Growth

Growth Hormone, IGF-1, and Metabolism
Growth: Growth Hormone, IGF-1, and Metabolism

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Leading Article

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Genetic Defects of the GH–IGF Axis Associated with GH Insensitivity
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Department of Pediatrics, Doernbecher Children's Hospital, Portland, OR, USA.

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Reader Survey
Foreword

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Professor of Endocrinology and Pediatrics, Director of Clinical Education in Endocrinology, UCLA Medical School, Los Angeles, CA, USA.

The understanding of endocrinology moves forward with relentless intensity. New epidemics erupt, in the form of obesity, diabetes, and insulin-resistance syndrome; and are continually challenged by new therapeutic options, developed on a seemingly daily basis. The production of one such option, that of recombinant growth hormone (GH), has allowed a greater understanding of the disease processes involved in growth and development, although the controversy surrounding its use in therapeutics continues unabated.

Advances in the field of growth disorders continue to pose significant questions to clinicians:

• Does partial GH deficiency exist in children and/or adults?
• Explain the pathophysiology of radiation-induced GH neurosecretory dysfunction. Does it occur in adults? [1]
• How does GH replacement change levels of T4 and cortisol? [2]
• If the GH stimulation test is normal upon presentation, under what circumstances should it be repeated and when? [3]
• Is there value in the IGF-1 generation test?
• What is the best GH stimulation test and what are the target values?
• Which patients benefit from IGF-1 therapy?
• Which patients benefit from leuprolide and/or an aromatase inhibitor?

These are some examples of the dozens, perhaps hundreds of questions regarding the use of GH in adults and children and it is with many of these questions in mind that we bring you volume 2 of Current Medical Literature – Growth, a review journal providing commentary and analysis on the most important advances in the field of growth medicine. Each issue of this journal presents specially commissioned review articles exploring issues of current and emerging clinical importance, in addition to a systematic review of the recent international literature

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We look forward to providing you with an interesting and valuable publication and welcome your feedback and your suggestions for future content. Together, we can eliminate some concerns and improve the quality of care for children and adults in need of GH and/or IGF-1 replacement.

Growth hormone (GH) is widely used to treat short stature resulting from a variety of conditions, including GH deficiency, Turner syndrome, and chronic renal failure. Until 2005, GH was the only medication available for growth promotion in children to be approved by the US Food and Drug Administration (FDA). Since then, recombinant human insulin-like growth factor-1 (IGF-1; mecasermin) has also been approved for the treatment of short stature resulting from severe primary IGF-1 deficiency.

**GH, IGF-1, and the control of growth**

The physiology of mammalian growth has been thoroughly investigated over the last 30 years. The hypothalamic–pituitary–growth plate axis is a complex system that regulates human growth. Two hypothalamic peptides, GH-releasing hormone and somatostatin – each regulated by an integrated system of hormonal, neural, and metabolic factors – control the secretion of GH by the anterior pituitary gland. GH then interacts with its receptor to stimulate the production and secretion of IGF-1 by the liver as well as by many other tissues, including the growth plate. Thus, IGF-1 is the single most important hormonal growth regulator.

Hypothalamic and pituitary abnormalities can result in insufficient GH secretion and, thus, an IGF-1-deficient state – one that is secondary to GH deficiency (Figure 1). This must be differentiated from primary IGF-1 deficiency, which can be defined as short stature associated with low IGF-1 concentrations in the setting of normal or elevated GH concentrations and an adequate nutritional status. As hormone replacement is the basis of endocrine therapeutics, the notion of correcting GH deficiency with recombinant human GH is logical. Similarly, primary IGF-1 deficiency could, in theory, be corrected with recombinant human IGF-1 administration.

The first patients treated with IGF-1 were children with severe growth failure resulting from defects in GH action caused by GH receptor abnormalities. A decade of experience with IGF-1 treatment of GH-resistant/insensitive patients confirmed that IGF-1 can promote statural growth. However, at first, it was not so obvious that exogenously administered IGF-1 would produce sustained anabolic effects in humans. The original somatomedin hypothesis indicated that IGF-1 produced in the liver would circulate through the vascular space to reach distant targets in order to effect growth [1]. It was later discovered that IGF-1 mRNA is expressed in a variety of non-hepatic tissues, implying that autocrine or paracrine IGF-1 might also be important for growth. Without this effect, simply restoring circulating IGF-1 may turn out to be insufficient.

In addition, complete lack of GH action in these GH-insensitive patients might attenuate the response to IGF-1. Actions of GH...
independent of IGF-1 may be required for the full growth response to occur. Furthermore, each component of the ternary complex (IGF-1, its carrier IGF-binding protein-3 [IGFBP-3], and the acid-labile subunit [ALS]) is dependent on GH for expression. Although IGF-1 is the active agent, it is possible that these other components are required for maximal physiological response. Following the FDA approval of IGF-1 in late 2005, a recombinant IGF-1/IGFBP-3 complex (mecasermin rinfabate) was also approved as a therapeutic agent for the treatment of growth failure resulting from severe primary IGF-1 deficiency. However, because of patent right issues, the complex is, at present, no longer available. The discussion below will, therefore, address the experience with recombinant human IGF-1 alone.

**Therapy for severe primary IGF-1 deficiency**

Severe IGF-1 deficiency is the hallmark of GH insensitivity syndrome (GHIS). Laron syndrome, the classic form of GHIS, results from mutations of the GH receptor gene causing reduced or absent GH signaling and profound IGF-1 deficiency (IGF-1 standard deviation score [SDS] \( \leq -3 \)) [2]. In such patients growth failure begins immediately after birth, persists throughout childhood, and results in an adult height of \( \leq 130 \) cm on average [3]. Recombinant human GH therapy is ineffective in these patients. Laron syndrome is clinically quite similar to severe GH deficiency, except that GH secretion is increased. In addition to low serum IGF-1 concentrations, IGFBP-3 and ALS are significantly reduced [4]. Post-receptor defects in GH signaling due to deficiency of signal transducer and activator of transcription factor 5b have recently been identified in GHIS patients, and are also associated with poor growth and IGF-1 deficiency [5,6]. Alternatively, a defect in the synthesis of IGF-1 can lead to severe primary IGF-1 deficiency [7]. Finally, GHIS can be acquired when patients with GH gene deletion develop antibodies to GH during the course of GH treatment [8].

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**Figure 1.** The hypothalamic-pituitary-growth plate axis. The major hormonal factors involved in human growth are noted on the left. Secondary IGF-1 deficiency is due to abnormalities involving the hypothalamus or pituitary gland, leading to GH deficiency. Primary IGF-1 deficiency results from defects at or beyond the level of the GH receptor, when GH concentrations are normal or elevated.

(+) stimulatory effect; (-) inhibitory effect; GH: growth hormone; GHR: GH receptor; GHRH: GH releasing hormone; IGF-1: insulin-like growth factor-1; IGFD () IGF deficiency.
Treatment of Severe IGF-1 Deficiency with Recombinant Human IGF-1

Results of IGF-1 therapy for severe IGF-1 deficiency due to GHIS have been reported by several investigative groups (Table 1). In the study by Backeljauw et al., eight children were treated for up to 7.5 years with IGF-1, with doses between 80 and 120 µg/kg twice daily [9]. Growth velocity improved during the first year of therapy from a pretreatment mean of 4.0 cm/year to 9.3 cm/year. During the second year of therapy, growth velocity was 6.2 cm/year and remained slightly below this during the following years (mean height velocity range 4.8–5.5 cm/year). This resulted in an overall improvement in the height SDS of +1.4 (from −5.6 to −4.2) after up to 7 years of therapy.

A multicenter European study followed 17 subjects for ≥4 years; IGF-1 therapy improved the mean height from −6.5 SDS to −4.2 SDS [10]. Other shorter studies of IGF-1 therapy showed similar growth responses during the initial years of therapy [11,12]. Finally, an expansion of the aforementioned long trial [9] with a larger patient cohort (n=76) further substantiated the findings [13]. IGF-1 therapy for up to 12 years improved pretreatment height velocity from an average of 2.8 cm/year at baseline to 8.0 cm/year during the first year of treatment (p<0.0001). First year height velocity was dose-dependent and decreased during the subsequent years, but remained higher than at baseline. From the limited number of patients who achieved final or near-final height, it appears that these individuals achieve an adult height significantly greater than would be expected in the absence of therapy [13]. However, although most patients experience some degree of catch-up growth and have significant improvements in height velocity, they are unlikely to attain heights within the normal range.

Variation in the growth response to IGF-1 was observed in all of these studies. Moreover, the growth response to IGF-1 therapy in patients with severe primary IGF-1 deficiency was less than that previously observed in GH-treated patients with GH deficiency. According to data from the National Cooperative Growth Study, growth velocity in GH-deficient children increases from 4.4±2.8 cm/year to 10.0±3.1 cm/year after 1 year of treatment [14]. The patients’ growth velocity in the subsequent therapy years remains above baseline, improving the height SDS from −2.6±1.1 to −0.5±1.1 after 7 years.

Effects of IGF-1 treatment on specific organ- and tissue-growth

A disproportionate increase in body fat at the expense of lean body mass is common in patients with severe primary IGF-1 deficiency [15]. A mild reduction in the percentage of body fat during the first years of IGF-1 therapy has been observed [9]. This may reflect an increase in lean tissue resulting from improved growth and/or an anabolic effect, but may also represent a true reduction in fat mass. With more prolonged use of IGF-1, body fat proportion returned to the pre-treatment state [13].

