

Lucas P, Arai L, Baird J, Kleijnen J, Law C, Roberts H. A systematic review of lay views about infant size and growth. *Arch Dis Child* 2007;92:120-7.

Editor's Comment: *Given the many auxologic criteria (Table) for the identification of an infant with FTT and the observation that one criterion is little better than another, it appears that this diagnosis falls into those typified by "I can't define it, but I know it when I see it." The critically essential finding in most of these subjects is that despite a poor appetite, relatively restricted caloric intake, and low weight for stature, linear growth rate remains normal. (Indeed, this pattern of growth is the diametric opposite of the voracious infant/child who steadily gains weight and crosses weight and height percentiles!) It is particularly important not to designate the normal, slowly growing or small child as abnormal, both because of the need to avoid unnecessary diagnostic and therapeutic interventions as well as to support the parents' confidence and sense of competence to care for their child and to avoid a misplaced charge of negligence.*

Clearly, the clinician needs to know not only her/his patient but also the child's parents. The criterion for FTT of downward crossing of weight percentiles certainly reflects in most subjects normal variations of growth as such changes are indeed quite frequent.⁵ It is of interest that the term FTT has been adopted by the geriatricians to denote "an elderly patient who undergoes a process of functional decline, progressive apathy and a loss of willingness to eat and drink that culminates in death."¹ Were there such a precise definition for the pediatric population, the identification and management of such children would be far more precise.

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GH and GnRHa Therapy for Short Stature

This study assessed the final height (FH) and adverse effects of combined growth hormone (GH) and gonadotropin-releasing hormone agonist (GnRHa) treatment in short adolescents with relatively early puberty. Van Gool et al studied 32 adolescents born small for gestational age or with normal birth size, in Tanner stage 2-3, with age and bone age of <12 years for girls and <13 years for boys. Subjects had a height SDS of either <-2 SDS or between -1 and -2 SDS and a predicted adult height (PAH) of <-2 SDS. Patients were randomly allocated to receive GH and GnRHa (n=17) or no treatment (n=15) for 3 years; FH was determined at the age of 18 years or older in girls and 19 years or older in boys.

The FH was not different between treated and untreated subjects. However, treated patients had a greater height gain (FH minus PAH at the beginning of treatment) than the untreated patients (4.4 ± 4.9 vs. -0.5 ± 6.4 cm, respectively; $p < 0.05$). Of the treated and control subjects, 76 (60%) had a FH that was greater than the PAH. A significant gain in PAH of 9.3 cm after 3 years of combined therapy was noted in the treated group compared with a 1.2 cm gain in the untreated group. However, during the period of time between treatment discontinuation and FH, 50% of the PAH gain during treatment was lost, resulting in a mean height gain of 4.9 cm (range of -4 to 12.3 cm). Although, treatment did not seem to affect BMI or hip bone mineral density (BMD), the mean lumbar spine BMD and the bone mineral apparent density (BMAD) tended to be lower in treated males. The authors concluded that given the expensive and intensive treatment regimen and the modest height gain attained, as well as the possible adverse effect of therapy on bone mineralization in males, GH and GnRHa treatment cannot be considered

for routine treatment of short stature in children entering into early puberty. However, treatment could be considered in children, particularly females, with extremely low adult height prediction, early pubertal onset, and considerable psychosocial problems.

Van Gool SA, Kamp GA, Visser-van Balen H, et al. Final height outcome after three years of growth hormone and gonadotropin-releasing hormone agonist treatment in short adolescents with relatively early puberty. *J Clin Endocrinol Metab*. 2007;92:1402-8.

Editor's Comment: *The final height of short children entering into puberty at an early age may be quite limited due to premature epiphyseal fusion induced by the early secretion of gonadal steroids. Treatment with GnRHa to delay or halt pubertal onset has been attempted in this group of patients, but the growth velocity of some of them has been noted to decrease to levels below the normal pubertal velocity, possibly as a result of accelerated growth plate senescence induced by previous estrogen exposure. GH treatment in short children with idiopathic short stature or born small for gestational age has been shown to increase final height, particularly if begun at an early age. Combined GH and GnRHa therapy in short children entering into puberty at an early age has been attempted in several studies with a height gain of between 1 to 10 cm and the effectiveness of this form of therapy remains controversial. Treatment response has been generally analyzed by comparing treated patients to patients treated only with GH, to an untreated group not randomly assigned, or to no controls at all; most studies included only females.*

Treatment of short, but otherwise healthy children with medications that require parenteral administration, close

supervision, frequent laboratory testing, and are extremely expensive, should only be considered if the height gain obtained is significant and if the medications are proven to be safe. As clearly stated by the authors, the costs of this form of therapy seem to overshadow the modest benefit in height gain obtained; therefore this form of therapy should not be recommended for routine use in short but otherwise healthy patients who enter into puberty at an early age.

