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Foreword

By Richard Ross
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The production of recombinant growth hormone (GH) in the mid-1980s and its use to replace GH-deficient adults in the 1990s has led to an explosion in our understanding of the hormones that regulate body composition. Over the next decade, it is likely that new growth factors and metabolic treatments will continue to expand our therapeutic options for treating patients with growth disorders.

Embracing new developments is essential in any medical specialty, but the growing volume of literature in the field of growth medicine places an increasing burden on healthcare professionals.

We are delighted to bring you the fourth issue in the new Current Medical Literature series Growth, Growth Hormone, and Metabolism, 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.

The first Leading Article in this issue, by David R Clemmons from the University of North Carolina at Chapel Hill, NC, USA, reviews the latest literature utilizing insulin-like growth factor-1 (IGF-1) and insulin-like binding proteins for the treatment of diabetes. In the second article, Stephen Kemp and Paul Frindik from the University of Arkansas, AR, USA, discuss the recent literature concerning the role of GH and IGF-1 in the treatment of children with idiopathic short stature.

Future issues of the journal will explore a wide range of topics including IGF-1 treatment of Laron Dwarfism, and GH testing in GH deficiency.

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We look forward to providing you with an interesting and valuable publication. We welcome your feedback and your suggestions for future content.
Insulin-like growth factor-1 (IGF-1) is a small peptide that has significant structural homology with proinsulin. Specifically, proinsulin and IGF-1 have approximately 48% amino acid sequence identity [1]. Despite these similarities, significant differences exist in the residues that account for interaction with the insulin receptor, the IGF-1 receptor, and with the IGF-binding proteins (IGFBPs). As a result, IGF-1 has an affinity for the IGF-1 receptor that is at least 1000-fold greater than insulin and, conversely, insulin has an affinity for the insulin receptor that is at least 200-fold greater than IGF-1 [2]. Under normal physiological conditions, this degree of specificity means that IGF-1 does not stimulate glucose uptake through the insulin receptor, and equally, insulin does not significantly stimulate IGF-1 receptor activation. An additional significant difference is that insulin circulates in a free form and has a short half-life, whereas IGF-1 circulates bound to IGFBPs and its most stable form in plasma has a half-life of 16 h [3]. In practical terms, this means that IGF-1 levels fluctuate minimally after meals, whereas insulin concentrations vary greatly throughout a 24-h cycle.

In spite of its binding protein properties, IGF-1 levels vary as a function of changes in nutrient intake, but the degree of change and the time course of the changes are very different compared with insulin. Specifically, severe caloric restriction results in a major reduction in serum IGF-1 concentrations after 3–5 days; however, unlike insulin, deliberate overfeeding of either carbohydrate or fat does not result in supraphysiological increases in IGF-1 [4]. Postprandially, one of the IGFBPs, IGFBP-1, is suppressed by insulin [5]. This allows a modest increase in free IGF-1 to occur, but the exact physiological significance of this increase has not been definitively determined [6].

Variations in nutrient intake also result in interactions between the IGF-1 and insulin signaling systems. In particular, following severe caloric restriction and/or the development of type 1 diabetes, major reductions in portal vein insulin concentrations result in decreased IGF-1 synthesis in the liver [7]. This is due to the fact that IGF-1 gene transcription requires adequate portal vein insulin concentrations for the IGF-1 promoter to be activated in response to growth factor (GH). Thus, in severe type 1 diabetes, IGF-1 concentrations are reduced. Administration of insulin via the portal vein or intraperitoneally results in a substantial improvement in IGF-1 levels that cannot be completely duplicated using peripheral insulin administration [8,9]. At the target cell level, the ability of IGF-1 to alter insulin action is cell-type specific. In skeletal muscle, which contains both insulin and IGF-1 receptors as well as insulin/IGF-1 hybrid receptors, IGF-1 acts to enhance insulin sensitivity [10]. In contrast, in hepatocytes
and mature adipocytes only insulin receptors are expressed and, therefore, IGF-1 has no direct effect on insulin action in these cell types. However, multiple other cell types, such as smooth muscle or renal epithelial cells, possess IGF-1 receptors as well as insulin receptors, but the extent to which IGF-1 influences insulin action in these has not been rigorously analyzed as yet. In summary, insulin and IGF-1 both have overlapping actions and distinct, cell-type–specific mechanisms for regulating their target tissue effects. Understanding these differences is important for rationally utilizing IGF-1 in the treatment of diabetes.

