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# Final Height in Patients with Congenital Adrenal Hyperplasia: The Controversy of Under Treatment Versus Overtreatment

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## Abstract

*Background:* Growth patterns in congenital adrenal hyperplasia (CAH) are challenging. Androgen excess can occur at any age leading to accelerated growth, early epiphyseal closure and compromised final height (FH). The FH in CAH is usually expected to be lower than predicted based on parental height or compared to the healthy population.

*Aim of Study:* To evaluate growth and FH in patients with CAH.

*Patients and Methods:* This retrospective study included 34 patients diagnosed with classic CAH (27 salt wasting and 7 simple virilizing). An anthropometric assessment was done for the patients and their parents to estimate the FH, target height (TH) and corrected FH (FH – TH). Therapeutic and biochemical data were obtained from their clinical records.

*Results:* FH and FH SDS were 161.35±6.56cm; -1.74 SD and 151.16cm; -1.46 SD in males and females respectively. FH showed more than 5cm reduction compared to TH ($p$<0.05). However, there was no significant difference between the corrected FH SDS and TH SDS in both sexes ($p$>0.05). Patients with SV CAH had worse FH and TH as well as their SDSs ($p$<0.05). Males with earlier onset of puberty had reduced FH ($p$<0.05). Mean androgen levels and glucocorticoid doses did not significantly impair FH in our patients ($p$>0.05).

*Conclusion:* The corrected FH of our CAH patients, despite being lower than the normal population, was appropriate to their TH. FH was influenced by genetic potential in both sexes as well as onset of puberty in males.

***Key Words:*** *Androgens – CAH – Glucocorticoids – Height.*

## Introduction

**CAH** comprises a group of genetic disorders leading to defects in adrenal steroid biosynthesis with or without aldosterone deficiency and an increase in the production of ACTH through negative feedback **[1]**. The most common form is 21-hydroxylase deficiency (21OHD), which forms more than 90% of the cases **[2]**. In classic CAH, 75% of the patients have the salt-wasting (SW) and 25% have the simple-virilizing (SV) phenotype. CAH is suspected shortly after birth if there is genital ambiguity, ranging from slight clitoromegaly to complete masculinization with the acceleration of growth and pubertal development **[3]**. Glucocorticoid therapy aims to reduce the excessive secretion of corticotropin (CRH) and Adrenocorticotropic hormone (ACTH) and thus suppress the inappropriate production of adrenal sex steroids. Clinicians usually monitor growth parameters and androgen levels [i.e., androstenedione, testosterone, and 17-OH progesterone] and adjust medical therapy to achieve age-appropriate bone age and linear growth **[4]**.

Final height (FH) in early and late-onset CAH patients has been reported as diminished **[5]**. Several factors contribute to the failure to achieve optimal FH in patients with CAH. Excess adrenal androgens could result in accelerated linear growth, accompanied by premature fusion of the epiphyses, ultimately compromising adult stature. Additionally, central precocious puberty might develop in patients with CAH due to androgen activation of the hypothalamic-pituitary-gonadal axis, thus exacerbating premature epiphyseal fusion. Finally, chronic glucocorticoid therapy in CAH, even at replacement doses, has been shown in previous studies to be associated with poor growth, and long-term glucocorticoid therapy during childhood, particularly during the pubertal growth spurt, can compromise FH **[6]**.

## Patients and Methods

Thirty-four patients with a documented history of classic CAH with regular follow-up were en-

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rolled. The exclusion criteria included patients with non-classic CAH, those treated with growth hormone, or chronic use of medications which might affect growth like immunosuppressive drugs. Patients who received GnRH analogues or aromatase inhibitors were also excluded.

*Study proper:*

Data considering height, weight, body mass index (BMI) and their SDSs were analyzed at different ages [at birth, 6 months, 1 year, 2 years, then yearly until reaching puberty] and then till FH was achieved **[7]**. FH was defined as GV less than 1cm per year and fused epiphyses in radiographs. Target height (TH) was obtained using the formula: [maternal height + paternal height – 13cm for girls and + 13cm for boys]/2 **[8]**. FH and TH SDSs were calculated. Corrected FH was defined as the difference between FH and TH SDS (FH SDS – TH SDS), thus comparing the FH to the genetic height potential. Values above zero were interpreted as genetically appropriate height and values less than zero as height below the genetic potential.

