Improvement of cardiac performance and cardiovascular risk factors in children with GH deficiency after two years of GH replacement therapy: an observational, open, prospective, case-control study.

Salerno M, Esposito V, Farina V et al. University “Federico II” of Naples and Regional Hospital of Bolzano, Italy

J Clin Endocrinol Metab 2006; advance online publication.

Editor’s note: As well as its effects on linear and skeletal growth, growth hormone (GH) has other important physiological and metabolic functions. It is well established that GH deficiency is associated with the development of an “adverse metabolic profile” and contributes to the increased risk of cardiovascular disease and its associated mortality rates in adults. It remains unclear whether these metabolic abnormalities are present in children with GH deficiency, and whether these individuals are at a higher risk of developing cardiovascular disease at an earlier age.

In this prospective, longitudinal, case-control study, a group of GH treatment-naïve prepubertal children (n=30) were tested for a number of cardiovascular risk markers (lipid profile, insulin sensitivity measured using the homeostasis model assessment [HOMA] score, echocardiographic parameters) before and at 1 and 2 years of treatment. At baseline, GH deficient subjects had evidence of significantly reduced left ventricular mass compared with matched healthy controls, whereas plasma lipid profiles and HOMA values were similar in the two groups. After 2 years of GH therapy, cardiac mass had “normalized”, and small, but significant, increases in insulin resistance were observed, especially in those children with partial or less severe GH deficiency. In addition, GH therapy exerted a beneficial effect on lipid profiles, with a lowering of total cholesterol and overall atherogenic index.

Pharmacokinetic studies of rhIGF-I/rhIGFBP-3 complex administered to patients with growth hormone insensitivity syndrome.

Camacho-Hübner C, Rose S, Preece MA et al. William Harvey Research Institute, Queen Mary, University of London, London, UK.

J Clin Endocrinol Metab 2006; advance online publication.

Editor’s note: Over the last decade, there has been increased interest in the clinical application of recombinant human insulin-like growth factor-I (rhIGF-I) as therapy for the treatment of conditions associated with IGF-I deficiency, such as growth hormone insensitivity syndrome (GHIS) and type 1 diabetes. However, rhIGF-I has yet to establish its role as a treatment for these conditions, not least because of concerns that it can be associated with a number of acute side effects, for example, headache and optic disc swelling. The latter is related to the adverse pharmacokinetic profile and high free circulating levels of IGF-I achieved after subcutaneous administration of rhIGF-I. The recent development of a new rhIGF-I product in which it is formulated in a 1:1 molar complex with rhIGF binding protein-3 (rhIGFBP-3) offers the possibility of delivering rhIGF-I...
in a more favorable physiological manner, with fewer side effects.

In this study by Camacho-Hübner and colleagues, the pharmacokinetic profile of the rhIGF-I/rhIGFBP-3 complex was characterized in four patients with a confirmed molecular diagnosis of GHIS. The rhIGF-I/rhIGFBP-3 complex was administered as a single injection at doses of 0.5 and 1.0 mg/kg on separate occasions (72 h apart). Times to peak plasma IGF-I level (which were within the normal range) were approximately 20 and 16 h after the low and higher doses, respectively. The rhIGF-I/rhIGFBP-3 complex half-life was significantly enhanced when compared with previously published data for rhIGF-I administration in GHIS (21 h vs. 6 h). Despite the fact that the low and high doses of rhIGF-I/rhIGFBP-3 complex delivered supraphysiological doses of rhIGF-I that were equivalent to 100 μg/kg and 200 μg/kg, respectively, none of the expected adverse effects were observed.

Overall, these data suggest that the rhIGF-I/rhIGFBP-3 complex was effective at increasing circulating IGF-I levels to within the normal range, and that administration was safe and well tolerated.

Growth hormone therapy in short children born small for gestational age.

Ong K, Beardsall K, de Zegher F. Strangeways Research Laboratory, Wort’s Causeway, Cambridge, UK.


Editor’s note: This review focuses on the background of the clinical trials that have led to the relatively recent approval of growth hormone (GH) treatment for short children born small for gestational age (SGA), initially in the US in 2001, but latterly by European license authorities in 2003. The authors are mindful of the lack of full understanding of the mechanisms for the initial growth impairment within this very heterogeneous group of patients. Moreover, they acknowledge the extent to which intermediary metabolism, nutrient intake and disposal, and insulin resistance are interlinked with the causes of poor growth, post-natal catch-up growth mechanisms, and possibilities of metabolic and cardiovascular risk factors for adult life. These are closely related to some of the changes to the metabolic milieu that accompany GH treatment. The lack of long-term safety data from clinical trials, as well as variable quality outcome data on final height and quality of life measures, inevitably leads to clinicians having differing opinions on whether GH treatment for these children is appropriate in the setting of current health economics. This report is a concise review that poses a number of questions, with uncertainty as to whether gaining a few centimeters of final height or childhood “normality” should be the aim if the trade-off is metabolic morbidity, which requires additional, protective, therapies.

Growth hormone induced lipolysis during short- and long-term administration in adult Prader-Willi patients.


Editor's note: The present availability of growth hormone (GH) to treat obesity and induce beneficial anabolic effects on height and muscle in patients with Prader–Willi syndrome (PWS) is limited to the attainment of final height and fusion of epiphyses. Whilst it is difficult to match PWS patients with control subjects, evidence of continued sensitivity to the lipolytic effects of growth hormone over 1 year of treatment, as presented in this study of six adult PWS patients, is encouraging. If the continued use of GH in adulthood (to maintain or further reduce fat mass) is to become established, then more extensive evidence will be required than that provided in this small study. This also needs to be combined with assessments of a wider variety of metabolic and body composition parameters, and more extensive GH dose adjustment in order to achieve “optimal” therapeutic targets within affordable dosing schedules.
Growth hormone benefits children with 18q deletions.
Cody JD, Semrud-Clikeman M, Hardies LJ et al.
University of Texas Health Science Center, San Antonio, TX, USA.