**Table 1. Comparison of several trials of IGF-1 therapy for primary IGF-1 deficiency due to GHIS.**

<table>
<thead>
<tr>
<th>Authors [Ref]</th>
<th>Subjects (n)</th>
<th>Height at start (SD)</th>
<th>IGF-1 dose (µg)</th>
<th>Duration (years)</th>
<th>Growth velocity baseline</th>
<th>Year 1</th>
<th>Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Backeljauw et al. [9]</td>
<td>8</td>
<td>−5.6</td>
<td>80–120 bid</td>
<td>7.5</td>
<td>7.5</td>
<td>4.0</td>
<td>9.3</td>
</tr>
<tr>
<td>Ranke et al. [10]</td>
<td>17</td>
<td>−6.6</td>
<td>40–120 bid</td>
<td>4</td>
<td>8</td>
<td>8.8</td>
<td>8.8</td>
</tr>
<tr>
<td>Klinger et al. [11]</td>
<td>9</td>
<td>−5.6</td>
<td>175–200 qd</td>
<td>1–3</td>
<td>1–3</td>
<td>4.7</td>
<td>8.2</td>
</tr>
<tr>
<td>Guevara-Aguirre et al. [12]</td>
<td>7</td>
<td>−8.0</td>
<td>80 bid</td>
<td>2</td>
<td>2</td>
<td>3.0</td>
<td>9.1</td>
</tr>
<tr>
<td>Chernausek et al. [13]</td>
<td>76*</td>
<td>−6.5</td>
<td>80–120 bid</td>
<td>8+</td>
<td>8+</td>
<td>2.8</td>
<td>8.0</td>
</tr>
</tbody>
</table>

*Subjects include those from [9]. bid: twice per day; qd: once daily; n: number of patients; GHIS: growth hormone insensitivity syndrome; IGF-1: insulin-like growth factor-1; SDS: standard deviation score.
Children with severe primary IGF-1 deficiency may have underdeveloped facial bones (small facial dimensions and a retrognathic maxilla and mandible) [16]. Head circumference is also diminished in these children, but less so than their height. Laron et al. reported catch-up growth of the head circumference with IGF-1 therapy [17]. Detailed analysis of craniofacial development has shown rapid growth of the mid-facial area and mandible during the initial years of IGF-1 therapy [16,18]. However, after 6 years of treatment, there was no evidence of disproportionate growth in a study by Backeljauw et al. [Unpublished data].

Soft tissue enlargement of the face (thickening of the glabella, eyebrows, nasal tip, and lips) has been observed in some patients [9,13]. These changes were more apparent in patients entering puberty. This soft tissue hypertrophy seems at least partly reversible, and in several patients improved considerably after completion of IGF-1 therapy.

Kidney and spleen overgrowth has been observed with IGF-1 treatment in rats [19]. The growth of these organs has been studied by ultrasonography in the human trials [9,13,20]. A rapid increase in spleen size was observed during the first 2 years of therapy, but spleen growth reverted to normal during extended treatment. At the same time, notable growth of lymphoid tissue has also been observed. This tonsil and adenoid growth caused some children to experience the onset of snoring and led, in some, to obstructive sleep apnea, requiring tonsillectomy and/or adenoidectomy [13]. Renal growth also increased significantly during early IGF-1 treatment, but kidney size remained low-for-age in most patients. No functional abnormalities of the kidneys were observed [9,13].

Safety of IGF-1

Hypoglycemia has been observed during IGF-1 therapy. This is unsurprising because IGF-1 clearly retains insulin-like properties at therapeutic doses. In addition, children with severe primary IGF-1 deficiency are predisposed to hypoglycemia because of their underlying condition. At least one-third of these patients have a history of hypoglycemia prior to the institution of IGF-1 therapy [13]; nearly half experience hypoglycemia during the course of the therapy. Hypoglycemia is mostly a concern at the onset of therapy, especially in the shortest and youngest children. Studies have demonstrated that hypoglycemia is avoided when children consume a meal or snack shortly before or after IGF-1 injection [13,21]. It is recommended that patients should have their glucose monitored at home after initiation of IGF-1 therapy, especially if they are very young and/or have severe short stature.

Lipohypertrophy at injection sites has been reported in 32% of patients receiving IGF-1 [13,21]; this occurs when the IGF-1 injections are not rotated properly. As discussed in the previous section, lymphoid tissue hypertrophy is relatively common at the beginning of therapy. Less common adverse events include intracranial hypertension, which has been reported with IGF-1 administration [22] as well as during GH therapy for GH deficiency [23]. Transient, mild increases in intracranial pressure may also be the reason for headaches, which one experienced frequently, often during the first month of therapy.

In general, it appears that IGF-1 has an acceptable safety profile, especially considering the lack of alternative therapies for these patients. The published experience has mainly been in children with severe primary IGF-1 deficiency and the number of long-term treated patients is only in the dozens. As a result, it has been reassuring to observe that reduced blood glucose has been reported as an adverse event in only 5% of patients treated with IGF-1 and enrolled in the IGF deficiency registry, a post-marketing surveillance database in the US (safety assessment on 237 children for a total of 156 years of follow-up) [24]. It should be noted that most patients in the IGF deficiency registry did not have the severe form of IGF-1 deficiency (the mean IGF-1 SDS was –1.7), but the findings are consistent with other reports indicating that IGF-1 therapy may not
necessarily increase the risk of hypoglycemia as much as was initially expected [25,26].

**Therapy for less-than-severe primary IGF-1 deficiency**

In contrast to patients with GHIS, who have severe primary IGF-1 deficiency, patients with less severe IGF-1 deficiency (defined as height and IGF-1 SDS <–2, and stimulated GH ≥7 ng/mL) are relatively common. In the last year, preliminary data from clinical studies of IGF-1 therapy for such patients have been reported. A prospective study at eight pediatric endocrinology clinics in the US found that the less severe form of IGF-1 deficiency occurred among 26% of untreated children with short stature during two subsequent endocrinology clinic visits [27]. Patients with the lowest IGF-1 concentrations also had the lowest annualized height velocities, suggesting that IGF-1 deficiency may be an etiological factor for short stature.

In a multicenter, open-label, observational study (using the IGFD registry), the growth response to IGF-1 treatment during the first year of therapy in prepubertal children with IGF-1 deficiency was dependent on the mean IGF-1 dose used [28]. Patients treated with higher doses (≥100 µ/kg twice daily) had better growth rates, underscoring the importance of weight-based IGF-1 titration to achieve the optimum growth response. In a prospective, multicenter, randomized, parallel-dose comparison trial of children with primary IGF-1 deficiency (height and IGF-1 SDS <–2), for which a preliminary analysis was presented at the 13th International Conference of Endocrinology (Rio de Janeiro, Brazil, November 8–12, 2008) therapy with IGF-1 significantly increased the mean first year height velocity compared with no treatment, (mean height velocities of 8.0 cm/year vs. 5.2; p<0.0001). Again, this effect was dose-dependent [29]. Preliminary data from another ongoing, single-arm, open-label trial assessing once-daily dosing of IGF-1 in similar children (height and IGF-1 <–2 SDS) also showed that daily dosing significantly increased first year height velocities in a dose-dependent manner (p<0.0001) [30]. The effect of once-daily dosing on first year height velocities was similar to that observed with twice-daily dosing. Although preliminary, efficacy data for these less severe IGF-1-deficient patient groups are promising. Treatment with IGF-1 may turn out to be an alternative option for such patients with idiopathic short stature and IGF-1 deficiency, provided that these initial reports are further substantiated. From a safety perspective, hypoglycemia continues to be observed, but with a much lower incidence than previously reported. For example, in one of the clinical trials with twice-daily IGF-1 dosing, hypoglycemia occurred in 14% of treated versus 8% of untreated subjects [31]. In the trial with once-daily dosing of IGF-1, hypoglycemia was suspected or confirmed in 11% of patients [30].

**Conclusion**

IGF-1 treatment of children with severe primary IGF-1 deficiency due to GHIS effectively promotes statural growth. Initial catch-up growth lasts about 2–3 years, after which linear growth is maintained at a near-normal growth velocity for several more years. Long-term studies of IGF-1 in severe primary IGF-1 deficiency have led to important advances in the understanding of the physiology of the GH–IGF-1 axis, and have opened the door for the therapeutic use of IGF-1. Recombinant human IGF-1 (mecasermin) has now been approved in both the US and Europe for the treatment of growth failure resulting from severe primary IGF-1 deficiency. As the effect of IGF-1 on growth and metabolism are so complex, there is certainly a need for additional studies to determine the optimal treatment regimens. The number of treatment candidates so far has been rather limited, although the potential number of children with growth failure who may benefit from IGF-1 therapy may be much larger. Several clinical investigations are already underway to evaluate the efficacy and safety of IGF-1, alone or in combination with GH, for less severe forms of short stature associated with
less severe IGF-1 deficiency. Finally, other potential therapeutic uses of IGF-1, apart from its specific role in growth promotion, need to be explored.

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References

Genetic growth hormone (GH) insensitivity (GHI), also known as insulin-like growth factor-1 (IGF-1) deficiency, is characterized by impaired linear growth in association with reduced IGF-1 and elevated (or at least normal) GH secretion. In recent years, the identification and characterization of subjects with this condition has provided many insights into the functioning of the GH–IGF-1 axis in humans and the factors controlling human growth.

Currently, there are four known genetic causes of GHI:

- GH receptor gene deficiency (also known as Laron syndrome).
- IGF-1 gene deficiency (IGF–1).
- Signal transducer and activator of transcription 5B (STAT5B) gene deficiency.
- Acid labile subunit (ALS) gene deficiency.

Although all four genetic defects are associated with growth deficiency and the classical biochemical features of GHI, they all have distinct phenotypic features. This review will discuss these defects in turn, focusing on the unique features of each and the insights afforded by each defect into the functioning of the GH–IGF axis.