**Effects of IGF-1 on glucose homeostasis**

Due to its insulin-like properties, IGF-1 has been investigated extensively in animal models in order to determine its role in glucose homeostasis. Administration of adequate doses of IGF-1 to normal rats results in hypoglycemia through stimulation of both peripheral glucose uptake and glycolysis, as well as modest suppression of hepatic glucose production [11]. Similarly, in dogs, IGF-1 has minimal effects on the suppression of hepatoglucose output, and some studies have concluded that all of the effects of IGF-1 in suppressing hepatic glucose output in animals may be due to suppression of GH secretion [12]. Co-administration of IGF-1 and insulin to pancreatectomized rats restored glucose utilization to a normal level [13]. Furthermore, in the diabetic BB rat (a model of insulin-dependent diabetes), the metabolic actions of insulin, but not those of IGF-1, were decreased and the administration of IGF-1 enhanced insulin action [14]. However, in obese Zucker rats, administration of IGF-1 was not able to overcome their severe insulin-resistant state [15]. IGF-1 resistance has also been observed in obese mouse models, and this defect cannot be normalized with exogenously administered IGF-1. Therefore, in models where there is severe insulin deficiency, IGF-1 appears to be more effective in enhancing insulin action compared with those where there is extreme insulin resistance.

The mechanism by which IGF-1 lowers glucose levels has not been extensively analyzed. In most animal studies, serum IGF-1 levels have not been increased to a point that would be expected to activate the insulin receptor directly. As noted previously, some studies have shown a reduction in glucose production rates, suggesting that IGF-1 is inhibiting gluconeogenesis. However, as hepatocytes do not have IGF-1 receptors, it has been proposed that this effect is modulated through the suppression of GH, a known insulin antagonist. Gene knockout studies have demonstrated that animals who are severely deficient in IGF-1 do not develop diabetes; however, deletion of the IGF-1 expression solely in the liver, which results in an 80% reduction in serum IGF-1 with a concomitant increase in serum GH concentrations, induces impaired glucose tolerance, and this defect can be reversed by administering either a GH receptor antagonist or IGF-1 [16,17]. This has led to the conclusion that IGF-1 is functioning by suppressing the anti-insulin actions of GH in the liver. More recently, studies in a mouse model of type 2 diabetes, in which there is no skeletal muscle response to IGF-1, have shown that IGF-1 can suppress renal gluconeogenesis and that this results in decreased glucose production and blood glucose levels [18]. As some studies have indicated that renal gluconeogenesis may account for as much as 50% of the endogenous overnight glucose production rates in patients with diabetes, this suggests that the ability of IGF-1 to lower endogenous glucose production rates may be mediated in part through the direct suppression of renal gluconeogenesis, as well as through a reduction in hepatic gluconeogenesis that is mediated indirectly through the suppression of GH and glucagon actions in the liver [19].

Animal studies have also shown that IGF-1 can improve insulin action in peripheral tissues and enhance postprandial glucose disposal. As skeletal muscle contains abundant IGF-1 receptors, it is thought to be an important target tissue wherein IGF-1 dependent changes in postprandial glucose transport are mediated [20]. A mouse model
has been created in which the IGF-1 and IGF-1/insulin hybrid receptor has been selectively deleted from skeletal muscle [20]. This resulted in the development of type 2 diabetes and severe insulin resistance, suggesting that IGF-I actions in muscle are required to maintain normal systemic insulin sensitivity. Although the mechanism by which this occurs is complex, these mice clearly have impaired postprandial glucose disposal responses, indicating that IGF-1 could be functioning to enhance insulin sensitivity postprandially.

**Physiological studies in humans**

Administration of IGF-1 to healthy humans shows that it has approximately one thirteenth of the potency of insulin [21]. Giving physiological doses of IGF-1 does not result in hypoglycemia, but does result in suppression of insulin and C-peptide levels, indicating that healthy subjects are capable of auto-regulating their response to IGF-1 by reducing insulin secretion. IGF-1 administration to healthy subjects also suppressed GH secretion, which may enhance insulin sensitivity, and glucagon [22]. During IGF-1-induced hypoglycemia, glucagon and GH responses remain suppressed, although epinephrine and cortisol responses are normal [23]. Administration of IGF-1 to healthy individuals causes suppression of endogenous glucose production. Patients with Laron-type dwarfism who are severely IGF-1 deficient respond to IGF-1 with a reduction in blood glucose concentrations [24]. The administration of IGF-1 to patients with type A severe insulin resistance shows that IGF-1 can enhance insulin sensitivity in these patients [25]. It results in a significant lowering of blood glucose and, more importantly, a significant decrease in insulin and C-peptide levels.