Editor’s note: This report focuses on studies performing comprehensive and longitudinal evaluations of individuals with deletions in chromosome 18q, which occur in an estimated 1:40,000 births. The clinical presentation varies but common characteristics include:

- Short stature.
- Dysmyelination of the brain.
- Delayed development and expressive language.
- Flat midface.
- Impaired growth.
- Proximally placed thumbs.
- Atretic or stenotic ear canals.

In these individuals the developmental process of myelination does not progress at the normal rate and never reaches normal adult levels. Thus magnetic resonance imaging (MRI) T1 relaxometry can be used to measure changes in myelination over time.

It has been suggested that the dysmyelination phenotype occurs due to hemizygosity of the gene for myelin basic protein (MBP), a major protein component of the central nervous system myelin sheaths. Indeed, all study participants were hemizygous for this region (as MBP is located near the telomere on 18q) and had the dysmyelination phenotype. Most individuals with 18q deletions have some degree of growth failure, with 68% of the population qualifying for growth hormone (GH) replacement therapy using standard assessment criteria. In addition a critical region of 18q that was hemizygous in all GH-deficient study participants was identified. This region is almost identical to the dysmyelination critical region, making the gene or genes responsible for these two phenotypes either the same, or tightly linked.

Thus far, researchers have not been able to unlink the two phenotypes. This study set out to determine whether GH treatment could affect the process of myelination as measured by MRI T1 relaxometry. Regardless of any correlation between myelination and GH therapy, the authors wanted to know whether the changes in brain microstructure correlated with changes in non-verbal intelligence quotient (IQ). Two groups were studied; those who qualified for GH were treated, while those who did not acted as controls. GH therapy increased linear growth, improved non-verbal IQ in the majority, and caused a change in the T1 relaxation times in specific areas of the brain (frontal white matter, caudate, and insula – although the last was non-significant).

It may be anticipated that children who had no growth failure, and who therefore did not qualify for treatment, would not benefit from or require GH. In these cases, the IQ scores of the untreated children would be comparable with the treated scores of the replacement group. However, the nonverbal IQ scores of untreated children did not differ significantly from those of the treated children prior to therapy. One explanation presented for this is that, although the children did not qualify for GH therapy, they were not truly growth hormone sufficient. This reasoning fits the hypothesis that individuals with 18q deletions have hypothalamic as opposed to pituitary dysfunction. The functional significance of the central nervous system changes visualized for MRI are not known. The practical consequences of improvement in non-verbal IQ resulted in the scores of all but one of the children, who began the study with a score in the measurable range (>50), improving to within the normal range (>70). This may improve the cognitive ability of these patients and have significant impact on their potential as adults. At present, none of the genes known to be involved in short stature caused by GH deficiency have been localized to chromosome 18q, nor has isolated GH
Deficiency been identified as a cause of intellectual disability. Therefore, the authors hypothesize that the intellectual disability in individuals with 18q deletions is due to the synergistic effects of the loss of ≥1 genes on 18q in combination with GH deficiency. Further research could include the relationship between T1 changes, myelination, and cognition. Furthermore, the cognitive and brain maturation effect of GH on children with idiopathic GH deficiency should be explored.

Effect of growth hormone therapy and puberty on bone and body composition in children with idiopathic short stature and growth hormone deficiency.
Höglera W, Briodyc J, Moorea B et al.
Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, Sydney, NSW, Australia.

Editor's note: Growth hormone (GH) and insulin-like growth factor-I have an established role in body composition. Some studies have shown that both adults with severe untreated childhood-onset GH deficiency and children with partial GH insensitivity undergo a reversal of bone mineral density (BMD). While the majority of previous studies in children with idiopathic short stature (ISS) have assessed only body composition, the present study also considered body size.

The authors used a four-step procedure to compare the total body measurements of 77 children (aged 3–17 years) with ISS or GH deficiency undergoing GH therapy with normative data from healthy men and women (aged 3–30 years). Of these children, 55 were followed-up for 24 months to detect changes in body composition, including rate of bone turnover. The results showed that prepubertal GH-deficient children gained more height and had an increased bone mineral content/lean mass (LTM) ratio compared with prepubertal children with ISS. Furthermore, a decrease in percentage body fat was observed in GH-deficient children but not in those with ISS. Puberty led to absolute increases in weight, LTM, body mass index, bone mass, and lumbar spine volumetric BMD.

Overall, the data from this study showed that, while GH therapy had great benefits on growth plate and body composition, leading to gains in height, LTM, bone turnover, and body mass accrual, no benefit was observed for volumetric BMD over 2 years.

The use of tamoxifen to improve height potential in short pubertal boys.
Kreher NC, Eugster EA, Shankar RR.
Indiana University School of Medicine, Indianapolis, IN, USA.

Editor's note: This is a review of seven pubertal boys treated with tamoxifen, a selective estrogen receptor modulator. Traditionally, long-acting gonadotropin-releasing hormone analogues have been used both in pubertal growth hormone (GH)-deficient patients, and as a way of delaying epiphyseal fusion and increasing final adult height in some non-GH deficient patients. Estrogen is known to be important in mediating the closure of the growth plates, and this has led to the development of therapies aimed at either decreasing estrogen synthesis or blocking estrogen effects. The authors were not aware of any previous use of tamoxifen for this purpose.

Of the seven boys included in the study, six were already on GH therapy. Initiation of tamoxifen occurred at a mean age of 14 years 11 months with an average height standard deviation of −2.27. The mean duration of drug therapy was 26 months (6–48 months) and the dosage used (10–20 mg twice daily) significantly decreased the rate of skeletal maturation from 1.1±0.97 before treatment to 0.44±0.13 during treatment. The average predicted adult height increased from 167.74±4.62 cm at baseline to 177.6±4.09 cm during therapy. The average growth velocity was 6.6±1.3 cm/year during treatment. All patients manifested normal secondary sexual development. On average, testicular volume increased from 8 mL before therapy.
to 20 mL at final examination. On average, pubic hair was at Tanner stage IV at the last evaluation.