**GH receptor deficiency or Laron syndrome**

In 1966, Laron et al reported on two Ashkenazi Jewish siblings of a consanguineous pedigree who exhibited the classical clinical features of severe congenital GH deficiency, yet had elevated levels of GH [1]. They suspected that there was a problem with either a bio-inactive GH molecule or tissue sensitivity to GH. However, it was not until 1989 that the GH receptor gene was cloned, and a partial deletion of the GH receptor gene was identified in the original family [2]. GH receptor gene deficiency was originally termed Laron syndrome, in recognition of this first report.

**GH receptor structure**

We now know that the human GH receptor is a cell surface bound transmembrane receptor, belonging to a structurally related superfamily of receptors including those for prolactin, leptin, and the interleukins (ILs). The mature GH receptor in humans spans 620 amino acid residues with three functional domains: an extracellular domain that contains the binding sites for GH; a single, transmembrane domain, which anchors the receptor in the cell membrane; and a 350 amino acid residue cytoplasmic domain, which associates with intracellular signaling molecules and transmits the intracellular signal.

**GH receptor gene mutations**

The gene encoding the GH receptor contains 10 exons. Exons 2–7 encode the signal peptide and extracellular domain, while exon 8 primarily encodes the transmembrane domain. The remaining exon 8 segment and exons 9 and 10 encode the intracellular domain. Since the original report in 1989, over 60 distinct mutations of the GH receptor have
now been described, the vast majority of which act in a recessive manner and are located in the extracellular domain of the receptor [3]. There are only two reports of dominantly acting GH receptor mutations. Although these mutations affect different nucleotides, both result in the skipping (or exclusion) of exon 9 from the GH receptor gene cDNA, producing a truncated GH receptor. The truncated receptor retains the ability to bind GH and anchor in the cell membrane, but not to transmit an intracellular signal [4,5].

**Clinical and biochemical phenotype of GH receptor deficiency**

The clinical phenotype of subjects with GH receptor deficiency is indistinguishable from that of subjects with severe congenital isolated GH deficiency, namely a relatively normal birth weight followed by profound postnatal growth failure (mean height standard deviation score [SDS] –6.5), central obesity, hypoglycemia in infancy, and the typical facial appearance of a prominent forehead and relatively small midface.

IGF-1 levels are very low (typically less than –4 SD below the mean) in both GH receptor deficiency and severe congenital GH deficiency. However, after several days of GH administration, IGF-1 levels will typically rise substantially in subjects with severe GH deficiency, whereas they will not change significantly in subjects with GH receptor deficiency. Similarly, levels of IGF-binding protein-3 (IGFBP-3) and ALS, which normally bind with and stabilize IGF-1 in the circulation to form the ternary complex, are also extremely low in both GH and GH receptor deficiency, but only increase after GH administration in GH deficiency. Typically, GH levels are markedly elevated in GH receptor deficiency, although GH pulsatility remains, and show an exaggerated rise after pharmacologic stimulation.

Another useful biochemical marker of GH receptor deficiency is GH-binding protein (GHBP). This is a circulating form of the extracellular domain of the GH receptor, formed by proteolytic cleavage at the cell surface and usually measured using assays that determine the GH-binding ability of serum. Low GHBP levels suggest a mutation of the GH receptor, which results in either reduced receptor binding activity or reduced receptor expression. However, it should be noted that normal, or even elevated, GHBP levels do not exclude a GH receptor defect, as mutations that result in an intact GH receptor extracellular domain may not interfere with GHBP generation [6].

**Treatment of GH receptor deficiency**

The profound short stature, despite elevated GH secretion seen in GH receptor deficiency, is a clear indicator that IGF-I, rather than GH, is the primary effector hormone of postnatal growth. Unsurprisingly, GH therapy is ineffective in promoting growth in GH receptor deficiency. The development of recombinant human IGF-1 (rhIGF-1) therapy has provided a potential new growth-promoting agent for subjects with this condition. Several studies have investigated the effects of administration of recombinant human IGF-1 in this condition. A persistent increase in growth velocity from pretreatment levels has been demonstrated in treated subjects for up to 7 years of therapy; however, this increase is not as great as that seen in subjects with severe GH deficiency treated with GH [7]. There are several potential reasons for this. Firstly, subjects with GH receptor deficiency lack both circulating IGF-1 (produced primarily as a result of hepatic GH receptor stimulation) and local IGF-1 (produced as a consequence of GH binding to GH receptors in local tissues). Systemic administration of recombinant human IGF-1 replaces only the former type of IGF-1 production, whereas GH administration to GH deficient subjects will stimulate both systemic and local IGF-1 production. Secondly, IGFBP-3 and ALS levels remain low in GH receptor deficient subjects treated with recombinant human IGF-1, resulting in low ternary complex formation, whereas they increase in GH-treated GH deficiency, allowing for increased ternary complex formation. Thus, systemically administered IGF-1 in GH receptor deficiency has a
shortened half life, and may not be delivered to the tissues as effectively as when ternary complex formation is normal. Thirdly, any direct (non-IGF-1 mediated) effects of GH on linear growth remain unreplaced in IGF-1 treatment of GH receptor deficiency.

**IGF-1 gene deficiency**

In 1996, the first genetic cause of GHI other than GH receptor deficiency was described [8]. The patient was a 15-year-old boy with severe growth failure (height SDS –6.8), elevated GH secretion, and low IGF-1 levels that did not increase after GH administration [10]. However, unlike the subjects with GH receptor deficiency described thus far, who exhibit a relatively normal birth size, this individual had severe intrauterine growth retardation (birth weight 1.7 kg at term). Additional phenotypic abnormalities included sensorineural hearing loss and mental retardation. He lacked the typical facial appearance (relatively large head with prominent forehead and midface hypoplasia) of patients with GH receptor deficiency, Furthermore, his IGFBP-3 and ALS levels, which are typically reduced in GH and GH receptor deficiencies, were normal, indicating that the genetic defect in this patient may lie downstream of the GH receptor. Analysis of his IGF-1 gene (IGF-1) revealed a homozygous partial gene deletion, predicting a mature IGF-1 peptide truncated from 70 to 25 amino acids, followed by an additional out-of-frame nonsense sequence of eight residues and a premature stop codon. There have now been three further cases of IGF-1 deficiency reported in the literature, all of which involve homozygous point mutations in different positions on the IGF-1 [9–11]. The affected patients share similar clinical features: pre- and postnatal growth failure (height SDS –8.8), mental retardation, and sensorineural deafness, and a homozygous missense mutation of the IGF-1 (G274A) leading to a valine to methionine substitution at residue 44 of the mature IGF-1 molecule. Functional studies of the mutant IGF-1 molecule demonstrated it had an almost complete loss of binding affinity for the IGF-1 receptor [9]. Despite this, the patient's IGF-1 levels were elevated, presumably as a consequence of increased GH secretion leading to increased expression of this bio-inactive molecule.

All four cases of IGF-1 deficiency described to date share a common growth pattern, namely severe growth failure originating in utero and continuing postnatally. This is an important differentiating feature of IGF-1 deficiency from GH and GH receptor gene deficiency, in which growth failure in utero is minimal. Thus, growth in utero appears to be IGF-1-, but not GH-dependent. The neurodevelopmental abnormalities seen in the cases of IGF-1 deficiency are also suggestive of an important role for prenatal (or possibly postnatally expressed non-GH dependent) IGF-1 in central nervous system development.

**STAT5B deficiency**

Upon GH binding, the GH receptor becomes activated and three main signaling pathways – the STAT pathway, the mitogen-activated kinase pathway, and the phosphatidylinositol-3 kinase pathway – are activated. Until recently, the importance and relative contribution of each pathway to the growth-promoting and IGF-1-generating effects of GH was unclear. However, the identification of the first case of STAT5B deficiency in 2003 helped to clarify this issue. Kofoed et al. described a 16-year-old female from Argentina with a homozygous missense mutation (A630P) located in a critical domain of the signaling molecule STAT5B [12]. The STATs are key signaling molecules for many receptors in the GH receptor superfamily and have a common mechanism of action, which involves becoming tyrosine phosphorylated upon receptor activation, allowing the STAT in question to translocate into the nucleus.
and bind to DNA to induce transcription of target genes. Functional studies of the mutant STAT5B A630P protein indicated that the mutant protein was functionally null – unable to be phosphorylated by GH or activate GH-responsive genes.

The growth pattern, clinical features, and GH–IGF axis abnormalities of the patient described by Kofoed et al. are remarkably similar to those of subjects with GH receptor deficiency. She exhibited severe growth failure, which was mainly postnatal in origin (height SDS –7.5 at 16 years); and had the typical prominent forehead, small midface, and high pitched voice of GH deficient subjects. IGF-1 and IGFBP-3 levels were both extremely low and did not increase after exogenous GH administration. GH levels were extremely high after pharmacological stimulation (Table 1).

In addition to the above findings, all typical of classical GHI, the patient exhibited immunological problems, suggesting a defect in T cell immunity. She had recurrent pulmonary infections from an early age, including an episode of Pneumocystis carinii pneumonia, and a lung biopsy consistent with lymphoid interstitial pneumonia. She had also suffered several serious viral infections, including hemorrhagic varicella and herpes zoster. Detailed studies of her immune function indicated a defect in T cell regulation, most likely as a consequence of impaired IL-2 signaling, as STAT5B is also a key signaling molecule for the IL-2 receptor [13].

