the age at AR. We and others have not found a relationship between glucocorticoid dose and AR [10]. AR occurs at a younger age in patients with CAH (3.4 ± 1.3 years in our study), a time around which glucocorticoid doses tend to be closer to physiological than at older ages and the disease easier to control overall. While it would be unethical to take patients with CAH off hormone replacement, a future study of youth with non-classic CAH, who have less severe cortisol deficiency and may be untreated with glucocorticoid replacement, may help to clarify the impact of glucocorticoid therapy on AR and adolescent growth and development. However, there was a significant relationship between AR and fludrocortisone dosage ($r = 0.31$, $p = 0.04$). Another prior study did not find an association between fludrocortisone dosage and age at AR [10]. The mechanism underlying the observed positive correlation between fludrocortisone dose and age at AR is unclear.

In conclusion, the age at AR in youth with classical CAH is predictive of future central obesity. Thus, estimating AR could be a non-invasive and simple tool to aid clinicians in identifying toddlers at high risk for obesity. Early identification would help initiate early nutrition and weight-monitoring interventions to prevent unhealthy weight gain and address the higher-than-expected rates of obesity observed in individuals with CAH across the lifespan.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Age at Adiposity Rebound by Sex, Weight Status, and CAH Phenotype in Youth with CAH due to 21-hydroxylase Deficiency

	Age at AR (Mean ± SD)	p
Sex		
Female	3.4 ± 1.1	1.0
Male	3.4 ± 1.5	
Weight Status at Latest Visit		
Non-obese (BMI percentile < 95th)	4.1 ± 1.3	0.001
Obese (BMI percentile ≥ 95th)	2.8 ± 1.0	
CAH Form		
Salt-wasting	3.4 ± 1.4	0.3
Simple-virilizing	2.9 ± 0.7	

Table 2.

Disease-specific Factors and Adiposity Rebound in Youth with CAH

Disease-specific Factors	Mean ± SD	r	p
17-hydroxyprogesterone at diagnosis (nmol/L)	951.6 ± 1182.4	−0.15	0.4
Average Bone Age SD	1.8 ± 2.2	−0.39	0.01
Average Hydrocortisone Dose (one year before age at AR; mg/m^2/day)	16.0 ± 7.1	−0.13	0.4
Average Fludrocortisone Dose (one year before age at AR; mg/day)	0.1 ± 0.03	0.31	0.04

AR, adiposity rebound

Table 3.

Prediction of Weight Status and Central Obesity by Adiposity Rebound in Youth with CAH

Dependent/Outcome Variable	Mean ± SD	r	β	p
BMI Z -score[a]				
BMI-z at 7 years (n = 42)	1.5 ± 1.2	−0.78	−0.70	<0.001
BMI-z at 12 years (n = 27)	1.6 ± 0.8	−0.65	−0.37	<0.001
BMI-z at 18 years (n = 11)	1.6 ± 0.9	−0.29	−0.22	0.4
BMI-z at Latest (n = 42)	1.5 ± 0.9	−0.47	−0.32	0.002
DXA[b] **(n = 22)**				
Total Body Fat Mass (kg)	22.2 ± 9.4	−0.49	−4.17	0.03
Percentage Body Fat (%)	37.7 ± 8.9	−0.37	−2.74	0.09
Total Body Lean Mass (kg)	32.9 ± 11.8	−0.48	−3.32	0.03
Trunk Fat Mass (kg)	9.2 ± 4.0	−0.51	−1.86	0.02
MRI[b] **(n = 16)**				
Subcutaneous Adipose Tissue Volume (L)	4.5 ± 2.7	−0.56	−1.29	0.03
Visceral Adipose Tissue Volume (L)	0.9 ± 0.6	−0.38	−0.19	0.2

[a]Predictive Model 1: Outcome = AR age

[b]Predictive Model 2: Outcome = Chronological age at measurement + AR age

Average age of measurement: 12.3 ± 2.9 years old

Table 4.

Cardiometabolic Risk Factors and Adiposity Rebound in Youth with CAH

Dependent/Outcome Variable	Mean ± SD or % (n)	r	β	p
Waist Circumference Percentile[a]	64.7 ± 25.5	−0.47	−10.14	0.02
Blood Pressure ≥ 90th Percentile[a]	43.5 (10)	--	0.17	0.06
Fasting Glucose (mmol/L)[b]	4.6 ± 0.4	−0.02	−0.14	0.9
HDL Cholesterol (mmol/L)[b]	1.4 ± 0.3	0.39	4.16	0.07
Triglycerides (mmol/L)[b]	1.0 ± 0.4	−0.10	−2.88	0.7
Metabolic Syndrome	0.0 (0)	--	--	--

[a]Predictive Model 1: Outcome = AR age

[b]Predictive Model 2: Outcome = Chronological age at measurement + AR age

Average age at measurement: 12.3 ± 2.9 years old