Cortisol levels in glucagon stimulation tests in children evaluating for short stature: clinical and laboratorial correlations

O. Maliachova, P. Triantafyllou, M. Dimitriadou, A. Christoforidis

1st Pediatric Department, Aristotle University of Thessaloniki, GREECE

Background

Glucagon stimulation test (GST) is used to assess growth hormone (GH) and cortisol reserves in children being investigated for GH deficiency, as a small percentage of children with idiopathic GH deficiency can also exhibit deficiency in the adrenocorticotrophic hormone (ACTH)-cortisol axis. However, the extent of normal cortisol response after glucagon stimulation and its associations with clinical and laboratory parameters have not been thoroughly studied.

Objective

The aim of this retrospective study was to assess total cortisol levels in children being evaluating for short stature with normal cortisol reserve and to correlate this response to clinical and laboratory data.

Methods

During the last 5 years, consecutively children being investigated for short stature or growth attenuation with glucagon test in our department were recruited retrospectively. Inclusion criteria were:

i) age > 1 year,
ii) absence of chronic illness or medication interfering with ACTH-cortisol axis,
iii) GH stimulation levels > 3ng/mL at least in one provocation test (glucagon or clonidine),
iv) absence of multiple pituitary growth hormone deficiency,
v) v) normal short Synacthen test in cases of low cortisol response in glucagon test

Results

- Two hundred and thirty-seven subjects (160 males, 67.5%) who underwent a GST were included in the final analysis.
- In 192 of them (127 males, 794%) a second GH provocation test (CST) was also performed.
- Mean age at the time of the evaluation was 9.02 ± 3.19 years (range: 1.86 – 16.45 years).

Parameter	Male	Female	P	Total
N	160 (67.51)	77 (32.49)		237 (100.00)
Age	9.19 ± 0.54 (8.68 – 9.70)	8.70 ± 0.34 (7.98 – 9.35)	0.236	9.02 ± 0.21 (8.61 – 9.43)
Prepubertal	126 (78.75)	60 (77.92)	0.885	186 (78.48)
Height Z-score	-1.96 ± 0.05 (-2.05 - -1.86)	-2.06 ± 0.06 (-2.18 - -1.94)	**0.046**	-1.99 ± 0.04 (-2.6 - -1.92)
Weight Z-score	-1.41 ± 0.09 (-1.58 - -1.23)	-1.54 ± 0.12 (-1.78 - -1.30)	0.379	-1.45 ± 0.07 (-1.59 - -1.31)
BMI Z-score	-0.24 ± 0.01 (-0.43 - -0.05)	-0.29 ± 0.12 (-0.54 - -0.05)	0.731	-0.26 ± 0.08 (-0.41 - -0.11)
MidParental Height Z-score	-0.35 ± 0.05 (-0.60 - -0.25)	-0.42 ± 0.09 (-0.9 - -0.25)	0.679	-0.37 ± 0.05 (-0.46 - -0.29)
Δ (MidParental Height - Height) Z-score	1.60 ± 0.07 (1.47 - 1.74)	1.64 ± 0.09 (1.46 - 1.82)	0.210	1.61 ± 0.05 (1.51 - 1.72)
GH peak (GST)	8.30 ± 0.42 (7.46 – 9.14)	8.02 ± 0.51 (7.00 – 9.04)	0.980	8.21 ± 0.33 (7.55 – 8.86)
GH AUC (GST)	0.60 ± 0.03 (0.54 - 0.65)	0.60 ± 0.05 (0.50 - 0.69)	0.959	0.60 ± 0.03 (0.5 - 0.65)
Cortisol peak (GST)	24.04 ± 0.57 (22.92 – 25.16)	26.83 ± 0.83 (25.17 – 28.48)	**0.002**	24.94 ± 0.48 (24.01 – 25.88)
Cortisol AUC (GST)	2.99 ± 0.08 (2.84 - 3.15)	3.16 ± 0.13 (0.29 - 3.41)	0.210	3.05 ± 0.07 (2.92 - 3.18)
Glucose AUC (GST)	18.46 ± 0.24 (17.98 – 18.93)	19.37 ± 0.52 (18.33 – 20.0)	0.189	18.75 ± 0.24 (18.29 – 19.22)
GH peak (CST) (n=192)	7.33 ± 0.28 (6.77 – 7.89)	6.98 ± 0.42 (6.14 – 7.83)	0.212	7.22 ± 0.24 (6.75 – 7.68)
GH AUC (CST) (n=192)	0.50 ± 0.02 (0.46 - 0.55)	0.51 ± 0.04 (0.43 - 0.59)	0.576	0.50 ± 0.02 (0.47 - 0.54)

Table 1. Demographic, anthropometric and biochemical data categorized by gender and in total
(Results are presented as Mean ± Std Error (Lower bound – Upper bound of 95% confidence interval for mean)).
Δ: difference, **GH:** growth hormone, **AUC:** area under the curve, **GST:** glucagon stimulation test, **CST:** clonidine stimulation test