Five other patients with molecular defects in STAT5B have now been described (Table 1) [14–17]. All of these mutations are homozygous, resulting in a STAT5B molecule that is likely to be non-functional. The phenotypic features of these additional cases mirror those of the case initially described, with clinical and biochemical features

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<tr>
<td>STAT5B defect</td>
<td>A630P</td>
<td>1191insG</td>
<td>R152X</td>
<td>1103insG</td>
<td>1680delG</td>
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<td>Age (years)</td>
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<td>16</td>
<td>16</td>
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<td>F</td>
<td>M</td>
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<td>Argentina</td>
<td>Caribbean</td>
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<td>-7.5</td>
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<td>-9.9</td>
<td>-5.8</td>
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<td>-5.6</td>
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<td>Birth weight (kg)</td>
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<td>2.5</td>
<td>3.27</td>
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<td>NA</td>
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<td>Baseline IGF-1 (ng/mL)</td>
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<td>7</td>
<td>&lt;10</td>
<td>14</td>
<td>&lt;10</td>
<td>&lt;10</td>
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<td>Peak generated IGF-1 after 5–7-day GH course (ng/mL)</td>
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<td>NA</td>
<td>NA</td>
<td>78</td>
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<td>NA</td>
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<td>IGFBP-3 (ng/mL)</td>
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<td>543</td>
<td>NA</td>
<td>180</td>
<td>700</td>
<td>800</td>
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<td>Basal GH (ng/mL)</td>
<td>9.4</td>
<td>14.2</td>
<td>6.6</td>
<td>1.1</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Stimulated GH (ng/mL)</td>
<td>53.8</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Prolactin (ng/mL)</td>
<td>102</td>
<td>NA</td>
<td>169</td>
<td>110</td>
<td>NA</td>
<td>NA</td>
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<td>Medical history</td>
<td>Pulmonary infections, lymphoid interstitial pneumonia, recurrent herpes zoster</td>
<td>Pulmonary infections, pulmonary fibrosis, pruritic skin lesions</td>
<td>Pulmonary infections, pulmonary fibrosis, excema, recurrent herpetic keratitis</td>
<td>Delayed puberty, hemorrhagic varicella as an adult</td>
<td>Juvenile idiopathic arthritis</td>
<td>Pulmonary infections</td>
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</tbody>
</table>

F: female; GH: growth hormone; IGF-1: insulin-like growth factor-1; IGFBP-3: IGF binding protein-3; M: male; STAT5B: signal transducer and activator of transcription Sb; Na: not available; NASH: non-alcoholic steatotic hepatitis; SDS: standard deviation score.
characteristic of GH receptor deficiency. All patients had problems suggestive of immune dysregulation, but of a diverse nature. Recurrent pulmonary infections and chronic lung disease were most common, but in one case juvenile idiopathic arthritis was the only immunologic presentation. Another subject had experienced no immunological issues as a child but developed hemorrhagic chicken pox as an adult. Interestingly, prolactin levels were mildly elevated in those patients in whom it was measured; this may reflect mild prolactin resistance as the prolactin receptor also signals through the STAT pathway.

**ALS deficiency**

ALS deficiency is the most recently reported cause of genetic GH insensitivity. ALS is a GH-dependent glycoprotein that stabilizes the IGF–IGFBP-3 complex, forming a ternary complex within the circulation. This 150-kD complex reduces the passage of IGF-1 to the extravascular compartment and extends its half life. Thus, ALS is important for maintaining circulating IGF-1 levels but does not influence local IGF-1 production. In 2004, the first case of human ALS deficiency was described in an Argentinean male [18]. This patient had a homozygous frameshift mutation of ALS (1338delG), encoding a severely truncated ALS protein that is likely to be non-functional. His circulating ALS levels were undetectable, and biochemical evaluation was consistent with severe GHI, with extremely low levels of IGF-1 and IGFBP-3, elevated GH secretion, and no increase in IGF-1 or IGFBP-3 levels after exogenous GH administration (Table 2). However, this patient had a much milder degree of short stature than would be expected for a patient with such low IGF levels (only 2.05 SD below the mean at 14.6 years of age). Furthermore, by the time he had finished growing, his adult height was within the normal range (height SDS –0.78) [19]. Other abnormalities reported included delayed puberty and insulin resistance, presumably as a consequence of elevated circulating GH levels.

There have now been a further eight cases of ALS deficiency reported in the literature (Table 2) [20–22]. All were associated with undetectable ALS levels, and extremely low levels of IGF-1 and IGFBP-3. The heights of reported cases range from adult statures just below normal (final height SDS –0.5) to more significant growth retardation (height SDS –3.17). Laboratory evidence of insulin resistance (as evidenced by elevated fasting insulin levels) has been found in several cases. One subject developed non-alcoholic steatotic hepatitis when receiving GH therapy, possibly reflecting an underlying insulin resistant phenotype exacerbated by the anti-insulin effects of GH. No patient demonstrated elevated glucose levels. Several subjects showed no response to GH therapy, in terms of either growth or acceleration in height velocity.

The profound reduction in circulating IGF-1 and IGFBP-3 levels seen in these cases appears to underscore the importance of ALS for maintaining IGF-1 in the circulation. It is intriguing that subjects with such low IGF levels can reach adult statures that are, in some cases, within normal limits. A similar phenotype is seen in the mouse model of ALS deficiency; inactivation of the murine Als results in severe reduction in circulating IGF-1 and IGFBP-3 levels (to 33% and 22% of wild type, respectively) yet only a minor effect on growth (adult weight 87% of wild type) [23]. This could be explained by a compensatory effect of local IGF-1 production, which should not be impaired by lack of circulating IGF-1, and may well be increased as a consequence of the elevated GH secretion seen in ALS deficiency.

**Conclusion**

In recent years, the known causes of genetic GHI have broadened beyond molecular defects in the GH receptor gene, to include defects in the IGF-1 gene, the GH signaling pathway, and IGF carrier proteins. Detailed phenotypic evaluation of affected patients has resulted in important insights into the functioning of the GH–IGF-1 axis, in particular the role of GH and IGF-1 in pre- and postnatal growth. In the future, further genetic defects in this pathway are likely to be identified. For the
Table 2. Details of the nine identified cases of ALS mutation associated with GH insensitivity. In all cases the identified mutation was homozygous or presumed compound heterozygous.

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<tbody>
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<td>ALS defect</td>
<td>1338delG</td>
<td>D440N</td>
<td>C540R/583_591dup9</td>
<td>1308_1316dup9</td>
<td>C605/L244F</td>
<td>L134Q</td>
<td>P73L/L241P</td>
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<tr>
<td>Age (years)</td>
<td>14.6</td>
<td>12.1</td>
<td>15.3</td>
<td>19.6</td>
<td>15.4</td>
<td>6.7</td>
<td>4.1</td>
<td>15.2</td>
<td>12.7</td>
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<td>M</td>
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<td>F</td>
<td>M</td>
<td>M</td>
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<td>Turkey</td>
<td>Norwegian/German</td>
<td>Mayan</td>
<td>Eastern European</td>
<td>Indian/Pakistani</td>
<td>Ashenazi Jewish</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (SDS)</td>
<td>-2.05 at 14.6 years, -0.78 at final height (21.2 years)</td>
<td>-2.9 at 12.1 years; -2.1 at final height (15.5 years)</td>
<td>-2.0 at 15.3 years; -0.5 at final height</td>
<td>-0.5</td>
<td>-1.0</td>
<td>-2.8</td>
<td>-2.14</td>
<td>-3.17</td>
<td>-2.87</td>
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<td>Birth weight (kg)</td>
<td>2.5 at 1 week</td>
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<td>NA</td>
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<td>NA</td>
<td>NA</td>
<td>2.38</td>
<td>2.94</td>
<td>3.54</td>
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<tr>
<td>ALS (mg/L)</td>
<td>ND</td>
<td>&lt;0.4</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td>Baseline IGF-1 (ng/mL)</td>
<td>31</td>
<td>38</td>
<td>10</td>
<td>14</td>
<td>49</td>
<td>13</td>
<td>37.4</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Peak generated IGF-1 (ng/mL) after 5–7 day GH course</td>
<td>39</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>38.2</td>
<td>45</td>
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<tr>
<td>IGFBP-3 (ng/mL)</td>
<td>220</td>
<td>449</td>
<td>390</td>
<td>380</td>
<td>430</td>
<td>390</td>
<td>300</td>
<td>500</td>
<td>400</td>
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<td>Basal GH (ng/mL)</td>
<td>4.5</td>
<td>3.7</td>
<td>6.8</td>
<td>0.19</td>
<td>0.59</td>
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<tr>
<td>Peak stimulated GH (ng/mL)</td>
<td>31</td>
<td>70.3</td>
<td>10</td>
<td>NA</td>
<td>NA</td>
<td>25.5</td>
<td>16.2</td>
<td>64.5</td>
<td>63</td>
</tr>
<tr>
<td>Puberty</td>
<td>Mild delay, onset 14 years</td>
<td>Mild delay, onset 13 years</td>
<td>Delayed, onset 16.5 years</td>
<td>Delayed, onset 13 years</td>
<td>Normal; menarche 13 years</td>
<td>Normal to early; onset 10.5 years</td>
<td>Delayed; prepubertal at 15.2 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
<td>Adopted at birth</td>
<td>Learning disabilities, mild speech disorder</td>
<td></td>
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</tr>
</tbody>
</table>

ALS: acid labile subunit; F: female; GH: growth hormone; IGF-1: insulin-like growth factor-1; IGFBP-3: IGF binding protein-3; M: males; NA: not available; NASH: non-alcoholic steatotic hepatitis; ND: not detected; SDS: standard deviation score.
practicing clinician, these cases underline the importance of careful clinical and biochemical analysis of subjects with low IGF-1 levels and normal GH secretion, particularly those subjects with profound reductions in growth or IGF-1 levels, or a poor response to a trial of GH therapy. In such subjects, a history of recurrent infections may point to a STAT5B defect, whereas low birth weight, sensorineural deafness, and mental retardation may suggest a defect in IGF-1. Measurement of GHBP and ALS levels may provide useful additional information. At present commercial testing for such genetic defects is not available. However, several research laboratories, both in the UK and the US, may offer genetic analysis of candidate genes in such subjects.

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References
Insulin-like growth factors, their binding proteins, and prostate cancer risk: analysis of individual patient data from 12 prospective studies.