There were no adverse effects of therapy. All liver function blood tests were normal. Tamoxifen was discontinued in the one patient who complained of blurred vision and an ophthalmological examination showed no abnormality. After the reintiation of tamoxifen this patient had no recurrent symptoms. This is a small and non-controlled study, but further trials are likely to evaluate the efficacy and metabolic effects of tamoxifen.

**Salutary effects of combining early very low-dose systemic estradiol with growth hormone therapy in girls with Turner syndrome.**


Editor's note: In this small, multicenter study the authors endeavored to clarify the complex issue of whether the timing of estrogen therapy for the induction of puberty in a girl with Turner syndrome (also receiving growth hormone [GH] treatment) will have an adverse effect on subsequent height gain and final height. In view of the recognized detrimental effects of oral estrogen replacement on circulating insulin-like growth factor-I (IGF-I) and growth potential, the study employed a depot monthly intramuscular schedule with estradiol cypionate. Patients were randomized to receive therapy either during the 13th year or on the 15th year at an initial low dose of 0.2 mg/month. The dosage was increased by 0.2 mg at 6-monthly intervals until a dose of 1 mg/month was reached, which was then increased by 0.5 mg every 6 months to a maximum of 3 mg/month. All girls had been receiving GH treatment at a standard dose of 0.05 mg/kg/day from a mean age of approximately 10 years; this was continued until attainment of near final/final height.

The study began in 1991 and only 14 girls were recruited (seven to each treatment arm). At near final/final height (reached at 3.5 or 4 years from the start of estradiol therapy) just five patients from the early estradiol treatment group and three from the late treatment schedule group remained. The rate of pubertal progression was broadly similar for the two treatment schedules, although only 15% of girls showed any breast development at the lowest dose of estradiol. Perhaps the most valuable observation from the study was that the desire for a faster pace of feminization was the sole reason for dropout from the group randomized to start estradiol late (four of the seven patients assigned to that group remained at the endpoint), with one patient withdrawing at the outset after randomization to that group.

No significant difference in height was present between the groups, although those in the early start group showed a significantly faster growth rate in the first 18 months of estradiol treatment. A more significant observation was made by comparing the growth outcomes in these two treatment groups with Turner syndrome patients from the NCGS (National Cooperative Growth Study) who were treated with GH and oral conjugated estrogen. Regardless of whether estradiol was initiated at an early (n=8) or late (n=11) stage, the NCGS patients achieved final/near final heights of, on average, approximately 5 cm less than those treated with parenteral estrogen in the present study. Thus, unless GH doses were adjusted to maintain target serum IGF-I levels (which would require another study, with possibly a more expensive therapeutic schedule), it is logical to suggest that careful evaluation of estrogen schedules that avoid oral preparations is the way forward.
Adult-onset deficiency in growth hormone and insulin-like growth factor-I decreases survival of dentate granule neurons: insights into the regulation of adult hippocampal neurogenesis.

Editor's note: There is increasing evidence to suggest that the growth hormone (GH)/insulin-like growth factor-I (IGF-I) system plays a pivotal role in the maintenance and regulation of normal levels of neurogenesis within the nervous system. It has been proposed that age-associated decline in cognitive abilities is related to concomitant reductions in circulating and tissue levels of GH and IGF-I that also occur with age.

The elegant experiments reported in this paper utilize the GH/IGF-I deficient dwarf (dw/dw) rat, which is an animal model ideally suited to investigating the effects of GH/IGF-I deficiency on lifespan, physiology, and neurocognitive function. After several months of GH/IGF-I deficiency, dw/dw rats show significant reductions in performance with respect to hippocampal-dependent neurocognitive tasks. In young dw/dw rats, GH/IGF-I-deficiency appears to have no effect on the rate of hippocampal neuroglial cell proliferation, but significant reductions in the lifespan and survival of newly generated cells are observed. The impact on rat hippocampal neurogenesis of restoring GH and IGF-I levels to within the normal physiological range by exogenous GH administration, and then withdrawal of GH in adulthood, was also studied. In this situation, GH withdrawal was also associated with a reduction in neurone survival.

Together, these results provide new insights into the neurogenic role of IGF-I and/or GH, and possibly a role of GH itself in the regulation of neurogenesis, through supporting the survival and perhaps the maturation of newly generated neurones.


Editor's note: Although hypothalamic or pituitary damage may be readily understood to result from head injury, it is rarely overt unless it is associated with diabetes insipidus, when neurological damage may be so severe that the result is death. In contrast, both temporary and permanent anterior pituitary hormone deficiencies have until now been under-recognized, perhaps because of their relatively subtle clinical features (e.g. tiredness, weight gain, reduced muscle bulk). These features might be dismissed as intrinsic to the post-trauma phase of rehabilitation, particularly in adults in whom signs of impaired growth or pubertal delay are absent. In recent years, a number of groups have sought to evaluate the prevalence and nature of neuroendocrine effects in head trauma. The present study investigated the natural history of neuroendocrine outcomes in consecutive adult patients with severe or moderate head trauma.

In industrialized countries, death or hospitalization from traumatic brain injury occurs in approximately 200–250/100 000 persons per year. This study, of 50 patients with head trauma recruited over a 6-month period, extends the previously published observations describing the clinical characteristics of this cohort in the acute/immediate post-trauma phase (J Clin Endocrinol Metab 2004;89:4929–36.). On a computed tomography scan, 70% of patients had focal brain injury and 30% had a diffuse brain injury; 66% of patients had co-existent cerebral edema. Operative evacuation to reduce mass effect was required in 50% of patients.
Prospective follow-up over a 12-month period found transient, delayed-onset, and permanent anterior pituitary deficits in a substantial proportion of patients, in keeping with retrospective reports that have identified hypopituitarism in up to 50% of long-term survivors. The intramuscular glucagon test was used to evaluate growth hormone (GH) and adrenocorticotrophic hormone reserve in patients compared with normal controls. Baseline free thyroxine (T4), thyroid-stimulating hormone (TSH), prolactin, and testosterone measurements were used to assess other aspects of anterior pituitary function, and serum insulin-like growth factor-I (IGF-I) was used as an additional marker for GH insufficiency. Tests were performed within 7–20 days of the acute insult, and again at 6 and 12 months after injury. GH deficiency was present in 18% of acute phase patients, but was permanent in just 10% at 12 months. An impaired adrenocortical response was present in 16% of patients during the acute phase. Half of these had recovered by 6 months, only to be replaced by five newly recognized cases. In these nine patients, the impaired adrenocortical response at 6 months persisted at 12 months. Gonadotropin deficiency was the most frequently observed problem (80%) in the acute phase, which has previously been recognized as being transiently associated with renal failure. However, 85% of these patients had normal gonadotrophic hormone status by 12 months. There was one case each of transient and late presenting but persistent TSH deficiency. Of the 52% of cases with early transient hyperprolactinemia, only 13% had a persistent elevation of prolactin at 12 months, with one patient receiving dopamine antagonist therapy.