Pubertal growth (PG) was defined as growth from the onset of puberty until FH was achieved. The onset of puberty was defined as breast stage B2 in girls and testicular volume of ≥4mL in boys **[9,10]**.

Regarding the therapeutic data, we recorded the type of glucocorticoid used, duration of glucocorticoid therapy and daily glucocorticoid dose. Different glucocorticoids used were converted to equivalent hydrocortisone doses. We added the daily doses to obtain the cumulative dose in mg throughout therapy. The cumulative dose was calculated by summating the quarterly doses in $mg/m^2$. The mean daily glucocorticoid dose in $mg/m^2$ was obtained by dividing the cumulative dose in $mg/m^2$ by the number of days in the corresponding duration. Androgen levels at diagnosis and mean androgen levels at different intervals were also recorded. Bone age was documented at puberty and FH. Bone age was estimated from X-ray films of the left hand and wrist according to **[11]**.

*Statistical analysis:* Quantitative data were presented as mean and standard deviation using SPSS version 20. An Independent *t*-test was used to compare the means of the two groups. Qualitative data were presented as numbers and percentages. The chi-square test or Fisher exact test was used to compare between two or more proportions.

## Results

*Sociodemographic data:*

The mean age at diagnosis was 1.9±3.01 and 1.75±2.47 years in males and females respectively. Seven patients had simple virilizing CAH (20.5%). Regarding the initially assigned sex, 24 patients were assigned as females at birth (70.5%), while 10 patients were assigned as males (29.5%); of which 4 patients were found to have a 46, XX karyotype, giving a total of 28 female patients with 46, XX karyotype (82.3%) and 6 patients with 46, XY karyotype (17.6%). The mean age of our patients at the time of recruitment was 18.23±3.58 years. Genital ambiguity was the most common presenting complaint in 25 patients (73.5%), followed by persistent vomiting in 11 patients (32.3%). Consanguinity was reported in 21 patients (61.7%) with similar conditions in a family member in 8 patients (38%).

*Auxological data:*

Length/height at diagnosis was 76.3±32.2 cm; -0.65 SD and 73.9±26.5 cm; 0.06 SD in males and females respectively. The mean age at FH was 14.1±1.95 and 13.5±1.75 years in males and females respectively with a mean bone age of 16.14±1.35 and 15.4±1.7 years.

Males had significantly higher pubertal growth compared to females ($p<0.05$). Patients with SV CAH had worse FH and TH as well as their SDSs ($p<0.05$). Auxological data are shown in Tables (1) and (2). About 47.2% of our patients had FH below their TH with significantly lower FH SDS ($p<0.05$). However, there was no significant difference between the corrected FH SDS and TH SDS ($p>0.05$) as shown in Table (3). Furthermore, nearly a quarter of our patients had genetically appropriate heights (7 patients). The biochemical and therapeutic data of our patients are shown in Tables (4,5) respectively.

*Growth pattern of our patients:*

*Infancy:* The height SDS was normal at birth with a slight decline during the first 2 years of life.

*Childhood and adolescence:* The height SDS increased significantly after the age of 3 years. The pubertal growth spurt was reached approximately at 9 and 10 years of age in females and males respectively. However, there was a deceleration between 11-15 and 12-16 years of age in females and males respectively. The patients' growth pattern is shown in Figs. (1,2).

Regarding the possible attributing factors, there was a negative correlation between FH and each of height and height SDS in the first 2 years of life in males only ($p<0.05$), and a positive correlation at 15 and 16 years of age ($p<0.05$), while a positive correlation was found between FH and each of height and height SDS from 3 till 16 years of age in females ($p<0.05$).

Twenty-one patients were overweight or obese (61.7%). Interestingly, there was a negative correlation between FH in males and each of BMI ($kg/m^2$) and BMI SDS from 9 to 14 years of age ($p<0.05$). We also found a negative correlation between FH in females and each of BMI ($kg/m^2$) and BMI SDS at 14 and 15 years of age ($p<0.05$).