Editor’s note: A number of studies have reported an association between circulating serum levels of insulin-like growth factors (IGFs) and their binding proteins (IGFBPs) and the subsequent risk for prostate cancer. However, many of these studies were not large enough to allow proper adjustment to observe subgroups such as stage and grade of the prostate cancer.

The authors of the present article analyzed data from 12 prospective studies, looking specifically at the effect of high levels of IGF-1 and IGFBPs on prostate cancer risk. A total of 3700 men with prostate cancer, as well as 5200 controls, took part in the study.

The data showed that the risk for prostate cancer increased as the IGF-1 level increased (based on division of the IGF-1 into quintiles). The odds ratio comparing the highest quintile of IGF-1 versus the lowest was 1.38. IGF-2 and its binding protein were not associated with prostate cancer risk. IGFBP-III was correlated, but only from its association with IGF-1 levels. IGF-1 concentration seemed to be more positively associated with low grade prostate cancer, but IGF-2 and the IGFBPs had no statistical correlation.

There are a number of limitations that are highlighted in this study. For example, each patient typically had only one IGF-1 measurement, and given that the data came from 12 studies, the methods for measuring the IGFs will have varied.

The authors conclude by emphasizing the need for identifying modifiable risk factors of prostate cancer and, on the basis of their results and the fact the IFG-1 is modifiable by lifestyle and dietary changes, suggest that IGF-1 is a possible candidate.

Insulin, insulin-like growth factors, and neoplasia.

Editor’s note: There have been many epidemiological studies and some mechanistic studies showing evidence for relationships between insulin-like growth factors (IGF) and neoplasia.

In the present article, the author gives a breakdown of these studies in terms of epidemiology and mechanism.

Insulin-like signaling pathways are well known for roles in cell proliferation, lifespan, and metabolism. IGF-1 receptors are distributed in normal and malignant tissues. Often, neoplastic tissues produce IGF-1 and/or IGF-2 locally, in an autocrine or paracrine manner. This provides a source of these ligands, other than that produced in an endocrine fashion by the liver.

IGF-1 receptor targeting strategies were first proposed over 20 years ago, when IGF-1 receptors were detected on human cancers.

From population studies, the author refers to early rigorous, prospective studies providing evidence of a relationship between
circulating IGF-1 levels and cancer risk, specifically to prostate, breast, and colorectal, as well as other cancers. In these studies the risk of cancer diagnosis was double in those at the high end of normal range of IGF-1 compared with those at the lower end. The author then briefly reviews plausible mechanisms on the cellular level to explain this observation.

Separate from risk, there is evidence that IGF-1 influences the prognosis of cancer, with measures of hyperinsulinemia such as C-peptide and fasting insulin levels cited as being associated with poorer outcome; IFG-1 levels, however, are less significant in terms of prognosis.

Pollak comments that, while there is no obvious prevention strategy to offer those with IGF-1 levels in the high-normal range, the risk associated with having high-normal (compared with low-normal) IGF-1 is significantly less than those associated inherited cancer predisposition syndromes or smoking. The author discusses some pharmaceutical avenues that are in development, such as anti-ligand and anti-receptor antibodies.

Pituitary Prevalence of GH and other anterior pituitary hormone deficiencies in adults with nonsecreting pituitary microadenomas and normal serum IGF-1 levels.

Editor’s note: The prevalence of clinically non-functioning pituitary lesions, as demonstrated by autopsy studies, range from 1.5 to 27%. With the use of imaging modalities such as computer tomography and magnetic resonance imaging (MRI), incidental findings of pituitary masses are frequent. Tumors of <10 mm (microadenoma) are much more common than larger lesions. Some studies have found a high prevalence of growth hormone (GH) deficiency in patients with pituitary macroadenomas. From experience with cancer patients who have received cranial irradiation, GH is typically the first hormone to become deficient.

The authors objective was to study the prevalence of GH deficiency in those with a non-secreting pituitary microadenoma and normal levels of serum insulin-like growth factor-1 (IGF-1).

In the present article, 54 patients (45 females, age 30–68 years) with pituitary microadenomas and no clinical/biochemical evidence of hormonal hypersecretion were identified from two academic centers. Of those initially identified, 38 patients with non-secreting pituitary microadenomas (mean size 4.2 mm) and normal IGF-1 levels (i.e. levels within the age appropriate normal reference range [IGF standard deviation score between –1 and 2]) were studied. Anterior pituitary function tests, including GH releasing hormone (GHRH)-arginine testing, were performed in all patients. GH deficiency was defined by GH peak ≤11 µg/L in lean subjects, ≤8 µg/L in overweight subjects, and <4 µg/L in obese subjects (body mass index [BMI] >30 kg/m²). GH responses were compared with 22 healthy controls matched for age and BMI. IGF-1 measurements were measured from blood samples taken after 10 h fasting at 8.30–9.00 am.

Of the 38 patients studied, 21 (55%) had their microadenoma discovered as a result of an MRI scan performed for unrelated medical issues. The rest were discovered because of abnormal laboratory results suggesting underlying pituitary dysfunction.

A total of 19 patients (50%) were found to be GH-deficient. By separate analysis, 19 patients were deficient in other pituitary hormones (15 thyroid stimulating hormone (TSH) deficient, 10 follicle stimulating hormone/luteinizing hormone (FSH/LH) deficient, and one adrenocorticotropic...
hormone-deficient). There was a negative correlation between peak GH levels and BMI, and no correlation between peak GH levels and IGFBP-1, tumor size and IGFBP-1 levels, nor tumor size and peak GH after provocative stimulation. Those patients who were GH deficient were at higher risk for having a second pituitary hormone deficiency. However, five cases of TSH deficiency and three cases of LH/FSH deficiency were found in the GH sufficient group.

Although one can debate the normal levels after provocative GH testing, this study highlights the need to follow pituitary hormone integrity in those with non-secreting pituitary microadenomas regardless of whether they have normal IGFBP-1 levels.

The results showed that 50% had failed the GHRH-arginine test and had higher BMI compared with those who passed the provocative test and with healthy controls. There was no correlation between peak GH and serum IGFBP-1 levels. Several patients had at least one other pituitary hormone deficiency, showing that non-secreting pituitary tumors may not be clinically harmless. The authors recommend long-term follow-up with periodic basal pituitary function testing and the consideration of dynamic pituitary testing should clinical symptoms arise.

**Diagnostic usefulness of the growth hormone-releasing peptide-2 test as a substitute for the insulin tolerance test in hypopituitarism.**


Editor’s note: Patients with structural hypothalamic–pituitary abnormalities may have additional anterior pituitary hormone deficits and are at risk of developing complete or partial adrenocorticotropin hormone (ACTH) deficiency. Evaluation of the integrity of the hypothalamic–pituitary–adrenal (HPA) axis is essential in these patients because, although clinically asymptomatic, their HPA axis cannot appropriately react to stressful stimuli, with potentially life-threatening consequences.

The insulin tolerance test (ITT) has been the gold standard test for assessing the HPA axis, as well as growth hormone (GH) deficiency. The ITT has many limitations, including risk of serious hypoglycemia in patients with hypopituitarism. It is also contraindicated in patients with coronary or cerebrovascular disease, ischemic heart disease, and seizure disorder.

GH-releasing peptides (GHRP-2, hexarelin, and ghrelin) are very potent peptides that stimulate GH secretion from the pituitary gland by binding to a specific receptor. GHRPs also stimulate ACTH release. In the present study, the authors examined the usefulness of GHRP-2 test as an alternative to ITT for assessing the HPA axis. Nine patients with a history of hypopituitarism, nonfunctional pituitary adenoma, ACTH deficiency, and delayed puberty were included in this study. Single-dose corticotrophin-releasing hormone injection, ITT, and GHRP-2 tests were conducted on all patients. A significant response was defined as more than a two-fold increase in ACTH from basal level.

The results showed that patients who responded positively to the ITT also responded appropriately to the GHRP-2 test. Patients with ACTH deficiency did not respond to either the ITT or GHRP-2 test. These results indicate that the GHRP-2 test is as an alternative for assessing HPA axis, given its very minimal side effects and limitations compared with ITT. Clearly, standardization of the test is required, especially with regards to age, gender, and body mass index.

**Clinical insights into the safety and utility of the insulin tolerance test (ITT) in the assessment of the hypothalamo-pituitary-adrenal axis.**

Editor’s note: The insulin tolerance test (ITT) is considered be the gold standard for the assessment of patients with suspected adrenocorticotropic hormone (ACTH)-dependent hypocortisolism or GH deficiency. A normal cortisol response to hypoglycemia is predictive of a normal cortisol response to major abdominal surgery. Because of concerns of the safety of inducing hypoglycemia, especially in the elderly, many endocrinologists have used the short synacthen test as an alternative test to ITT. While ITT is safe in children and young adults, fatalities have occurred in very young children with structural abnormalities in the brain. Furthermore, the risk when using ITT in patients with a history of epilepsy, cardiac ischemia, or arrhythmias is increased, as hypoglycemia can aggravate these disorders. One issue that is, as yet, unresolved, is the optimal duration of ITT (90 or 120 min) in terms of capturing the peak cortisol response.

The authors studied a cross-sectional review of 197 patients who underwent ITT over an 18-month period. Patients with low thyroxine (T4) levels received T4 replacement prior to ITT. Following an overnight fast, an electrocardiogram was performed on all patients. Rapid insulin was administered intravenously at a dose of 0.15 units/kg. Those with type 2 diabetes were given 0.2 units/kg. Patients with a previously documented basal cortisol level of <100 nmol/L were given a lower insulin dosage of 0.1 units/kg. Blood samples were collected at –15, 0, 15, 30, 45, 60, 90, and 120 min after insulin was administered, where upon glucose and cortisol concentrations were measured.