Unfortunately, there were no predictive correlates with adequate statistical strength to aid the development of a rational strategy to identify patients who might need transient or longer-term hormonal supplementation. The authors propose a management algorithm that would serve to identify those most at risk from adrenal insufficiency as a priority in the first week after trauma, with a view to reassessment at 3–6 months or 1 year, depending on whether glucocorticoid treatment had been introduced during the acute phase.

Residual pituitary function after brain injury-induced hypopituitarism: a prospective 12-month study.
Aimaretti G, Ambrosio MR, Di Somma C et al.
University of Turin, Turin, Italy.

Editor’s note: The last decade has seen increasing focus on the impact of traumatic head injury on pituitary function, with most studies demonstrating a clear loss of pituitary function. In this prospective multicenter study, the authors assessed whether pituitary function improves or worsens at 1 year after the index event.

Over 100 patients with a history of traumatic brain injury (TBI; n=70) or subarachnoid hemorrhage (SAH; n=32) were assessed for pan-hypopituitarism (PH), multiple hypopituitarism (MH), and isolated hypopituitarism (IH). The analyses were conducted at 3 and 12 months after the initial TBI or SAH. Growth hormone residual function was assessed by a growth hormone releasing hormone–arginine stimulation test. At 3 months after TBI, >30% of subjects had a degree of hypopituitarism, with 5.5%, 5.7%, and 21.4% having PH, MH, and IH, respectively. At 12 months, there was a slight improvement, with hypopituitarism being detected in 22.7% (5.7%, 4.2%, and 12.8%, for PH, MH, IH, respectively). However, a number of patients not previously identified were found to have pituitary dysfunction on retesting. Specifically, 5.5% of those without initial deficit demonstrated IH and 13.3% with IH at 3 months had MH at 12 months.

Patients with SAH showed a greater improvement in pituitary function than TBI patients, with 46.8% of SAH patients having some degree of hypopituitarism at 3 months compared with 37.5% at 12 months.

Overall, the findings of this study confirm the high likelihood of pituitary dysfunction following TBI or SAH. Furthermore, the
results support the requirement of routine long-term neuroendocrine evaluation both for patients who regain normal function and for those who might experience delayed onset of IH or MH.

**Prolonged stimulation of growth hormone and IGF-1 secretion by CJC-1295, a long-acting analogue of growth hormone-releasing hormone, in healthy adults.**

Teichman SL, Neale A, Lawrence B et al.
WinPharm Associates, San Ramon, CA, USA.

**Editor’s note:** The success of a polyethylene glycol-conjugated (PEGylated) growth hormone (GH) receptor antagonist in the treatment of acromegaly, and the evolution of PEGylated GH as a possible sustained-action alternative to daily GH injections, has seen a renewal of interest in the possible application of sustained-action GHRH, which is now also available in PEGylated form. This may be a viable therapeutic option for the proportion of GH-deficient children with a primarily hypothalamic defect in the regulation of GH secretion (idiopathic or post-irradiation), or for the augmentation of endogenous GH release in non-GH deficient children (Turner syndrome, Prader–Willi syndrome, small for gestational age infants). The pharmacokinetics and GH-responsiveness in these adult studies look promising, and support the potential use of this conjugate as a therapeutic agent.

**Trajectories of growth among children who have coronary events as adults.**

Barker DJP, Osmond C, Forsen TJ et al.
Southampton General Hospital, Southampton, UK.

**Editor’s note:** It is now well established that individuals with a low birth weight are at increased risk for the development of coronary heart disease. However, studies have not yet examined the subsequent effect of early childhood growth on the risk of coronary events. Of 8760 study participants, born in Helsinki from 1934–44, the present authors identified 357 men and 87 women who had been admitted to hospital with coronary artery disease or had died from the disease. The mean body size of children who had coronary events as adults was below average at birth. At 2 years of age these children were thin, but subsequent increases in body mass index, relative to that of other children, meant they showed average values by age 11 years. This pattern of improved growth was associated with insulin resistance in later life. The authors suggest these findings may only occur because babies who are thin at birth lack muscle, a deficiency that will persist into childhood because of low cell replication in muscle after birth. Therefore, the subsequent rapid weight gain in these children may lead to a disproportionally high fat mass:muscle mass ratio, which may underlie the strong associations between this pattern of growth and insulin resistance. Therefore, it is imperative that strategies to modify the prenatal and perinatal determinants of adverse adult health outcomes are developed.

**A densitometric and morphometric analysis of the skeleton in adults with varying degrees of growth hormone deficiency.**

Murray RD, Adams JE, Shalet SM.
Christie Hospital and University of Manchester, Manchester, UK

**Editor’s note:** Adult growth hormone (GH) deficiency is associated with low bone mass, and most studies to date have shown some degree of gain in bone mass following GH replacement therapy. The authors of this study conducted a cross-sectional study of 30 adults with childhood- or adult-onset GH deficiency, using dual-energy X-ray absorptiometry (DEXA) and peripheral quantitative computed tomography (pQCT) to define areal and volumetric densities and morphometry.

No densitometric or morphometric abnormalities were detected in patients with adult-onset GH deficiency. However, in childhood-onset GH-deficient patients DEXA showed decreased bone mineral density at the lumber spine and hip.
Furthermore, in these patients, pQCT detected an overall 25% reduction in cortical bone. Therefore, the low BMD detected by DEXA in these patients is mainly related to a reduced cortical thickness and smaller bone area.

