Serum Testosterone and Estradiol Serve as Markers of Growth Response During Puberty Promoting Treatment

H. Huttunen[1], T. Varimo[1], H. Huopio[2], R. Voutilainen[2], S. Tenhola[3], P. J. Miettinen[1], T. Raivio[1,4], M. Hero[1]

1. New Children's Hospital, Pediatric Research Center, Helsinki University Hospital, Helsinki, Finland.
2. Kuopio University Hospital, University of Eastern Finland, Kuopio, Finland.
3. Kymenlaakso Central Hospital, Kotka, Finland.
4. Stem Cells and Metabolism Research Program, Research Program Unit, University of Helsinki, Helsinki, Finland.

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INTRODUCTION

- In boys with constitutional delay of growth and puberty (CDGP), optimizing pubertal growth is of importance, since they may fail to reach their genetic target height[1-3].
- The relative roles of testosterone, estrogen, and estrogen-induced activation of the GH-IGF-I axis in the regulation of pubertal growth acceleration are currently unclear. Elucidation of their individual roles is of clinical importance, as aromatase inhibitors (AIs), which are compounds that block estrogen biosynthesis and increase endogenous gonadotropin and testosterone secretion, have emerged as a potential treatment modality for boys with CDGP[4].

AIM

- We aimed to clarify the relative roles of androgens and estrogens in the regulation of pubertal growth in boys with CDGP receiving puberty promoting treatment.

METHODS

- Thirty boys with CDGP were recruited to a randomized controlled trial, which compared 6-month low-dose intramuscular testosterone (T) with the aromatase inhibitor letrozole (Lz) treatment (2.5 mg/day)[5].
- The patients were evaluated at 0-, 3-, and 6-month visits, and morning blood samples were drawn.
- Lz-treatment produced a hormonal milieu characterized by substantially elevated testosterone, low estradiol, and low IGF-I, whereas treatment with T induced moderately elevated testosterone, estradiol, and IGF-I levels (Table 1).[5]

RESULTS

- In both groups, serum testosterone and estradiol concentrations correlated with growth velocity (from 0 to 6 months) during treatment (Figure 1), whereas IGF-1 concentration did not.
- Serum testosterone was the best predictor of growth velocity in a linear regression model in both treatment groups (Lz-group $R^2 = 0.56$, $p = 0.001$ and T-group $R^2 = 0.57$, $p = 0.003$). In the Lz-group, adding serum estradiol to the model significantly improved the growth estimate ($R^2 = 0.72$, $p = 0.02$).
- Each nmol/L increase in serum testosterone increased growth velocity 2.7 times more in the testosterone group (b=0.261 for T-group and b=0.096 for Lz-group).

	Serum testosterone (nmol/L)		Serum estradiol (pmol/L)		Serum IGF-1 (nmol/L)[a]	
Time (months)	Lz-group	T-group	Lz-group	T-group	Lz-group	T-group
0	1.86 (1.03)	2.29 (1.29)	9.69 (4.79)	14.02 (12.37)	31.40 (10.13)	36.15 (10.39)
3	20.98 (18.59)*	9.73 (6.34)*	6.87 (4.21)**	39.46 (37.16)**	26.47 (8.26)**	41.77 (16.52)**
6	30.24 (18.38)**	5.49 (2.74)**	15.67 (23.03)	21.98 (17.31)	32.00 (7.73)**	50.41 (13.42)**

Table 1 Change over time in hormonal markers of puberty.
Mean serum concentrations (and SDs) at 0, 3, and 6 months of study period. Hormonal data has been published previously[5]. In the Lz-group, hormone concentrations at 3 and 6 months represented the effect of ongoing Lz-treatment, whereas in the T-group, these concentrations reflected peak and trough concentrations of exogenous testosterone, respectively
* Difference between the groups at indicated time-point is significant at the 0.05 level
** Difference between the groups at indicated time-point is significant at the 0.01 level
[a] Normal values for serum IGF-I at bone age 12.5 years (mean bone age of CDGP boys at baseline): 12-60 nmol/L

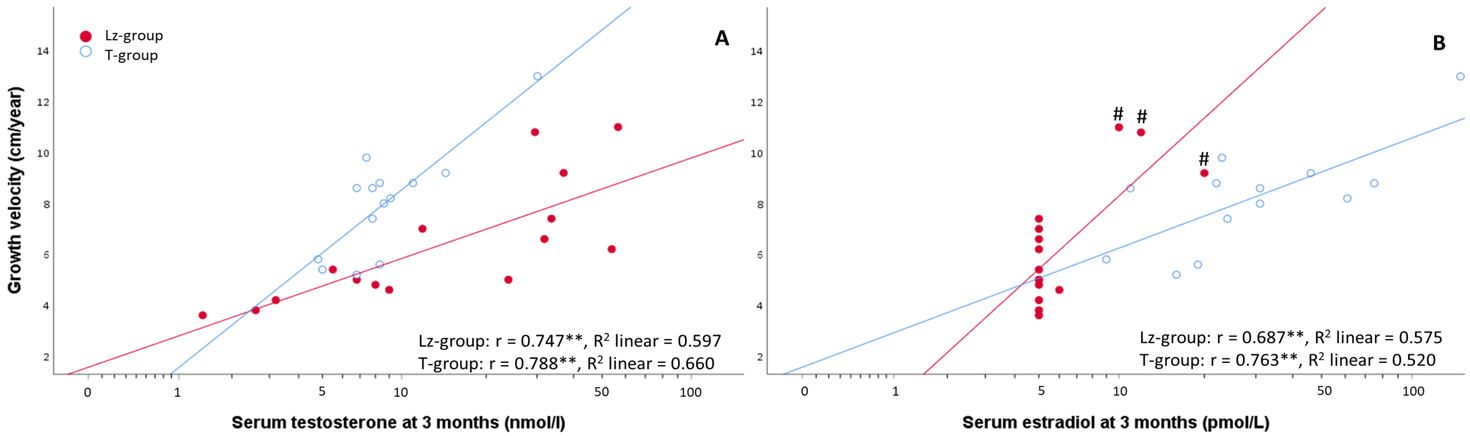

Figure 1. Correlation of growth velocity with serum testosterone (A) or serum estradiol (B) at 3 months. Closed (Lz-group) and open (T-group) circles represent serum estradiol and testosterone values of individual CDGP patient. Note logarithmic scale in X-axis.

CONCLUSIONS

- During puberty promoting treatment with testosterone or aromatase inhibitor letrozole, growth response is tightly correlated with serum testosterone level.
- A threshold level of estrogen appears to be needed for optimal growth rate that corresponds to normal male maximal pubertal growth velocity.
- Serum testosterone one week after the injection and serum testosterone and estradiol 3 months after the onset of aromatase inhibitor treatment can be used as biomarkers for treatment response in terms of growth.

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