INCREASES IN BIOACTIVE IGF DO NOT PARALLEL INCREASES IN TOTAL IGF-I DURING GROWTH HORMONE TREATMENT OF CHILDREN BORN SMALL FOR GESTATIONAL AGE

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INTRODUCTION

Some children born small for gestational age (SGA) experience supra-physiological Insulin-like growth factor-I (IGF-I) concentrations during growth hormone (GH) treatment. However, measurements of total IGF-I concentrations may not reflect the bioactive fraction of IGF-I which reaches the IGF-I receptor at target organs.

The aim of this study was to evaluate responses of bioactive IGF and IGF-I concentrations, respectively, with growth and metabolic responses in short GH treated SGA children in the North European Small for Gestational Age Study (NESGAS).

PATIENTS AND METHODS

The NESGAS is a study of GH treatment in short SGA children. The study was performed in order to gain more knowledge about the optimal GH dosage to short SGA children and to assess possible long-term side effects of the treatment. The study is a multicenter study including 7 investigating centres in the UK, Ireland, Sweden and Denmark. Patients were recruited over a 5 year period (2003-2008).

The inclusion criteria were: birth weight SDS (BW SDS) and/or birth length SDS (BL SDS) <-2 SD, gestational age (GA) > 28 weeks, height SDS (HSDS) at baseline<-2.5 SD, HSDS > 1 SD below midparental HSDS.

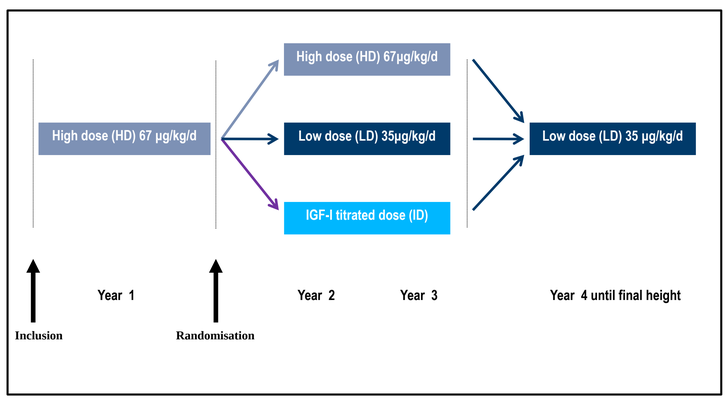

Figure 1: Study design for the North European SGA study (NESGAS)

Data on bioactive IGF was available in 101 pre-pubertal children (61 boys). All patients were treated with Norditropin SimpleXx® 67 µg/kg/day for the first year and were then randomised into three different groups of treatment (figure 1).

Insulin mediated glucose metabolism was assessed by a short intravenous glucose tolerance test (IVGTT). Insulin sensitivity (IS) and insulin secretion were estimated from HOMA and acute insulin response (AIR), respectively.

IGF-I concentrations were measured by Immulite immunoassay. We examined endogenous IGF-bioactivity using an IGF-I kinase receptor activation (KIRA) assay that measures the ability of IGF-I to activate the IGF-IR in vitro.

RESULTS

Bioactive IGF increased with age in healthy pre-pubertal children (n=94) (figure 2). SGA children had low-normal bioactive IGF levels at baseline (-0.12 SDS (1.8 SD)) increasing significantly after one year of high-dose GH treatment to 1.1 SDS (1.4) SD, p<0.01 (figure 2). Following high-dose GH, 68% (n=65) of SGA children had a total IGF-I concentration >2SD (mean IGF-I 2.8 SDS), whereas only 15% (n=15) had levels of bioactive IGF slightly above normal reference values (figure 3). At baseline, bioactive IGF (SDS) was significantly correlated to height (SDS) (r=0.29, p=0.005), in contrast to IGF-I (SDS) (r=0.17, p=0.10). IGF-I (SDS) was inversely correlated to delta height (SDS) after one year of high-dose GH treatment (r=-0.22, p=0.02).