The onset of GH deficiency, its duration, and timing of treatment clearly affect the bone in adult GH-deficient patients. Furthermore, the findings of this study are useful in illustrating the complexities of bone density analysis.

**Growth Hormone – Anabolic Usage**

**Effects of high-dose growth hormone on glucose and glycerol metabolism at rest and during exercise in endurance-trained athletes.**

Healy ML, Gibney J, Pentecost C et al. Guy's, King's and St Thomas' School of Medicine, St Thomas Hospital, London, UK. *J Clin Endocrinol Metab* 2006;91:320–7.

*Editor's note:* Growth hormone (GH) self-administration amongst athletes is believed to be an increasing problem within the world of top-flight competitive sport. Administration of supraphysiological doses of GH is thought to significantly enhance exercise performance; however, the effects of such GH “therapy” on performance and on glucose and lipid metabolism in otherwise healthy, non-GH-deficient, and endurance-trained athletes are not known.

This paper reports the results of a 4-week, double-blind, controlled study in which 12 athletes were randomized to receive daily injections of either recombinant human GH (rhGH; 0.2 U/kg/day) or placebo. Glucose and glycerol turnover studies were performed at baseline and at the end of therapy. As hypothesized, high doses of rhGH increased the rate of lipolysis and fatty acid availability; these elevations were observed during conditions of rest as well as during and immediately after exercise. Glucose turnover was increased after exercise only.

Notwithstanding the limitations in their study design (a small number of subjects and short administration schedule), this report makes an important contribution to the area of sports physiology, although the significance of their observations and the authors’ long-term implications for athletes who abuse GH remain unclear.

**Growth hormone treatment in children with rheumatic disease, corticosteroid induced growth retardation, and osteopenia.**


*Editor's note:* The possible indications for recombinant human growth hormone (rhGH) therapy continue to increase and the latest to be added to the list are chronic inflammatory disorders such as rheumatic disease (RD) and inflammatory bowel disease. Poor growth is a well-recognized feature of these conditions and may be due to the disease process itself (through the generation of inhibitory inflammatory cytokines) or the drugs used to treat them (e.g. corticosteroids). Several reports have suggested that rhGH therapy in patients with these conditions may have beneficial effects in terms of improving growth rate and bone mineralization, although most of these studies have been uncontrolled trials.

In this paper, Grote and colleagues report the results of the first randomized, controlled trial to examine the effects of rhGH therapy on growth, bone mineral density (BMD), and body composition in a group of prepubertal children (n=17) with RD. Ten subjects were treated with rhGH (4 IU/m²/day) whilst seven acted as controls and received no treatment. After 2 years of treatment, during which routine anti-inflammatory drug therapy did not differ between the groups, significant increases in height standard deviation scores
(ht SDS) were seen in the rhGH group (+0.42 SDS), whereas ht SDS decreased (−0.18 SDS) in the controls. Furthermore, significant improvements were seen in lean body mass (assessed by dual energy X-ray absorptiometry) in those receiving rhGH therapy compared with controls (+0.64 vs. −0.20 SDS; p<0.01), whereas BMD did not differ between the groups.

Notwithstanding the limitations in study design (e.g. the heterogenous mix of RD in the groups and the relatively small numbers studied) the results of this trial are, to date, the most robust data supporting the concept of rhGH therapy in these patients. However, longer-term studies are needed to evaluate the effects on final adult height outcomes and other metabolic parameters, as well as BMD.

Growth Hormone – Physiology

The impact of short-term fasting on the dynamics of 24-hour GH secretion in patients with severe radiation-induced GH deficiency.
Darzy KH, Murray RD, Gleeson HK et al.
Christie Hospital, Manchester, UK, and University of Virginia Health Science Center, Charlottesville, VA, USA.
J Clin Endocrinol Metab 2006;91:987–94.

Editor’s note: Interestingly, severe radiation-induced growth hormone (GH) deficiency is associated with the preservation of a normal pattern of GH pulsatility and diurnal variation, although GH amplitude is attenuated. Therefore, GH neuroregulation appears to be preserved and the effects of radiation on the hypothalamic–pituitary–GH axis seem to be quantitative rather than qualitative in nature. These observations, previously made under normal physiological conditions, have not been confirmed under fasting conditions, which itself induces well-defined changes in the GH axis (i.e. enhanced GH secretion).

In this study, eight young adults with severe GH deficiency secondary to cranial irradiation (CI) and 14 matched healthy controls were subjected to plasma GH profiling, in both the fed state and in the last 24 h of a 33 h fast. Fasting induced a significant rise in GH amplitude in both groups, whereas GH pulse frequency was significantly increased in the CI group only. Mean GH concentrations were increased in both groups with fasting, but less so in the CI group (3.7 vs 2.7 fold; p>0.05). Overall, the pulsatile pattern of GH secretion observed in the CI group with GH deficiency and the relative augmentation of GH release induced by fasting are similar to those seen in healthy controls, thus confirming that GH neurosecretory regulation is, to a large extent, preserved in GH deficiency.

Growth Hormone – Clinical

Noonan syndrome: relationships between genotype, growth, and growth factors.
Limal JM, Parfait B, Cabrol S et al.
University Hospital, Angers, France.
J Clin Endocrinol Metab 2006;91:300–6.

Editor’s note: The Noonan syndrome (NS) phenotype is characterized by short stature in >70% of subjects. Various explanations for short stature have been proposed, including growth hormone (GH) deficiency, GH neurosecretory dysfunction, and GH resistance; however, the underlying mechanisms are not entirely understood. The relatively recent discovery that NS is associated with a mutation of the protein-tyrosine phosphatase, nonreceptor type 11/(PTPN11) gene (Ch 12q24) in ≥50%
of subjects has caused significant interest in this area, given that PTPN11 encodes for the SH2-containing protein tyrosine phosphatase, SHP-2. This phosphatase is an important and integral component of intracellular signaling mechanisms downstream of several growth factor receptors, including the GH receptor.