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GH Inhibition of IGF-I in STAT5b Expression

Ligand binding of the growth hormone (GH) receptor activates, via the Jak2 tyrosine kinase, the Stat transcription factors and the MAP kinase and PI3 kinase/Akt pathways. As is well known to the readers of GGH, GH-stimulated transcription of the insulin-like growth factor (IGF)-I gene requires the Jak2/Stat5b mechanism. However, GH signaling also leads to transcriptional repression of a cohort of genes, including the IGF binding protein (IGFBP)-1. Ono et al sought to elucidate the mechanism of this facet of GH action.

Hypophysectomized Sprague-Dawley rats were given a single systemic pulse of GH, and hepatic RNA was isolated 30, 60 or 120 minutes afterwards. By both microarray and RT-PCR methods, GH acutely increased the mRNA levels of IGF-I and Socs-2 while decreasing that of IGFBP-1. GH also acutely induced the nuclear accumulation of phosphorylated Stat5b. Adenoviral-mediated delivery of a constitutively active Stat5b construct to livers of GH-deficient rats similarly increased IGF-I and Socs-2 expression while decreasing IGFBP-1.

To further examine the transcriptional regulation of IGFBP-1, Cos-7 cells were transiently transfected with a rat IGFBP-1 promoter-luciferase reporter construct as well as an expression vector for mouse GH receptor. Cotransfection with wild-type or constitutively activated FoxO1, a transcription factor important for *IGFBP-1* expression, stimulated promoter activity. GH treatment altered neither IGFBP-1 promoter activity nor the abundance of the FoxO1 proteins. In contrast, when wild type Stat5b was also co-transfected, GH treatment led to a 35%-50% reduction of IGFBP-1 promoter activity with either type of FoxO1; GH stimulated phosphorylation of the wild-type but not constitutively activated FoxO1, and abundance of the FoxO1 proteins again were not altered. Thus, GH-induced IGFBP-1 repression is mediated by Stat5b and not Akt (the constitutively activated FoxO1 is Akt resistant.)

Because IGFBP-1 expression is also repressed by insulin, which acts via Akt inhibition of FoxO1, the authors sought to further examine the interactions between Akt, Stat5b and FoxO1. A tamoxifen-inducible Akt fusion protein, iAkt, repressed IGFBP-1 promoter activity in the presence of wild type, but not a constitutively activated, FoxO1; the former form of FoxO1 was phosphorylated by

Akt while the latter cannot be. In contrast, a constitutively activated Stat5b did not phosphorylate FoxO1.

Further experiments were performed to mechanistically examine Stat5b inhibition of FoxO1. Using a luciferase reporter construct driven by a minimal promoter containing 3 copies of IRSA (one of the tandem FoxO1 binding sequences found in the IGFBP-1 promoter), the FoxO1 binding site was shown sufficient for GH and Stat5b inhibition of FoxO1-stimulated gene transcription. To examine the possibility of reciprocal inhibition, a luciferase reporter construct driven by the Stat5b-dependent HS7 response element (found in the IGF-I gene) was examined. It increased activity in response to GH in the absence of FoxO1, and increased further still when wild type or constitutively activated FoxO1 were cotransfected, even though there were no FoxO1 binding sites in the HS7-promoter sequences. Thus, competition for transcriptional co-factors does not seem to be the mechanism of Stat5b's inhibition of FoxO1 activity. A dominant-negative Stat5b was shown to lose the ability to mediate GH inhibition of IGFBP-1 promoter activity, in both co-transfected Cos-7 cells in vitro and in GH-treated hypophysectomized rats in vivo. Co-transfected Cos-7 cells further showed that GH induced nuclear accumulation of Stat5b, but neither nuclear levels of FoxO1 protein nor its DNA-binding ability were reduced by activated Stat5b. Direct protein-protein interactions between FoxO1 and Stat5b from Cos-7 nuclear extracts were not detected by co-immunoprecipitation assays or avidin-biotin complex DNA binding assay.

Finally, the authors returned to their hepatic microarray results from GH-stimulated hypophysectomized rats. They compared the list of GH-repressed genes to genes repressed by adenovirally introduced constitutively activated Stat5b. Eighty-nine gene transcripts were similarly reduced by both mechanisms. *In silico* search for FoxO1 binding sites within phylogenetically conserved (rat and human) regions of these genes revealed 19 hits, or 21% of the repressed genes. Of 322 randomly selected genes not regulated by GH or Stat5b 19% were also found to contain FoxO1 binding sites. Thus, FoxO1 inhibition accounts for only a subset of transcriptional repression by GH/Stat5b.