FH in males with earlier onset of puberty was reduced compared to those with normal pubertal onset (151.00±0.00 versus 163.60±4.18 cm) ($p<0.05$).

Bone age advancement didn't seem to affect FH in our patients ($r$=–0.739, $p$=0.058; $r$=–0.060, $p$=0.762) in males and females respectively. Also, there was no correlation between FH in both sexes and the mean serum androgen levels throughout treatment (17 OH-P ng/ml, DHEA ug/ml, free testosterone pg/ml) ($p>0.05$). However, there was a negative correlation between FH in females and their initial free testosterone level ($r$=–0.390, $p$=0.049).

Regarding the effect of glucocorticoid therapy, no correlation was found between FH in both sexes and age at starting glucocorticoid therapy ($r$=–0.403, $p$=0.594). Also no correlation was found between FH in males and females and each of cumulative glucocorticoid dose in mg ($r$=–0.344, $p$=0.449; $r$= 0.222, $p$=0.246), cumulative glucocorticoid dose in mg/m$^2$/day ($r$=0.135, $p$=0.773; $r$=0.187, $p$=0.332), mean daily glucocorticoid dose in mg/m$^2$/day ($r$= –0.324, $p$=0.478; $r$=–0.111, $p$=0.567) or glucocorticoid dose at the time of examination in mg/m$^2$ ($r$ =–0.247, $p$=0.594; $r$=–0.244, $p$=0.202) respectively.

Table (1): Auxological data of patients.

| | | Sex | | *p*-value |
|---|---|---|---|---|
| | | Females | Males | |
| Target height (cm) | Mean ± SD | 156.62±6.21 | 168.14±3.38 | 0.000 |
| Target height SDS | Median (IQR) | -0.92 (-1.63 – -0.15) | -0.88 (-1.23 – -0.77) | 0.786 |
| Final height (cm) | Mean ± SD | 151.16±7.54 | 161.35±6.56 | 0.004 |
| Final height SDS | Median (IQR) | -1.46 (-2.8 – -0.88) | -1.74 (-2.74 – -1.31) | 0.619 |
| Corrected final height SDS | Median (IQR) | -0.75 (-1.8 – -0.15) | -1.01 (-1.67 – -0.45) | 0.735 |
| Pubertal height (cm) | Mean ± SD | 145.67±8.67 | 143.48±6.15 | 0.563 |
| Pubertal height SDS | Median (IQR) | 0.74 (0.05 - 2.16) | 1.19 (0.55 - 1.78) | 0.619 |
| Pubertal growth (cm) | Median (IQR) | 5.5 (2.15 - 8) | 14.5 (6.3 - 20) | 0.028 |

cm: Centimeter. SDS: Standard deviation score. IQR: Interquartile range.

Table (2): Auxological data of patients regarding phenotype.

| | | Phenotype | | *p*-value |
|---|---|---|---|---|
| | | Salt wasting | Simple virilizing | |
| Target height (cm) | Mean ± SD | 160.54±6.84 | 153.42±6.09 | 0.010 |
| Target height SDS | Median (IQR) | -0.77 (-1.17 – -0.13) | -1.42 (-1.83 – -1.25) | 0.009 |
| Final height (cm) | Mean ± SD | 154.73±7.62 | 148.03±8.47 | 0.035 |
| Final height SDS | Median (IQR) | -1.5 (-2.42 – -0.86) | -2.84 (-3.34 – -1.22) | 0.101 |
| Corrected final height SDS | Median (IQR) | -0.83 (-1.77 – -0.29) | -0.3 (-1.67 – -0.12) | 0.668 |

cm: Centimeter. SDS: Standard deviation score. IQR: Interquartile range.