In this report by Limal and colleagues, the growth and hormonal growth factor characteristics of 35 patients with NS were documented; these were then compared in those with (M+) and without (M–) PTPN11 mutations. In the majority of NS subjects, GH secretion after pharmacological stimulation was within the normal reference range. Blood insulin-like growth factor-I (IGF-I) levels were low in ≥50% of individuals, especially those who were M+. Additionally, M+ subjects had significantly lower blood IGF-I and acid-labile subunit levels than M– subjects, although plasma IGF binding protein-3 levels were similar. Furthermore, in M+ subjects there was a tendency towards lower birth length and, during recombinant human GH therapy, catch up growth was significantly lower compared with M– subjects.

The authors conclude that their results suggest that NS is associated with a degree of GH resistance that may be more severe in M+ subjects compared with M– subjects.

**Genetics**

**A novel LHX3 mutation presenting as combined pituitary hormonal deficiency.**
Bhangoo AP, Hunter CS, Savage JJ et al.
Infants and Children's Hospital of Brooklyn at Maimonides, Brooklyn, NY, USA.

Editor's note: The LIM-homeodomain class of transcription factors, LHX3 and LHX4, play an important role in pituitary gland development, and mutations in their genes have been associated with the development of hypopituitarism. To date, only two types of LHX3 mutations have been described, each with a phenotype characterized by combined anterior pituitary deficiency and, curiously, neck rigidity.

In this report, Bhangoo and colleagues describe a novel mutation of the LHX3 gene in a 7-year-old child with evidence of anterior pituitary dysfunction (thyroid, growth hormone, and gonadotrophin axes) and neck rigidity. In addition, the child demonstrated other, not previously observed features, i.e. mental retardation and muscular focal amyotrophy (detected by electromyography). In this case, a novel single base-pair deletion in exon 2 of the LHX3 gene was detected. This was predicted to result in the production of a short, inactive, protein product, and was confirmed by *in vitro* translational experiments.

As well as expanding the phenotypic spectrum of LHX3 gene mutation-associated problems, this report suggests that LHX3 may have an important role in neurocognitive and neuromuscular development.

**Common polymorphisms of the growth hormone (GH) receptor do not correlate with the growth response to exogenous recombinant human GH in GH deficient children.**
Pilotta A, Mella P, Filisetti M et al.
University of Brescia, Brescia, Italy.

Editor's note: It is well recognized that the growth response to exogenous recombinant human growth hormone (rhGH) in GH deficient subjects varies between individuals. The reasons for this are unclear and may be secondary to a number of features, including the age of onset and the height deficit at the start of treatment, or due to factors such as the severity of the GH deficiency and the dose of rhGH used.

Differences in the underlying sensitivity of tissues to GH, which may be due to polymorphisms in the gene encoding for the
GH receptor (GHR), have also been proposed as a possible explanation. Pilotta and colleagues tested this hypothesis in a study of 54 children with idiopathic GH deficiency. Data on height velocity prior to the onset of rhGH therapy and during the first year of treatment were ascertained, and associations with underlying GHR gene polymorphisms were determined.

Molecular genetic analysis revealed a high frequency of known GHR polymorphisms, but no significant differences in height velocity data were observed between groups of subjects, when defined by polymorphic genotypes. These data suggest that, at least in children with GH deficiency, GHR polymorphisms do not affect the growth responses to rhGH.

Insulin-like growth factor I promoter polymorphism, risk of stroke, and survival after stroke: the Rotterdam study.

Editor’s note: Insulin-like growth factor-I (IGF-I) has been implicated in the development of several diverse disease processes, such as cancer, atherosclerosis, and cardiovascular disease, due to its role in cell proliferation and tissue repair. It has been suggested that IGF-I may be a risk factor for stroke, with data from studies of animal models showing that IGF-I expression is increased after hypoxic damage and the administration of IGF-I reduces infarct volume and improves neurological function after brain ischemia. In addition, low serum IGF-I levels have been found to influence the outcome of cerebrovascular disease.

The present group has previously identified a polymorphism (192-base pair [bp] allele) in the promoter region of the IGF-I gene that influences plasma IGF-I levels (Diabetes 2001;50:637–42). Non-carriers of the polymorphism have lower plasma IGF-I level compared with carriers. Utilizing this observation, the authors studied this IGF-I promoter polymorphism in relation to the risk of stroke and survival after stroke in a large cohort of subjects (n=6808) from Rotterdam, The Netherlands. In non-carriers of the 192-bp allele, Cox regression analysis revealed that the relative risk (RR) for the occurrence of any type of stroke (ischemic or hemorrhagic) was 0.8 (95% confidence interval [CI] 0.6–1.0). The RR for death after stroke in these patients was 1.5 (95% CI 1.0–2.2) compared with 1.0 for 192-bp homozygous carriers.

These data suggest that in non-carriers of the 192-bp allele, and thus in individuals with lower IGF-I levels, there is a protective effect from the occurrence of any stroke, although this finding was non-significant. However, it may be a significant predictor of poor outcome, mainly death, after stroke.


Editor’s note: These two papers illustrate novel mechanisms that contribute to the understanding of variable phenotypes in familial cases of autosomal dominant growth hormone (GH) deficiency. These were previously thought to result only in isolated GH deficiency type II (IGHD II) but now show clear overlap with causes of multiple pituitary hormone deficiency that may evolve with age.

IGHD II is most commonly caused by mutations that result in skipping of exon 3, resulting in a product that lacks amino acids...
32–71 (del32–71GH), and loss of the loop structure connecting helix 1 and helix 2 in the tertiary structure of the GH molecule. This is most commonly caused by mutations both at the donor splice site in 5’IVS3 and in the exon splice enhancer (ESE1 in exon 3).