Studies in humans have attempted to analyze this effect using the hyperinsulinemic clamp technique. They have revealed that IGF-1 has an effect on enhancing postprandial glucose transport (probably into skeletal muscle), but the degree to which this is due to suppression of GH secretion as opposed to direct enhancement of insulin action has not been determined [26]. IGF-1 suppresses GH in thin, type 1 diabetics. The suppression of GH reduces hepatic glucose output by reducing the antagonizing effect of GH on insulin-stimulated suppression of hepatogluconeogenesis [27]. In attempting to make this distinction, it has been shown that IGF-1 has an effect on enhancing insulin action even when GH actions are inhibited [28]. Therefore, the relative importance of improving hepatic GH action, the direct reduction in renal glucogeogenesis, and the enhancement of insulin-stimulated glucose disposal postprandially, in mediating the improvement in glucose metabolism that occurs in response to IGF-1 in humans has not been definitively determined.

**Administration of IGF-1 in diabetes**

An early study of 43 children with type 1 diabetes showed that the addition of IGF-1 to intensive insulin treatment could significantly improve hemoglobin A1c (HbA1c) levels [29]. The study showed that the additional improvement in HbA1c levels with IGF-1 was 0.5%. As these patients could not secrete insulin, it was concluded that IGF-1 increases insulin sensitivity in type 1 or 2 diabetes.

In a follow up clinical trial, IGF-1 was administered to 223 subjects who received either intensive insulin treatment alone or insulin treatment plus one of three doses of IGF-1 for 12 weeks [30]. Cotherapy with insulin and recombinant IGF-1 reduced HbA1c levels by 1.2%, compared with 0.7% in patients receiving intensive insulin therapy alone. Insulin utilization was reduced by between 11–19% in subjects who received IGF-1 compared with a 7% increase in subjects who received placebo. These were relatively thin, young adults with type 1 diabetes, ranging in age from 22–31 years, and who had an average body mass index of 25.4. To obtain these results required increasing total IGF-1 levels 2.5-fold above the normal physiological concentration. Adverse events included edema, jaw pain, headache, and arthalgias, as well as tachycardia. Free IGF-1 concentrations increased by approximately 18-fold.
IGF-1 alone has also been administered in several large, randomized, controlled trials to patients with type 2 diabetes. In one study with 228 patients, the subjects were given IGF-1 in one of four different dosages in place of their usual oral hypoglycemic therapy [31]. Administration of the two highest dosages, 40 or 80 µg/kg twice daily, for 12 weeks resulted in a substantial decrease in HbA1c levels of 1.1 and 1.25%, respectively, compared with the pretreatment levels. An even greater difference between these two treatment groups and the placebo group was noted. IGF-1 concentrations were increased 2.5- and 3.4-fold, respectively, above physiological levels with the two highest dosages. As was previously noted for type 1 diabetics, there was a significant increase in the side effect profile, with edema, arthralgias, headaches, jaw pain, Bell’s palsy, and tachycardia being present in the treatment groups. These side effects all resolved with the withdrawal of therapy. One large trial also administered IGF-1 with more intensive insulinization to type 2 diabetics [32]. In this study, 228 subjects were randomized to receive either one of three dosages of IGF-1 plus intensive insulinization, or intensive insulin therapy alone. The groups that received the higher doses of IGF-1 had an additional 0.7% decrease in HbA1c compared with the 0.6% reduction that was obtained with intensive insulinization alone. Again, the side effect profile was similar to other reported studies with IGF-1. As was shown in the other studies, there was a substantial increase in the incidence of one or more of these side effects, which occurred in 40% of the subjects. In summary, IGF-1 treatment in type 1 or 2 diabetics improves responsiveness to intensive insulinization; however, in both conditions there is a substantial increase in total and free IGF-1 concentrations that result in side effects, which, although reversible, cause significant morbidity.