Table (3): Relation between target height SDS and each of final height SDS and corrected final height SDS.

| | Females | Males | Total |
|---|---|---|---|
| | Median (IQR) | Median (IQR) | Median (IQR) |
| Final height SDS | -1.46 (-2.80 – -0.88) | -1.74 (-2.74 – -1.31) | -1.59 (-2.75 – -1.00) |
| Target height SDS | -0.92 (-1.63 – -0.15) | -0.88 (-1.23 – -0.77) | -0.92 (-1.59 – -0.21) |
| *p*-value | 0.001 | 0.046 | <0.001 |
| Corrected final height SDS* | -0.75 (-1.80 – -0.15) | -1.01 (-1.67 – -0.45) | -0.75 (-1.77 – -0.17) |
| Target height SDS | -0.92 (-1.63 – -0.15) | -0.88 (-1.23 – -0.77) | -0.92 (-1.59 – -0.21) |
| *p*-value | 0.873 | 0.917 | 0.871 |

SDS: Standard deviation score. IQR: Interquartile range.
*Values above zero were interpreted as genetically appropriate height and values less than zero as height below the genetic potential.

Table (4): Biochemical data of patients.

| | Males | Females |
|---|---|---|
| Mean free testosterone pg/ml at diagnosis | 1.24±1.2 | 1.55±1.1 |
| Mean serum 17 OH-P ng/ml at diagnosis | 17.1±4.9 | 22.3±15.47 |
| Mean free testosterone pg/ml at final height | 11±3.77 | 2.26±2.9 |
| Mean serum 17 OH-P ng/ml at final height | 7.15±5.5 | 35.4±29.1 |

ng/ml: Nanograms per deciliter.

pg/ml: Picograms per milliliter.

17 OH-P: 17 hydroxyprogesterone.

Table (5): Therapeutic data of patients.

| | | |
|---|---|---|
| Duration of glucocorticoid therapy (years) | Mean ± SD | 15.14±3.42 |
| glucocorticoid dose at the time of enrollment ($mg/m^2$) | Mean ± SD | 16.24±6.41 |
| Cumulative glucocorticoid dose (mg) | Mean ± SD | 91457.19± 35687.82 |
| Total cumulative glucocorticoid dose ($mg/m^2$) | Mean ± SD | 83270.26± 24707.93 |
| Mean daily glucocorticoid therapy ($mg/m^2$/day) | Mean ± SD | 15.67±3.26 |

SD: Standard deviation.

mg: Milligram.

$mg/m^2$: milligram per squared meters.

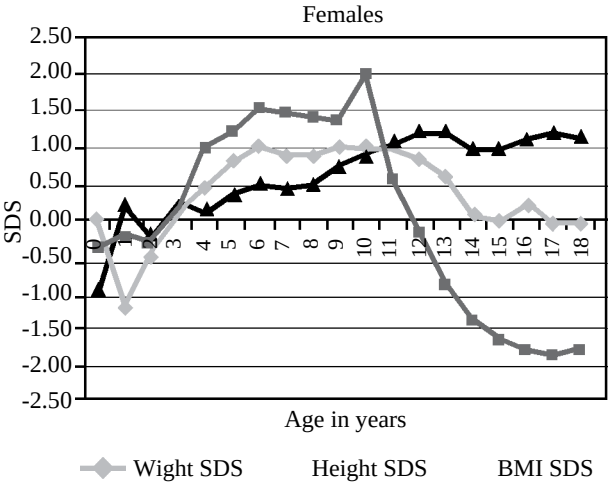


Fig. (1): Anthropometric measurements in females at different points of follow-up.


Fig. (2): Anthropometric measurements in males at different points of follow-up.

## Discussion

Patients with CAH due to 21OHD usually show reduced FH compared to the general population. This could be either due to overtreatment by excessive steroid doses or under treatment resulting in increased androgen levels **[12].**

Our patients had a FH and FH SDS 161.35 ± 6.56 cm; -1.74 (-2.74 - -1.31) SD and 151.16 ± 7.54 cm; -1.46 (-2.8 - -0.88) SD for males and females respectively, these values were lower than the height ranges in normal adult Egyptians (170.3 cm and 158.9 cm for males and females respectively), similar results were reported in other studies conducted in Egypt, Turkey, Europe and Canada **[13 -20].** Multiple factors affect the FH in CAH patients including the presence or absence of routine neonatal screening for CAH with early detection and treatment of cases **[21]** and the potential effect of steroid therapy on FH **[22]** or poor disease control in some patients reducing FH **[13].**