Of the 197 patients who underwent ITT, 87% achieved the desired hypoglycemia (blood glucose levels <2.2 mmol/L or 40 mg/dL) while 17% did not achieve their peak cortisol until 120 min. There were no significant adverse events even in those >65 years of age. A total of 18 patients had previously documented basal cortisol of <100 nmol/L, 78% of whom achieved adequate hypoglycemia, of these patients 29% had an adequate peak cortisol level >500 nmol/L.

The authors concluded that ITT is safe in assessing the hypothalamo–pituitary–adrenal axis in elderly patients and in those with hypocortisolism. The standard 90 min cut-off for the ITT misses one in six peak cortisol responses, thus, a sampling test duration of 120 min would appear to be preferable.

Associations with multiple pituitary hormone deficiency in patients with an ectopic posterior pituitary gland.

Editor’s note: The presence of ectopic posterior pituitary gland (EPP), as defined by magnetic resonance imaging (MRI), is a marker of pituitary dysfunction and may be associated with an abnormal pituitary stalk as well as a small pituitary gland. Diabetes insipidus is not typically found in such patients, presumably due to the presence of functional vasopressin secreting cells in an ectopic position. EPP can be detected by MRI, found in the workup of a child with growth hormone (GH) deficiency, or found as part of an evaluation of someone with septo-optic dysplasia. The cause of EPP is not known.

The present authors studied 67 patients (45 male) with EPP upon MRI. A total of 32 patients had multiple pituitary hormone deficiency (MPHD), while 35 had isolated GH deficiency (IGHD). Patients with MPHD were younger at presentation compared with those patients with IGHD (1.4 vs. 4.0 years, respectively; p<0.005). In addition, patients with MPHD had a higher number of incidents during pregnancy compared with IGHD patients (47% vs. 20%, respectively), as well as admission to a neonatal intensive care unit (60% vs. 26%, respectively). In those where the EPP was located at the high level of the hypothalamus, the incidence of MPHD was 55% compared with 9% of those with stalk sited EPP, p<0.05. The incidence of MPHD was also higher when the calculated surface area of the pituitary was smaller.
The authors conclude that adverse factors during pregnancy may be important in the development of EPP. In addition, their study corroborates previous studies in that if the location of the bright spot is seen at the level of the hypothalamus, there tends to be a higher incidence of MPHD whereas if the bright spot is seen on the stalk, the incidence is lower and IGHD is the usual finding.

**Long-term basal and dynamic evaluation of hypothalamic-pituitary-adrenal (HPA) axis in acromegalic patients.**
Ronchi CL, Ferrante E, Rizzo E et al.
University of Milan, Milan, Italy.
Clin Endocrinol (Oxf) 2008;69:608-12.

Editor’s note: In the majority of acromegaly patients, hypopituitarism is a well known long-term side effect of radiation treatment. There are limited data available concerning the hypothalamic–pituitary–adrenal (HPA) axis in acromegalic patients who have been treated with trans-naso-sphenoidal surgery (TNS) or with somatostatin analogues (SSA) as a primary medical therapy.

This retrospective study investigated 36 acromegalic patients with pituitary adenoma. The cure was defined by “safe” growth hormone (GH) levels and normal levels of insulin-like growth factor-1 relative to the patient’s age. The 20 patients who underwent TNS were cured, while the acromegaly in the 16 patients receiving SSAs was controlled (12 of these patients had previously undergone TNS). None of the patients in this study had previously received radiotherapy. HPA axis function was assessed by measuring baseline cortisol and adrenocorticotropic hormone (ACTH) levels, 24-h urinary free cortisol and cortisol response to low-dose short synacthen test (LDSST). The function of the HPA axis was assessed at various stages during long-term follow up (median 72 months, range of 12–240 months).

The results demonstrated normal morning cortisol, ACTH, and 24-h urinary cortisol levels. The LDSST showed that 12 patients developed biochemical hypoadrenalism. Patients who were treated with SSA as a primary medical therapy did not develop adrenal insufficiency. The patients who developed hypoadrenalism did not display any correlation in terms of duration of disease, functional GH axis, or any other pituitary hormone abnormality. It is not clear what mechanism may be responsible for the apparent lack of impact of SSA on HPA axis (i.e. it is unclear whether SSA selectively act on GH only).

Hypoadrenalism may have severe consequences if not treated, especially when the patient is under stress (surgical or otherwise). Since no correlation has been observed in these patients in terms of HPA axis deterioration and follow-up duration, the authors conclude that the function of the HPA axis should be subject to careful monitoring in the long-term, regardless of the type of treatment the patient has received.

**A critical analysis of clinically available somatostatin analog formulations for therapy of acromegaly.**
Murray RD, Melmed S.
Leeds Teaching Hospitals National Health Service Trust, Leeds, UK.
J Clin Endocrinol Metab 2008;93:2957–68.

Editors note: Short- and long-acting somatostatin (SRIF) analogues are the mainstay of primary medical therapy for acromegaly. Growth hormone (GH) receptor agonists can be used alongside somatostatin analogues or as a second line of therapy. Biochemical control of acromegaly is achievable with these agents. Over many years, different formulations of somatostatin analogues have become available, and have been approved for the use in the treatment of acromegaly. A novel aqueous formulation of lanreotide – lanreotide Autogel (ATG) – has recently been approved in the US and is the predominant formulation of lanreotide used clinically.

These authors provide a critical analysis of the relative efficacy of three clinically available SRIFs – octreotide LAR, lanreotide SR, and lanreotide ATG – for the treatment of acromegaly. Using MEDLINE and the
The conclusion from this review is that there is no significant difference in biochemical efficacy (i.e. the lowering of GH and insulin-like growth factor-1 levels) between these two agents. Thus, the authors conclude that in terms of controlling the symptoms of acromegaly, the two agents can be considered equivalent. However, octreotide LAR has to be given by deep intramuscular injection and needs special preparation for injection, whereas lantreotide ATG can be administered subcutaneously.

SGA Children

Safety and efficacy of growth hormone treatment in small for gestational age children.
Poduval A, Saenger P.
Albert Einstein College of Medicine, Bronx, NY, USA.

Editor’s note: In the present study, the authors review information and guidelines concerning the use of growth hormone (GH) in the treatment of children born small for gestational age (SGA). They discuss how endocrine workup of SGA children prior to treatment should include ruling out other causes of poor growth, such as nutritional deficiency, renal disease, thyroid disease, emotional deprivation, and syndromes such as Bloom syndrome (a rare, autosomal condition characterized by short stature, distinctive facial features, appearance of a facial rash upon exposure to sun, and a high risk of developing cancers).

While classic GH deficiency is uncommon in the SGA population, insulin-like growth factor-1 (IGF-1) and IGF-binding protein-3 (IGFBP-3) levels are reduced by approximately 1 standard deviation (SD) in such patients. However, the range of levels seen in SGA patients suggests that the mechanisms for growth failure may have multiple origins.

The dosing of GH is an important predictor of the response to therapy. Those who received a dosage of 0.48 mg/kg/week for 10 years elicit a gain in adult height of 0.4 SD more than those who received a dosage of 0.22 mg/kg/week.

Prior to therapy, fasting glucose, insulin, lipid, IGF-1, and IGFBP-3 levels should be measured. With treatment, IGF-1 levels will rise often with at least a doubling from baseline after approximately 3 months from initiation of therapy.

GH improves body composition, blood pressure, and lipid metabolism. Body mass index was lower than average and increased with GH therapy. Muscle mass improved, though fat mass remained the same in a study of 14 children treated with GH.

Bone age may be normal or delayed in those born SGA. Therapy with GH will be met with some acceleration of bone age. Bone age is a poor predictor of pubertal timing and adult height in those born SGA. The authors therefore do not recommend monitoring the bone age with treatment (although many insurance companies may require an annual bone age, especially during the pubertal years).

Given the known association of insulin resistance and those born SGA, it is important to follow carbohydrate metabolism in patients annually and family history of type 2 diabetes should be elicited. The majority of prepubertal children who are SGA are not at risk for glucose intolerance.

The authors discuss issues concerning the safety of GH therapy, highlighting that there is no evidence for an association with risk of malignancy. However, as with GH deficient children treated with GH, there is a risk of
benign intracranial hypertension. Overall, GH therapy is well tolerated in those born SGA who do not achieve catch-up growth by 2–3 years of age.

**Growth hormone treatment for short stature in children born small for gestational age.**


**Editor’s note:** Growth hormone (GH) therapy has been approved for use in children born small for gestational (SGA) age in both the USA and Europe. This excellent review provides a clear and extensive definition of SGA, as well as sections on treatment and dosing guidelines, and safety and monitoring data of GH therapy for short stature in children born with SGA. Further sections concerning psychological, social, and academic problems associated with GH therapy provide an excellent reference point for pediatricians and endocrinologists alike.

**Thyroid function in short children born small-for-gestational age (SGA) before and during GH treatment.**


**Editor’s note:** Normal thyroid function is crucial for healthy pre- and postnatal development. Severe hypothyroidism may lead to mental retardation at birth and short stature in childhood. Thyroid hormone replacement therapy can lead to catch-up growth in children, although this catch-up is rarely complete.

Thyroid function has been reported to be variable in children who are small for gestational age (SGA), and its impact on ultimate height is unclear in SGA children undergoing growth hormone (GH) therapy. The authors investigated whether GH treatment alters thyroid functions in 264 children born SGA. A total of 145 males and 119 female children (mean age of 7.39 years) were treated with GH injections of 1µg/m²/day. The children were assessed at baseline and at 6, 12, and 24 months post-GH therapy for height, weight, body mass index, thyroid-stimulating hormone (TSH), free thyroxine (FT4), insulin-like growth factor-1 (IGF-1), and IGF-binding protein-3 levels.

