

# Increased adrenal and testicular androgen concentrations before puberty and in early puberty correlate to adult height outcomes in males with Silver-Russell syndrome

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**Introduction and objectives:** In a previous study, we reported that adult height (AH) outcomes in growth hormone treated males with Silver-Russell syndrome (SRS) were negatively correlated with estradiol concentrations before start of puberty and in early puberty<sup>1</sup>. Whether elevated estradiol concentrations originated from adrenal or testicular androgens is unclear. We aimed to describe androgen secretion patterns and investigate correlations between androgen concentrations and AH outcomes in this group of patients.

**Conclusion:** Elevated androgen concentrations in early pubertal stages are common in boys with SRS. Androgen concentrations before start of puberty and during early puberty correlated negatively to AH outcome in males with SRS. Both adrenal and testicular androgen secretion seem to contribute to elevated serum androgen concentrations.

**Methods:** In a retrospective longitudinal single-center study 13 males with SRS and normal timing of adrenarche and pubertal onset were followed from 6 years of age until AH. Subjects were retrospectively divided into two groups: eight subjects with AH >1 standard deviation score (SDS) below the midparental height (MPH) were defined as nonresponders (NRs), and five subjects with AH ≤1 SDS below the MPH were defined as responders (Rs). Yearly, blood samples drawn in the morning, were stored at -80°C after separation and auxology and pubertal development were recorded. Dehydroepiandrosterone-sulfate (DHEAS) and androstenedione (A<sub>4</sub>) were determined by liquid chromatography-tandem mass spectrometry, testosterone (T) and dihydrotestosterone (DHT) were determined by gas chromatography-tandem mass spectrometry. Correlations between androgens at different ages and AH outcomes were calculated using Spearman's nonparametric rank correlation. A P-value < 0.05 was considered significant.