Even though the FH of our patients was lower than the absolute normal adult ranges in Egypt as well as their TH, comparing the patients' corrected FH SDS to their corresponding TH SDS showed no statistical significance, indicating that our patients achieved their genetic potential. Interestingly, the height ranges of the parents in our study were slightly below the reference means. It is questionable if the parents could harbor the mutation with variable phenotype and missed diagnosis. The high consanguinity rate in our country and the complexity of the CYP21 (CYP21A2) and its pseudogene together with genotype-phenotype interaction could be responsible for unidentified variants in the parents, with different phenotypes which could have passed undiagnosed **[23].**

Regarding the growth pattern, our patients had a mediocre growth pattern between birth and the second year of life, more observed in males. The observed pattern could be explained by the fact that most of our patients had the SW phenotype, presenting earlier and necessitating higher glucocorticoid dosage, which could have impaired their growth during infancy. Additionally, males might experience several attacks of salt-wasting crises before

being diagnosed. Similar results were previously reported in other studies **[17,24]**. During childhood, male CAH patients had more accelerated linear growth, followed by a greater pubertal growth spurt compared to female CAH patients. This could indicate that the signs of androgen excess were more concerning in females, who could have been given more suppressive doses of glucocorticoids, resulting in the observed growth pattern. Interestingly, females showed better FH SDS and corrected FH SDS than males, however, the difference didn't reach significance.

In our study, FH was significantly lower in the SV phenotype compared to the SW phenotype 148.03±8.47 cm versus 154.73±7.62 cm respectively. Similarly, Juan et al., 2016 found that FH was lower among the SV phenotype **[25]**. On the contrary, other studies revealed that patients with the SV phenotype had better FH in comparison to the SW phenotype **[15]**. It has been shown that patients with SW phenotype are usually diagnosed earlier, with early intervention preserving their FH **[17]**.

In the current study, the mean daily glucocorticoid dose was 15.67±3.26 mg/m$^2$/day. In another study improvement in FH in patients receiving a glucocorticoid dose of 13.05 mg/m$^2$/day was observed compared with 14.85 mg/m$^2$/day, suggesting a relatively narrow therapeutic margin **[26]**. Furthermore, Juan et al., **[25]** and Aycan et al., **[27]** found that a mean daily glucocorticoid dose of 18.91 mg/m$^2$/day and 17.64±3.60 mg/m$^2$/day respectively, ended up with FH below the TH. Injudicious increases in glucocorticoid doses, despite their role in inhibiting androgen production, could be associated with poor growth velocity. This directs us to the importance of using the lowest possible dose **[26]**. However, in our study, we found no correlation between FH and the cumulative doses or mean daily doses of glucocorticoids. Similar to other studies, no correlation was found between dexamethasone and FH in our patients **[15,28]**. Dexamethasone is estimated to be almost 100 folds more potent than hydrocortisone, thus the liability to overtreatment is more likely **[29]**. However, previous studies reported that children who received dexamethasone showed normal linear growth with acceptable FH **[30,31]**.

There was no correlation between each of FH and FH SDS in both sexes and age at starting glucocorticoid therapy. Similar results were observed in other studies **[24,32]**. It is expected that patients who started therapy at earlier ages could achieve FH closer to their TH. However, infants and children were sometimes found to receive excess glucocorticoid doses, especially those with an earlier diagnosis who have severe clinical courses, resulting sometimes in poor growth **[17]**. This might explain the reduced FH in females in our study having severe forms of genital ambiguity at birth, indicating a more severe phenotype, necessitating more aggressive treatment. Variations regarding the effect of glucocorticoids could also be attributed to the broad genotypic spectrum of 21OHD **[23]** or the influence of demographic or other relevant patient factors **[33]**.

The bone age of our patients was advanced on average by 2 years compared to chronological age at FH. This is comparable to previous observations in one study **[34]**, however, other studies observed smaller variations between bone age and chronological age at the onset of puberty **[13,35]**. This could be explained by the relationship between bone maturation and the degree of disease control where bone age was found to be significantly delayed with tight control and advanced by poor control **[36]**.