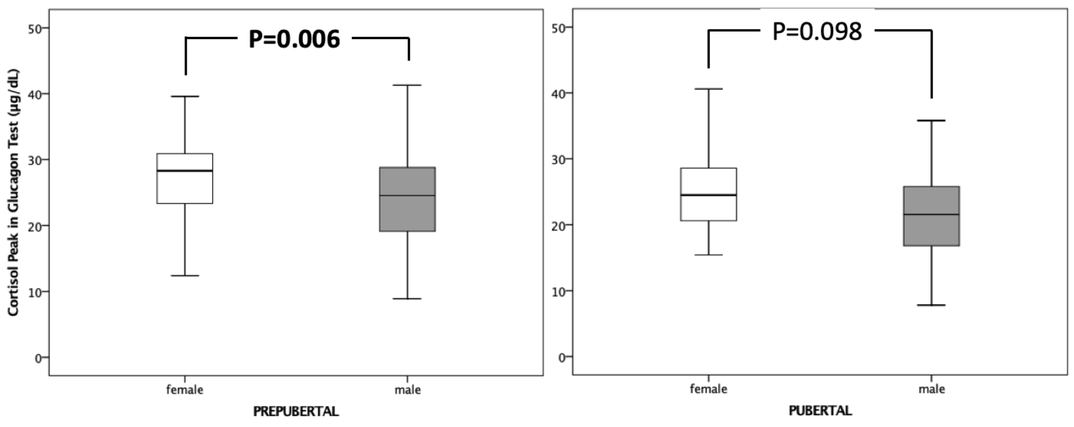
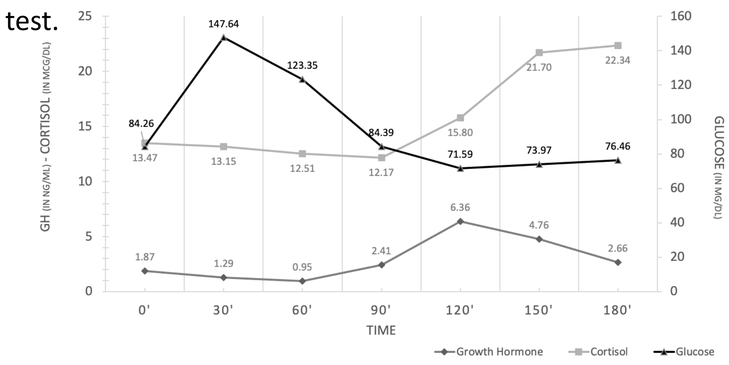


Figure 1. Prepubertal girls showed significantly increased cortisol peak levels compared to boys (p=0.006) but this difference was smoothed over in pubertal subjects (p=0.098).

Cortisol peak levels but not cortisol AUC were significantly increased in females compared to males (26.83 ± 7.31 μg/dl versus 24.04 ± 7.20 μg/dl, p=0.002).

Figure 2. Graphical demonstration of mean GH, cortisol and glucose levels at various time points of the Glucagon stimulation test.



In 179 GST (75.52%), GH peaked at 120 and 150 minutes. Cortisol peaked 30 minutes later with the majority of the tests exhibiting a cortisol peak at 150 and 180 minutes (175, 73,8%) Glucose peaked at 30 minutes.

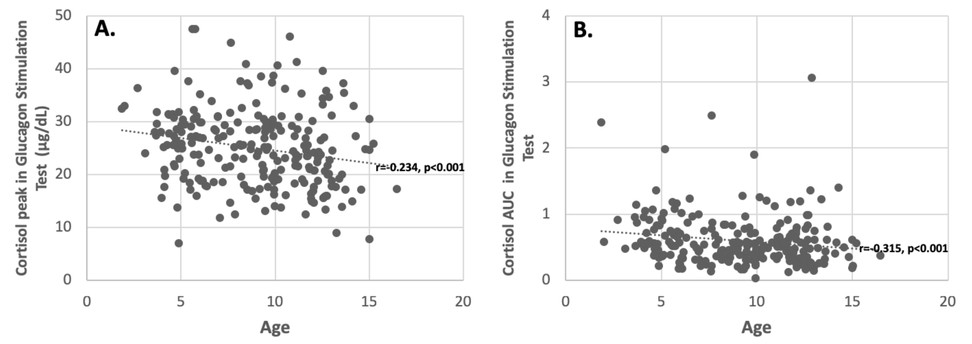


Figure 3. Cortisol peak levels (A.) and cortisol AUC (B) were linearly but inversely correlated to age.

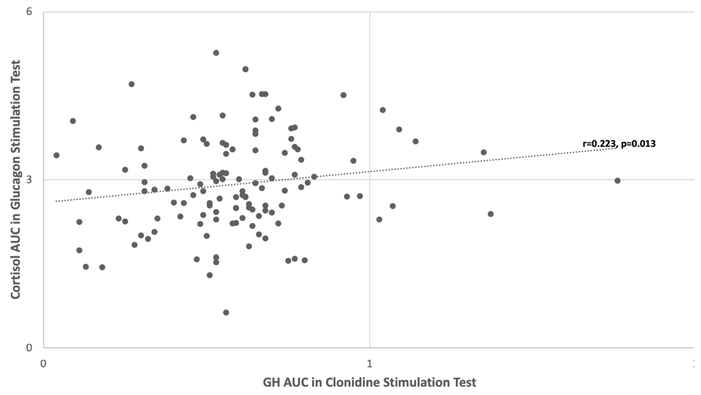


Figure 4. In GH sufficient patients, cortisol AUC was linearly correlated to GH AUC assessed with clonidine test.

Conclusions

- In a large cohort of children assessed with glucagon stimulation test for short stature that there is a considerable variation in cortisol values depending on age and gender :
  - Girls and younger children seems to exhibit a higher cortisol response to glucagon test (Higher Cortisol peak levels)
  - Younger and thinner subjects exhibit a greater cortisol response (Increased Cortisol AUC)
- In subjects with intact GH reserve, a greater cortisol response in glucagon test was linearly correlated with a greater GH response in clonidine but not in glucagon test.