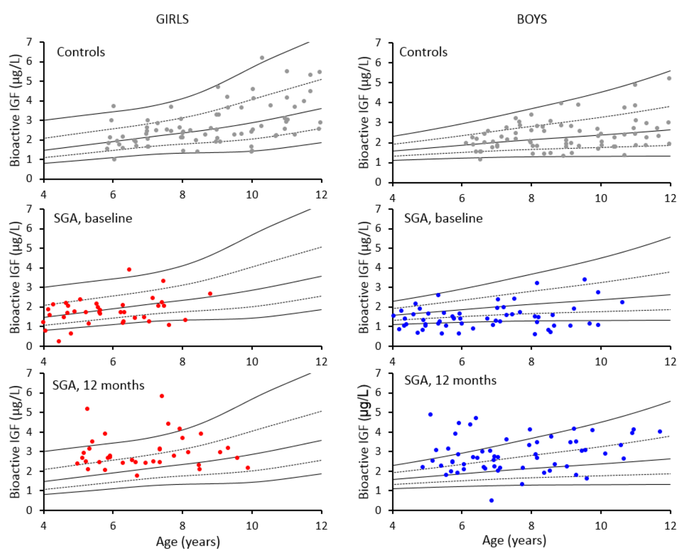

Figure 2: Lines represent normal reference for Bioactive IGF. Normal reference cohort (upper panel), bioactive IGF in the NESGAS cohort at baseline (middle panel) and after 1 yr of treatment (lower panel).

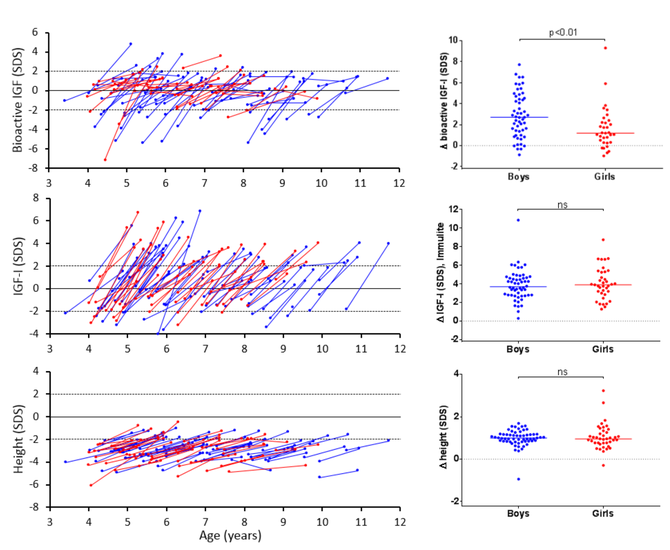

Figure 3:Lines represent changes in Bioactive IGF (SDS) (upper panel), IGF-I (SDS) (middle panel, Height (SDS) (lower panel). Red lines represent girls and blue lines represent boys. Mean change in boys and girls (right column).

	Bioactive IGF (SDS)	IGF-I (SDS)	IGFBP-3 (SDS)	IGFBP-1 (ng/mL)	Height (SDS)	Delta height (SDS)	Weight (SDS)	BMI (SDS)	Insulin sensitivity (HOMA-S)	Insulin secretion
Bioactive IGF (SDS)	1									
IGF-I (SDS)	0.35***	1								
IGFBP-3 (SDS)	0.62***	0.78***	1							
IGFBP-1 (ng/mL)	-0.18	-0.15	-0.19	1						
Height (SDS)	0.29**	0.17	0.15	-0.02	1					
Delta height (SDS)	-0.06	-0.22*	-0.35**	0.22*	0.004	1				
Weight (SDS)	0.37***	0.20	0.20	-0.03	0.59***	0.04	1			
BMI (SDS)	0.18	0.10	0.11	0.10	0.16	0.24*	0.80***	1		
Insulin sensitivity (HOMA-S)	-0.29**	-0.27*	-0.33**	0.42***	-0.08	0.28**	-0.22*	-0.09	1	
Insulin secretion	0.18	0.13	0.23	0.25*	0.17	0.06	0.07	-0.12	-0.47***	1

Spearman non-parametric correlations
*correlation is significant at the 0.05 level (two-tailed); **correlation is significant at the 0.01 level (two-tailed); ***correlation is significant at the 0.001 level (two-tailed)

Table 1: Correlation matrix

CONCLUSION

In contrast to IGF-I concentrations, bioactive IGF stayed within the normal reference ranges for most SGA children during the first year of treatment with high-dose GH.