BMI SDS of the studied CAH patients were higher than in the general population. Furthermore, FH correlated negatively with BMI SDS. Our findings agree with other studies that concluded that children and adults with CAH are at an increased risk of developing obesity which could be associated with reduced height potential **[37,38]**. On the other hand, a positive correlation was observed between FH SDS and weight in one study **[13]**. Elevated BMI and obesity could be linked to higher glucocorticoid doses **[39]**. Glucocorticoids may exert direct effects on the growth plate as well as prompting earlier menarche in obese girls with CAH and eventually poor FH. However, in our study we didn't find a correlation between the glucocorticoid doses and each of BMI or FH, furthermore, the bone age advancement in our patients doesn't point to overtreatment.

The limitations of our study include a small sample size from a single center. Additionally, it would be useful to assess growth patterns in different genotypes taking into consideration family members.

*Conclusion:*

we found that the FH of patients with 21OHD was on average -1.01 (-1.67 – -0.45) SD and -0.75 (-1.8 – -0.15) SD lower than that of the normal population, after adjustment for the genetic height potential, among males and females respectively. Our results could highlight the genetic impact on the FH. In addition to their genetic potential, modifiable factors such as weight and therapeutic regimen should be regularly assessed among these patients.

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## الطول النهائي فى المرضى الذين يعانون من تضخم الغدة الكظرية الخلقى: الجدل حول نقص العلاج مقابل الإفراط فى العلاج

أنماط النمو فى تضخم الغدة الكظرية الخلقى صعبة. يمكن أن يحدث فائض الأندروجين فى أى عمر مما يؤدى إلى تسارع النمو وإغلاق المشاش المبكر وانخفاض الطول النهائى. من المتوقع عادة أن يكون الطول النهائى فى مرضى تضخم الغدة الكظرية الخلقى أقل من المتوقع بناء على طول الوالدين أو مقارنة بالسكان الأصحاء.

كان الهدف من الدراسة هو تقييم النمو والطول النهائى فى المرضى الذين يعانون من تضخم الغدة الكظرية الخلقى.

شملت هذه الدراسة بأثر رجعى ٣٤ مريضاً تم تشخيصهم بتضخم الغدة الكظرية الخلقى الكلاسيكى. تم إجراء تقييم أنثروبومترى للمرضى وأولياء أمورهم لتقدير الطول النهائى والطول المستهدف والطول النهائى المصحح. تم الحصول على البيانات الخاصة بمتابعة المرضى وتحاليلهم المعملية السابقة من ملفات المتابعة فى عيادة الغدد الصماء للأطفال بجامعة عين شمس.

كان متوسط الطول النهائي والانحراف المعيارى للطول النهائى ١٦١,٣٥ ± ٦,٥٦ سم. –١,٧٤ SD و١٥١,١٦ سم؛ –١,٤٦ SD فى الذكور والإناث على التوالى. أظهر الطول النهائى انخفاضاً بأكثر من ٥ سم مقارنة ب الطول المستهدف.

ومع ذلك، لم يكن هناك فرق كبير بين الانحراف المعيارى لكل من الطول النهائي المصحح والطول المستهدف فى كلا الجنسين ($p$<٠,٠٥). كان ال طول نهائى لدى مرضى تضخم الغدة الكظرية الخلقى الذين يعانون من ترجيل بسيط أسوأ من مرضى فقد الملح. كما أظهر الذكور اللذين عانوا من البلوغ المبكر انخفاضاً فى الطول النهائى. لم تؤثر مستويات الأندروجين وجرعات الجلوكوكورتيكويد بشكل كبير على الطول النهائى في مرضانا.

الخلاصة: الطول النهائى المصحح لمرضى تضخم الغدة الكظرية الخلقى لدينا، على الرغم من كونه أقل من السكان العاديين، الا أنه كان متناسباً مع الطول المستهدف. تأثر الطول النهائى بالإمكانات الوراثية فى كلا الجنسين وكذلك بسن بداية البلوغ عند الذكور.