Vivenza et al. report a novel mutation in a mother and child with severe GH deficiency and severe growth failure (–6.9 height standard deviation score [SDS] and –5.8 height SDS, respectively, at diagnosis) [1]. This mutation is a 22-base pair (bp) deletion in IVS3 (IVS3 del +56–77), which results in removal of a putative branch point sequence (BPS). The functional result, detected in lymphocyte mRNA, was excessive exon 3 skipping. However, when the mutated allele was transfected into rat pituitary cells the result was the production of four differently spliced products. The main product detected was mRNA lacking exon 3; lesser amounts of full-length mRNA and two novel mRNA isoforms were also produced. One of these novel isoforms lacked the first 86 bases of exon 4, and exon 4 was absent in the other. Additional studies with a mutant construct deficient in the 7-bp sequence for the BPS generated just two products: the exon 4-skipped and the full-length isoforms. The authors conclude that the ability of this mutant, which lacks just the BPS sequence, to continue to generate full-length transcripts implies that there is an alternative BPS sequence within IVS3. Thus, it is clear that the clinical severity of the IGHD II phenotypes may depend on specific mutations and the impact of specific transcript products on GH release and biological activity.

Salemi et al. focused their work on the less common genotypes that may contribute to the spectrum of IGHD II [2]. Apart from the abnormalities that result in exon skipping, there are three recognized missense mutations within the GH-1 gene that may cause variable degrees of GH deficiency. R183H and V110F appear to be limited to isolated GH deficiency, whereas the P89L mutation is now recognized as being associated with evolving multiple pituitary hormone deficiencies. As described in this paper, the P89L families have a clear potential to develop impaired pituitary–adrenal and thyrotrophin deficiencies upon retesting as adults, and these may be severe enough to require additional hormone replacement. This has serious implications for the need for long-term surveillance and active reassessment at intervals throughout adult life in individuals with this mutation. It emphasizes the importance of identifying the genotype in IGHD II patients, since this may also (as with R183H) preclude the need for a similar degree of long-term medical management.

The co-authors have worked extensively to characterize the in vitro differences in intracellular protein processing associated with these different mutations in order to identify different secretory/organellar processing dynamics that might account for interference with the release of other anterior pituitary hormones. How the somatotrophic lineage of cells impinges on adjacent adrenocorticotrophic and thyrotrophic cells through the production of abnormal GH protein requires further clarification. The families studied here showed no apparent difference in anterior pituitary size, whether P89L or R183H upon initial assessment, but there are some data suggesting that pituitary size may further reduce with time in the P89L patients.

**Heterozygous mutations of growth hormone receptor gene in children with idiopathic short stature.**

Bonioli E, Taro M, Rosa CL et al.
Largo G, Gaslini, Genova, Italy.

Editor’s note: The authors investigated growth hormone receptor (GHR) gene status in 37 children designated “idiopathic short stature” after primary investigations had failed to identify any medical explanation for their apparent poor growth. Heights ranged from −2 to −4.7 standard deviation score (SDS) and mid-parental heights ranged from +1 to −2.8 SDS (most subjects were below 0.0 SDS). Peak GH to standard provocation test ranged from 10 to 50 ng/ml, and all had
serum IGF-I levels below 0.0 SDS (range –0.02 to –3.3 SDS). Single strand conformational polymorphism (SSCP) assay was performed, followed by direct gene sequencing. The common synonymous change polymorphism (A>G at position 3 of codon 168) was found in 22/37 patients (12 homozygous, 10 heterozygous) compared with 16 homo- and 7 heterogenotypes in 23 of 50 controls (non-significant frequencies). Two novel transitions were identified: T>C at position 3 of codon 94; and a synonymous change and T>C at position 2 of codon 144 (yielding missense V144A), which were not present in 100 control samples. This incidence of approximately 5% heterozygous mutations of the GHR gene is similar to previous reports and suggests that, if significant heterozygous mutations that account for non-classical Laron type dwarfism/GH resistance are found, a more severe phenotype of short stature/abnormal GH/IGF imbalance than that examined in this study should be sought.

Genetic variation in the type 2 insulin-like growth factor receptor gene and disparity in childhood height.

Petry CJ, Ong KK, Wingate DL et al. University of Cambridge, Addenbrooke’s Hospital, Cambridge, UK.

Editor’s note: Insulin-like growth factor-II (IGF-II) and its receptor (type 2 IGF receptor [IGF2R]) are clearly linked with fetal growth, as evident in studies of transgenic IGF-deficient mice and by the overgrowth associated with altered IGF-II imprinting in Beckwith–Wiedemann syndrome. Subtle contributions to population growth variation that could arise from polymorphisms of the IGF2R might be expected to contribute more to prenatal growth variation than postnatal growth, since postnatal growth becomes progressively GH and IGF-I dependent. The IGF2R gly1619arg genotype affects a portion of the IGF2R that is not in a domain thought likely to have a highly significant effect on the regulation of IGF-II activity, but nonetheless could hypothetically have some impact on pre- or postnatal growth.

The ALSPAC (Avon Longitudinal Study of Parents and Children) is a contemporary childhood cohort study, conducted in the west of England, from which evidence has already emerged that cord blood IGF-II concentrations are positively related to size at birth (J Clin Endocrinol Metab 2000;85:4266–9). It has also demonstrated that the ratio of IGF-II to the soluble component of the IGF2R was related to birth weight, although in multiparous pregnancies there was a negative relation between IGF2R and birth weight and length. Polymerase chain reaction and restriction fragment length polymorphism analyses were used to ascertain genotype and compare G/G homozygotes with A/A homozygotes. Remarkably, there was no association between the genotype variations and any measures of size at birth, but a postnatal effect was apparent at age 3 years, which was maintained at 7 years of age. The A/A homozygotes grew more slowly, reaching a mean height deficit of –0.70 (SD 0.72; n=12) compared with G/G homozygotes (0.00, SD 1.09; n=561) (p=0.03). This persisted at age 7 years (p=0.01), even after correction for parental heights and gender. Moreover, there was no significant difference in weight between the two genotypes. Unlike the G/G genotype children, no A/A children underwent postnatal catch-up in weight. This may be linked to a subtle regulatory role for the IGF2R.

The intellectual capacity of patients with Laron syndrome (LS) differs with various molecular defects of the growth hormone receptor gene. Correlation with CNS abnormalities.

Shevah O, Kornreich L, Galatzer A et al. Schneider Children’s Medical Center of Israel, Petah Tikva, Israel.