Baseline TSH was significantly higher in preterm SGA children compared with normal control subjects. TSH levels did not change significantly during therapy and even higher levels did not correlate with gestational age, height standard deviation score, or any biochemical marker. FT4 levels declined during the first 6 months of therapy, but remained within the normal range. During treatment, none of the children developed overt hypothyroidism. This study suggests that no significant alteration in the thyroid axis of GH-treated SGA children occur, and that there is no need for aggressive monitoring of thyroid functions during GH therapy in such children.

**Muscle function improves during growth hormone therapy in short children born small for gestational age: results of a peripheral quantitative computed tomography study on body composition.**


**Editor’s note:** The recently granted European Medicines Agency license for the treatment of short 4-year old children who were underweight at birth has introduced an enormous amount of new data on treating such children with growth hormone (GH). The greatest conundrum has been to establish whether such children are just small for gestational age, small as a consequence of a twin pregnancy, or small for some other medical or pregnancy-related reason. Nonetheless, similarly small children may all potentially benefit from GH treatment.

The jury will be out for the next few years, trying to absorb the real benefit of GH treatment in these children – medically,
auxologically (real growth centile benefit), and economically – until the UK National Center of Clinical Excellence is able to reach a verdict. The results of the present study, which concern the body composition and functional muscle status of 34 prepubertal, short children, suggest increased performance parameters in this group of children after GH treatment (increases in height, muscle mass, and function, and a reduction in fat mass). The authors recognize that these results were achieved with supraphysiological doses of GH (57 µg/kg/day), and in the wider context those involved in the care of such patients should be considering just how appropriate “routine” supplementation with GH actually is.

**Longitudinal changes in insulin sensitivity and body composition of small-for-gestational-age adolescents after cessation of growth hormone treatment.**


**Editor’s note:** Dr Hokken-Koelega and colleagues have taken advantage of a unique opportunity in the last decade, monitoring the progress of 48 small for gestational age (SGA) children and a control population of 38 appropriate for gestational age (AGA) children. The two cohorts were age- and sex-matched. Those who were SGA received growth hormone (GH) therapy, while AGA children received no treatment. Using the intravenous glucose tolerance test, the authors measured changes in Si-and β-cell function in response to GH treatment. Body composition was also measured using dual-energy X-ray absorptiometry. Measurements were taken when the patient had reached near-final adult height (whilst still receiving GH), and at 6 months after stopping therapy.

This article is reassuring, in that the early and sustained changes of increased insulin resistance that were apparent in the SGA children treated with GH showed evidence of resolution after discontinuation of GH treatment. Furthermore, body composition changes with respect to reduced fat percentage and increased lean muscle mass showed evidence of return towards the levels of normal controls. Fat (anatomical) distribution was not altered compared with controls with the relative change in body total percentage.

It will clearly take another 2–4 decades of surveillance of treated cohorts of patients such as this one to determine the long-term impact of GH treatment on risk factors.

**GH Treatment**

**Growth hormone responsiveness: peak stimulated growth hormone levels and other variables in idiopathic short stature (ISS): data from the National Cooperative Growth Study.**


**Editor’s note:** The present article concerns the National Cooperative Growth Study, which was established in North America by Genentech (San Francisco, CA, USA) in 1985 as a post-marketing surveillance study. While suffering from a lack of depth in terms of data provision, the article nonetheless offers an intriguing insight into the benefit of GH therapy as well as possible diagnostic categories for children labeled as having idiopathic short stature (ISS). The purpose was to examine the relationship between pre-treatment peak growth hormone (GH) stimulation test results and subsequent first year growth velocity on GH treatment, with respect to the usual variables that are likely to influence growth response. The particular focus was on dividing the children into three pre-treatment assessment groups with respect
to their peak GH levels on stimulation test: >10–25, 25–40, and >40 ng/mL (µ/L).

The authors hypothesized that children with higher stimulated GH levels would have lower first year increments in growth velocity, indicating a subgroup of children with relative GH resistance (i.e. children perceived as having primary insulin-like growth factor-1 deficiency, but not conforming to the classical phenotype recognized as GH insensitivity syndrome/Laron dwarfism). This hypothesis has been studied in similar formats in many individual units worldwide. However, the present study benefits from the large combined total population of subjects: 2309 patients with a peak GH level of 10 to <25 ng/mL; 262 patients with peak GH level of 25 to <40 ng/mL; and 63 patients with peak GH level of >40 ng/mL. Remarkably, the baseline and 1 year treatment growth velocities were not significantly different between these groups, ranging 4.4–4.5 cm/year and 8.2–8.7 cm/year, respectively. It is worth comparing these data with European data reported by Ranke et al. (Horm Res 2007;68:53–62), which show that the first year growth response was related not only to younger age at GH initiation (as in this report) but also to starting dosage.

Clearly, grouped data such as these can not reveal any unique patient characteristics that might unmask the few patients with specific GH receptor signaling problems. Individual clinicians will need to seek phenotypic, growth response, and biochemical data to select the few patients harboring definable single gene defects in GH responsiveness.

**Long-term GH treatment improves adult height in children with Noonan syndrome with and without mutations in protein tyrosine phosphatase, non-receptor-type 11.**


Editor’s note: The authors of the present study report a series of 27 Noonan syndrome patients treated with growth hormone (GH) from a mean age of 11 years until final height. The average GH treatment dose was 0.05 mg/kg/day, representing a dose mid-range between the standard dose GH replacement and the supraphysiological doses of close to 0.05–0.07 µg/day given to some Turner syndrome patients or small for gestational age children. It has been hypothesized – as discussed in the present article – that Noonan syndrome children might need higher than standard replacement doses of GH because of relative resistance to GH resulting from a tyrosine phosphatase non-receptor type II protein (PTPN11) mutation associated with impaired post-GH receptor signaling. Hence, in this study the authors compared the growth responses of patients with and without a proven mutation in this gene.

There was no difference in the final height achieved by the 22 children with mutant PTPN11 compared with the five children with the normal gene. Average height gain was only a modest +1.3 standard deviation score – approximately 8 cm in real terms. This is well worth discussion with respect to lifetime benefit. Patient numbers were small in the study and the authors emphasize the need for larger patient samples before conclusions regarding the safety of GH treatment in Noonan syndrome can be drawn. The genetics underlying this syndrome are highly complex and may yet reveal common growth-disorder pathways linked to the major clinical phenotype.

**Growth hormone treatment in short children with chronic kidney disease.**


Editor’s note: This review presents a refreshing update on the role of growth hormone (GH) treatment in children with chronic renal insufficiency. The authors address the mechanisms underlying GH resistance as a specific result of compromised renal metabolism within the domain of insulin-like growth factor-1 and its binding proteins, set alongside the careful clinical
management of protein restriction balanced against adequate calorie nutrition. The treatment of these children has clearly entailed a fine balance of multidiscipline management over nearly 20 years since GH was first introduced to pediatric renal physicians as a treatment option to improve their patients' health beyond simply improving renal metabolism, with improvements in both body composition and growth to final height.

Perhaps unsurprisingly, the earlier GH treatment is instituted, the better the long term outcome in those patients suffering from chronic kidney disease, as is the case with GH replacement in hypopituitarism or isolated GH deficiency. The adverse event profile is a reassuring aspect of this report; to date, this is similar to that of patients receiving GH therapy for non-renal failure indications. The greatest concern remains that GH treatment may exert some adverse effect on immunomodulation, which could impact on the prevalence of renal transplant rejection. This must remain a point of observation for clinicians who work with children of short stature who have undergone liver transplantation. In such cases, a catastrophic liver rejection event may not be amenable to a repeat organ transplant compared with those children with renal disorders who can revert to dialysis in the interim.

**PEGylation of somatropin (recombinant human growth hormone): impact on its clearance in humans.**


Editor’s note: There is a widespread commercial wish to introduce a growth hormone (GH) preparation with extended pharmacokinetic properties that will reduce the frequency of injection from daily or three times per week to once-weekly or less. This article documents one attempt – based on polyethylene glycol modification (PEGylation) of GH – to achieve a 10–20-fold increase in clearance time for somatropin. This is practically the same technique applied to the development of PEGvisomant as an enhanced antibody inhibitor of GH receptor activation, used in the the control of acromegaly. To date, the problems have been related to product hypersensitivity, volume of injected medium, appropriate needle size for injection of the preparation, and reliance on normal renal function to facilitate this process as a whole. This article is essentially one of the technical publications leading towards the potential objective.

**Obstacles to the prescribing of growth hormone in children with chronic kidney disease.**


Editor’s note: Chronic kidney disease (CKD) in children is associated with significant growth retardation. Growth hormone (GH) has been approved for use in children with CKD, and has been proven to be safe and efficacious. Compliance is a major factor in any chronic medical condition, especially in children of short stature who require daily injections.

In this study, the authors investigated the factors affecting GH use in children with CKD, reviewing data on 307 children from seven different clinical centers, among whom 110 were at a height below fifth percentile. A total of 54 (49%) had received GH and 56 (51%) had not. In addition to factors determining compliance, the authors evaluated treatment efficacy and increase in height in those children treated with GH compared with those who were not.

The results showed that among those patients with heights below the fifth percentile, boys were more than twice likely to receive GH than girls. The authors also observed a number of reasons as to the lack of GH prescription in the 56 patients with a height below the fifth percentile. These included psychosocial factors such as family refusal or non-adherence (30%)
and hyperparathyroidism (16%). Fourteen children (25%) had no apparent identifiable reason, and 7% of children were deemed too young for treatment. In those children who had received GH, there was a significant increase in height standard deviation score, compared with those who had not received GH (+0.5 vs. +0.03, respectively). The authors note that patients were not randomized in this study and, given that secondary hyperparathyroidism and adherence were common reasons for patients not receiving GH, this comparison is somewhat limited.