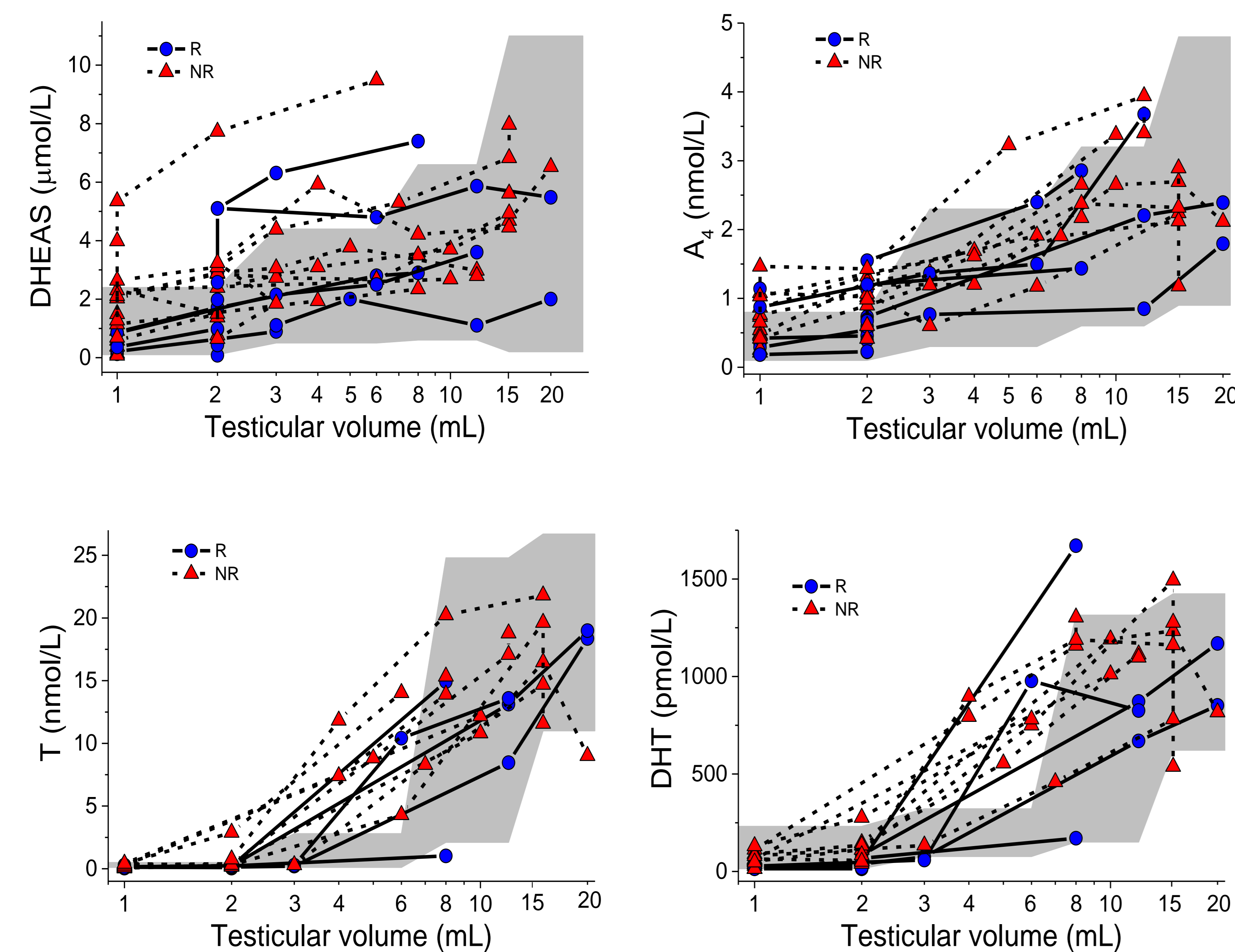


Figure 1: Androgens plotted against testicular volumes. The grey areas depict normal reference intervals

Table 1 shows normal reference intervals for different androgens at different testicular volumes. For each patient "0" indicates androgen concentrations within reference intervals and "1" indicates elevated androgen concentrations.

Testes volumes	Testes 1-2 mL				Testes 3-6 mL			
	DHEAS (0.1-2.4 µmol/L)	A <sub>4</sub> (0.1-0.8 nmol/L)	T (0.1-0.5 nmol/L)	DHT (<27-232 pmol/L)	DHEAS (0.5-4.4 µmol/L)	A <sub>4</sub> (0.3-2.3 nmol/L)	T (0.1-2.8 nmol/L)	DHT (77-322 pmol/L)
Patient 1 (R)	0	0	0	0	0	0	0	0
Patient 2 (R)	1	0	0	0	1	0		
Patient 3 (NR)	0	1	0	0	0	0		
Patient 4 (R)	0	1	0	0	0	1		
Patient 5 (NR)	0	1	0	0	0	0		
Patient 6 (NR)	1	1	0	0	0	0	1	1
Patient 7 (R)	0	1	0	0	0	0	1	1
Patient 8 (NR)	0	1	0	0	0	0	1	1
Patient 9 (NR)	1	1	0	0	0	1	1	1
Patient 10 (R)	1	1	0	0	1	0	0	0
Patient 11 (NR)	1	0	0	0	0	0	0	0
Patient 12 (NR)	1	1	1	1	1	0	1	1
Patient 13 (NR)	1	1	1	0	1	0	1	1

**Results:** Several boys had elevated androgen concentrations prepubertally and in early pubertal stages compared to reference intervals. Before puberty, at testis volumes of 1-2 mL, five NRs and two Rs had elevated concentrations of DHEAS, and seven NRs and three Rs had elevated A<sub>4</sub> concentrations. Moreover, two NRs had elevated T concentrations, and one NR had elevated DHT. In early puberty, at a testis volume of 3-6 mL, two NRs and two Rs had elevated DHEAS concentrations, and one NR and one R had elevated A<sub>4</sub> concentrations, whereas five NRs and one R had elevated concentrations of T and DHT.

AH outcomes correlated negatively to DHEAS at 8 (r=-0.72, P=0.006), 10 (r=-0.79, P=0.001) and 12 years (r=-0.72, P=0.006), T at 10 (r=-0.94, P=0.000), 12 (r=-0.70, P=0.008) and 14 years (r=-0.64, P=0.018) as well as DHT at 10 (r=-0.62, P=0.025) and 12 years (r=-0.57, P=0.041). No correlations with A<sub>4</sub> were found at any age.

References:

<sup>1</sup>Kvernebo-Sunnergren K *et al* Hyperestrogenism Affects Adult Height Outcome in Growth Hormone Treated Boys With Silver-Russell Syndrome. *Front Endocrinol (Lausanne)* (2018) 9:780.