Editor’s note: The importance of normal insulin-like growth factor (IGF) expression and regulation of its activity for healthy brain development (see the review by Russo et al.,...
The d3-growth hormone (GH) receptor polymorphism is associated with increased responsiveness to GH in Turner syndrome and short small-for-gestational-age children.


Editor’s note: The action of growth hormone (GH) is complex and is affected by polymorphisms in the GH receptor (GHR). Recently, a polymorphism of the GHR (deletion of exon 3 of the gene [d3-GHR]) has been implicated in the growth response of short children without GH deficiency undergoing GH therapy. In this retrospective study, the authors attempted to determine the effect of the d3-GHR polymorphism on growth velocity during the first year of GH therapy.

In all, 75 children with Turner syndrome and 60 children born small for gestational age (SGA) were treated with GH (38 μg/kg/day and 56 μg/kg/day, respectively). During the first year of therapy, growth velocity was greater in Turner syndrome patients with d3/d3 GHR genotype than in those with the d3/full length (fl) and fl/fl genotypes. Serum insulin-like growth factor (IGF)-I and IGF binding protein-3 levels did not differ among the three groups. Both Turner syndrome and SGA children carrying one or two d3-GHR alleles grew significantly faster than predicted; however, in SGA children, growth velocity was not significantly different between the groups.

Although the mechanism responsible for the increased responsiveness of the d3-GHR allele to GH treatment is unclear, this and similar findings in other genes might help in developing more specific and effective therapies.
Insulin-like Growth Factor-I – Effects

Chellakooty M, Juul A, Boisen KA et al.
Copenhagen University Hospital and University of Copenhagen, Copenhagen, Denmark. J Clin Endocrinol Metab 2006;91:820–6.

Editor's note: Whilst it is known that insulin-like growth factor-I (IGF-I) plays an important role in the regulation of postnatal growth from late infancy onwards, its contribution to normal fetal and early postnatal growth remains unclear.

In this longitudinal, prospective, cohort study of pregnant mothers and their offspring, serum IGF-I and IGF binding protein-3 (IGFBP-3) levels were determined in infants at age 3 months, and the relationship of these measurements with early postnatal growth were explored. The study included approximately 900 appropriate for gestational age (AGA) and 50 small for gestational age (SGA) infants. As well as providing an invaluable resource of normal reference data for IGF-I and IGFBP-3 for this age group, the authors made a number of interesting observations. Significant, but weak (p=0.05) associations between serum IGF-I and IGFBP-3 levels and postnatal growth (weight and height gain) were observed during the first 3 months of life in AGA, but not in SGA children. Infants receiving breast milk had lower IGF-I levels compared with infants receiving milk formula, which may be a reflection of the higher protein content of the latter.

AGA children who showed rapid weight or height gain during the first 18 months of life had the highest levels of serum IGF-I at 3 months of age. IGF-I levels did not correlate with the catch-up growth seen in the SGA group. Overall, it appears that IGF-I explains only a minor part of the variation in infancy growth patterns.

Insulin-like Growth Factor-I – Actions

The insulin-like growth factor system and its pleiotropic functions in brain.
Russo VC, Gluckman PD, Feldman EL et al.
Royal Children's Hospital, Parkville, VIC, Australia. Endocr Rev 2005;26:916–43.

Editor's note: This is a comprehensive review by collaborating scientists and clinicians from three centers in Australia, New Zealand, and the US that brings together the important, informative discoveries, mainly from the last 15 years, of the many roles of the insulin-like growth factors and the various components of the paracrine networks with which they interact, in the central nervous system (CNS). It assesses their contribution to normal development, plasticity, and repair of cell damage, and also discusses potential therapeutic developments for acute and chronic degenerative disorders, and cancer. Whilst most of the work relates to animal models, particularly transgenic mice and models of CNS injury, and in vitro study techniques, the avenues for exploration that are of direct relevance to humans are growing in number.
**Insulin-like Growth Factor-I – Expression**

The insulin-like growth factor-I gene and osteoporosis: a critical appraisal.
Niu T, Rosen CJ.
Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA.

Editor’s note: Osteoporosis is a systemic skeletal disease characterized by low bone mineral density (BMD) and deterioration of bone tissue. It commonly affects elderly patients (although a juvenile-onset form does exist) and, as the population ages, is becoming an increasingly major health issue. The disorder is associated with significant morbidity and mortality, and is the strongest predictor of fracture risk. Various factors play a significant role in the etiology of osteoporosis, including heredity, family history, dietary factors, and lifestyle. In addition, a number of hormones are responsible for final BMD.

The importance of insulin-like growth factor-I (IGF-I) in the formation and maintenance of BMD in adults has gained prominence. In an extensive analysis of the importance of IGF-I gene in osteoporosis, Niu and Rosen conclude that a number of distinct mechanisms underlie the role of IGF-I in bone modeling, including:

- The skeletal IGF regulatory system.
- The systemic growth hormone/IGF-I axis.
- Parathyroid hormone signaling.
- Sex steroids.
- The OPG/RANK/RANKL cytokine system.

Since options for the treatment of osteoporosis are currently limited, a better understanding of these molecular mechanisms may lead to the development of novel targeted therapies for patients with osteoporosis.

**Miscellaneous**

Decreased bone speed of sound in children with growing pains measured by quantitative ultrasound.
Friedland O, Hashkes PJ, Jaber L et al.
Tel Aviv University, Tel Aviv, Israel.

Editor’s note: Growing pains, the most common cause of recurrent childhood musculoskeletal pain, have an unknown etiology. This group hypothesized that growing pains may represent a local overuse syndrome, and may be associated with decreased bone speed of sound (SOS), as measured by quantitative ultrasound. The study included 39 children with growing pains. Bone SOS was measured by ultrasound, according to a protocol, in the midsections of both the tibial and radius bones. The results showed that the tibial SOS was significantly reduced in children with growing pains compared with controls (p=0.04 for boys, p<0.001 for girls). The radius SOS was also significantly reduced, but only in girls (p=0.006). There was no correlation between bone SOS and various demographic and clinical factors besides ethnicity and body mass index.