In their conclusion, the authors highlight the fact that, despite the benefits of increase height, >50% of children did not receive GH, and that although in some patients there are accepted contraindications (e.g. hyperparathyroidism), the improved education of patients’ families and GH providers should go some way to reducing the number of patients in whom there is no identifiable reason for not prescribing/using GH.

The main limitation to this study was that patient records from just seven centers were used. This may highlight differing prescribing habits between centers more so than studies that include more centers. It was also difficult to understand the factors that caused the 193 children below the fifth percentile of height, to not receive GH therapy. However, the benefits, safety, and efficacy of GH therapy in children with CKD dictate the requirement for open and informal discussion with parents, and the need to alleviate fears among the parents and children.

### Miscellaneous

**Homozygous and heterozygous expression of a novel mutation of the acid-labile subunit.**

van Duyvenvoorde HA, Kempers MJ, Twickler TB et al.

Leiden University Medical Center, Leiden, The Netherlands.


Editor’s note: Over the last 20 years, the development of phenotype association with particular genotypes (i.e. single gene abnormalities/mutations) has proven a fascinating introduction to previously unrecognized clinical features arising from specific gene abnormalities. This article is a clear example of new phenotype–genotype information.

The recognition in early reports that mutations in the acid labile subunit (*ALS*) gene are associated with short stature/delayed puberty, somewhat similar to constitutional delay, suggested that these abnormalities may prove to be widespread within the population. We are still in the early days of investigating this association, as the costs and availability of the tests are limiting. The authors of this report investigated three brothers with short stature and pubertal delay and revealed a mutation in the *ALS* gene inherited from parents, which may account for their growth pattern.

Perhaps more significantly, they also identified an association between this mutation and reduced head circumference, which might infer a reduced intelligence quotient as well as the possibility of mild insulin resistance in this population. These observations highlight the need to start increasing our genetic investigations into conditions perceived as normal variants with the support of clinical geneticists, who are increasingly in a position to examine for more subtle genetic disorders.

**Frequency and characteristics of TBII-seronegative patients in a population with untreated Graves’ hyperthyroidism: a prospective study.**

Vos XG, Smit N, Endert E et al.

University of Amsterdam, Amsterdam, The Netherlands.


Editor’s note: Graves’ hyperthyroidism is caused by thyrotropin receptor (TSH-R)-
activating antibodies, which bind to and activate TSH-R on thyroid epithelial cells. Assays of TSH-R antibodies have improved over recent years. In 1982, Shewring and Smith measured the ability of the antibodies to inhibit the binding of radiolabeled thyroid-stimulating hormone (TSH) to porcine thyroid membrane extracts (thyrotropin-binding inhibitory immunoglobulin [TBII]) (Clin Endocrinol (Oxf) 1982;17:409–17). The reported sensitivity of this test to make a diagnosis of Graves’ disease is 70–90%. Since 2000, a second generation assay has become available, which uses recombinant human TSH receptors instead of porcine TSH receptors (J Clin Endocrinol Metab 1999;84:90–7). Studies of this assay have shown a sensitivity of 91–98% in diagnosing Graves’ disease, though they are mostly retrospective and often with patients already on antithyroid treatment.

In the present article, the authors performed a multicenter, observational study of 259 consecutive patients newly diagnosed with Graves’ disease. The levels of second generation TBII were correlated with thyroid function and clinical characteristics.

TBII was positive in 94.6% of patients and negative in 5.4%. TBII-negative patients with Graves’ disease had significantly lower thyroxine (T4), iodothyronine (T3), and free T3 (fT3) index. None of the TBII-negative patients had a TSH receptor-activating mutation or exophthalmos. Serum TBII levels were positively correlated to T4 index and fT4 indices, goiter size, and the presence of Graves’ orbitopathy. No differences in environmental factors in the two groups were discovered and there was no difference between the two groups in terms of levels of TSH, T4, fT4-index, and thyroid peroxidase-antibodies.

The size of the goiter, and the level of fT4 and fT3 index correlated with the degree of elevation of TBII. None of the seronegative patients had eye disease, whereas 20% of the seropositive group had orbitopathy. There was no correlation with gender.

In summary, TBII-negative patients presented with less severe thyrotoxicosis. However, a lack of TBII does not rule out clinical Graves’ disease.

Growth hormone responses to 3 different exercise bouts in 18- to 25- and 40- to 50-year-old men.


Editor’s note: Growth hormone (GH) release is affected by exercise and ageing. While ageing blunts GH release, exercise has a potent stimulatory effect. The magnitude of the GH response to exercise varies according to the type, intensity, and duration of exercise, as well as factors such as age, gender, and body type. Currently, data in the literature are variable in terms of the effects of the exercise type, its duration, and inter-subject variability. To minimize these variations, the authors of the present study investigated the effects of three different exercise bouts amongst men of two age-groups on GH response. Eight men aged 18–25 years and eight men aged 40–50 years completed three trials, at least 7 days apart, in a random order. The exercise bouts consisted of a 30-s cycle-ergometer sprint, a 30-min resistance exercise bout, and a 30-min cycle at 70% maximal oxygen consumption (endurance). All subjects fasted the night before the trial, maintained a consistent diet 48 h before each exercise bout, and consumed no alcohol in the 24 h before exercise. Blood samples were taken before, during, and after exercise, and area under the curve (AUC) for GH versus time was calculated for a total of 120 min.

While GH versus time AUC was higher in the younger group, the resting GH concentrations were similar in both groups. Likewise, in the younger group, the GH response was significantly higher than in the early middle-age group subjects in all three modes of exercises. Endurance elicited a greater GH response than sprint or resistance exercise. This indicates that while exercise induces an increase in GH release, the mode and duration of exercise can have a different impact. The early middle-age group did attain
an increase in GH release in the endurance type of exercise, although this was still lower than that of the younger group. This suggests that the older population may need to increase the exercise duration to achieve the so-called positive benefits of GH in terms of ageing and overall health benefits.

Scoliosis in patients with Prader-Willi Syndrome.

Editor’s note: For many years Scoliosis has been recognized as a natural feature of the full spectrum of disorders associated with Prader–Willi Syndrome (PWS). Understandably, the possible exacerbation of scoliosis during growth hormone (GH) treatment has always been considered a relevant risk. Hopefully, most pediatric endocrine units work in close harmony with their respective orthopedic services to monitor and manage any spinal problem specific to their patients, in the same way that they should work with the ear, nose, and throat units with respect to overnight sleep disorders and upper airway sleep obstruction. Individual experience within this field is likely to be limited, so it is a welcome response to see the multidiscipline trans-continental unit collaboration that generates this report. This editor’s own unit supports nearly 30 patients with PWS – mostly under the age of 10 years – so a prospective insight such as this creates much hope for the future.

The present authors report on 145 children who were followed between 1980 and 2006 across just two referral centers. As GH is a treatment option that has been introduced relatively recently, only 64% of patients received it during the course of the study.

A total of 63 patients (43%, mean age 10.2±6 years) had scoliosis. By skeletal maturity approximately 67% had scoliosis, but this was not related to diagnostic genotype or history of GH treatment. Perhaps unsurprisingly, patients with a higher body mass index had an increased risk of developing kyphotic deformity together with scoliosis. Kyphosis was significantly associated with the need for spinal surgery.

Overall, there was no evidence that GH treatment influenced the need for surgical interventions for spinal deformities. Nonetheless, there remains a clear need for close collaboration between pediatric endocrinologists and their PWS patients’ orthopedic surgeons.

Heterozygous mutation of HESX1 causing hypopituitarism and multiple anatomical malformations without features of septo-optic dysplasia.

Editor’s note: The HESX1 gene was among the new generation of transcription factors associated with developmental pituitary defects following the early characterization of Pit-1 and POUF-1, associated with previously recognized models of congenital hypopituitarism. The mouse transgenic equivalent of HESX1 knockout/mutations has such a strong phenotype that we have expected to find more human cases than are hitherto reported in the literature.

This particular case report brings the realization that the variance in phenotypic expression of gene mutations will continue to test clinicians attempting to match molecular defects with specific phenotypes. The authors report a case of proven HESX1 heterozygous mutation with a classic clinical picture of congenital hypopituitarism, but lacking the midline/optic nerve pathway pathology expected in the typical septo-optic dysplasia patient.

Molecular biologists will continue to work on the possible biological–functional explanation for cases such as this – chasing the additional gene regulatory abnormalities that may be present – and in a few years we may better understand the causes of this fascinating condition.
Variations in the ghrelin receptor gene associate with obesity and glucose metabolism in individuals with impaired glucose tolerance.

Editor’s note: Ghrelin is implicated in growth hormone (GH) release, energy balance, food intake, and long-term regulation of body weight. Ghrelin is the only known endogenous ligand for the GH secretogogue receptor (GHSR). The GHSR gene is located on chromosome 3q26.31, within a quantitative trait locus strongly linked to multiple phenotypes related to obesity and the metabolic syndrome. Recent studies have suggested a possible link between obesity, insulin levels, and GHSR single nucleotide polymorphisms (SNPs) and GHSR variants.

In this study, the authors investigated SNPs in the GHSR gene and their association with obesity, glucose and insulin metabolism, and the conversion from impaired glucose tolerance to type 2 diabetes in participants of the Finnish Diabetes Prevention Study (DPS). Using various genetic analyses, including genotyping of seven SNPs in the GHSR gene, the association of one genotype (rs9819506-AA) in the promoter region with the lowest body weight was observed, and another genotype (rs490683-cc) was associated with the highest weight loss.

While studies have shown some association of SNPs and obesity, and a possible association with diabetes, this study suggests polymorphism in the GHSR promoter may modify changes in body weight during long-term lifestyle interventions. Obesity and weight loss are complex, multigenetic problems and environmental factors also have to be considered.