**IGF-1/IGFBP-3 combination**

IGFBP-3 is the most abundant form of IGFBP in serum [33]. Administration of the IGF-1/IGFBP-3 complex to experimental animals shows that the half-life of IGF-1 in the administered complex is substantially greater than when administered alone [34]. Although IGF-1 alone binds to unsaturated binding proteins in serum, most of the IGFBP-3 is saturated under normal conditions; therefore, the only available binding sites are those that are present on IGFBP-1 and -2 [35]. As these two proteins do not bind to the third component of the ternary complex, acid labile subunit (ALS), the half-life of these binary IGF-1/IGFBP-1 or IGF-1/IGFBP-2 complexes is considerably shorter than the IGF-1/IGFBP-3/ALS complex. This probably explains the fact that when concomitantly administered with IGFBP-3, IGF-1 has a substantially greater half-life in serum than when given alone. In addition, although direct comparison studies have not been carried out, the absolute increase in free IGF-1 in serum of diabetics appears to be substantially greater than after administration of IGF-1 with IGFBP-3. Specifically, in studies where this has been reported, the relative increase in free IGF-1 following a dose of IGF-1 is 18-fold in 90 min when IGF-1 was administered alone [30], whereas administration of IGF-1/IGFBP-3 results in an eight-fold increase in free IGF-1 over a period of 16 h [36]. Therefore, the rate of exposure of tissues to free IGF-1 is likely to be substantially different when these two treatment regimens are compared directly. Administration of the IGF-1/IGFBP-3 complex (2.0 mg/kg) to adult patients with type 1 diabetes for 2 weeks resulted in a 23% reduction in mean daily blood glucose and a 54% reduction in insulin requirements [37]. This was accompanied by a substantial reduction in overnight GH secretion, suggesting that one mechanism whereby IGF-1 enhanced insulin sensitivity was through the suppression of GH secretion. Although this study was only for 2 weeks, the patients reported no significant side effects other than injection site pain.

In a larger study, the combination of IGF-1/IGFBP-3 was administered in four different dosage regimens to type 2 diabetic patients. Fifty-two patients were randomized to one of four treatment groups, which
included the administration of 2 mg/kg of the complex as a subcutaneous infusion over 6 h [36]. The second group received the same regimen, but as a 24-h infusion; the third group received 1 mg/kg twice daily by subcutaneous injection; and a fourth group received 1 mg/kg once daily. IGF-1/IGFBP-3 reduced insulin requirements in these patients by 54–82%. Fasting glucose levels decreased by 32–37%, and mean daily glucose levels showed a 9–23% decrease. The reduction in insulin dosage was significant for all four treatment groups and was greatest in the groups that received the subcutaneous infusions. The change in fasting glucose was substantially greater than the change in postprandial glucose, with a statistically significant reduction occurring in all four treatment groups. In contrast, postprandial glucose levels showed that only the group that had received IGF-1/IGFBP-3 1 mg/kg twice daily had a significant reduction in postprandial glucose at lunch, dinner, and bedtime. Side effects reported included headache, injection site pain, back pain, and nausea, with a frequency that was comparable to administration of IGF-1 alone. Other side effects that were detected, but were relatively infrequent compared with previous studies using IGF-1 alone, included jaw pain, arthralgias, edema, and Bell’s palsy. Total IGF-1 concentrations were increased by 3.8-fold, whereas IGFBP-3 concentrations appeared to increase by only 37%. When the IGF-1/IGFBP-3 ratio was analyzed, it was seen to increase from a baseline value of 0.26 to values that varied from 1–1.23 in the treatment groups, indicating that the IGFBP-3 that was present in serum was saturated.

A more recent study attempted to compare a broader range of dosing regimens and to determine what happened to other components of the IGF system. In this study, 37 type 2 diabetics who were being treated with insulin received dosages of IGF-1/IGFBP-3 that varied from 0.125–2 mg/kg/day. The results demonstrated that only the two highest dosage groups, 1 mg/kg and 2 mg/kg, had reductions in fasting and mean daily glucose values that were significantly greater than the changes that occurred in control subjects who received more intensive treatment with insulin alone. Importantly, analysis of IGF-2 and ALS concentrations showed that the increase in IGF-1 that occurred in each group was accompanied by a parallel decrease in IGF-2, and that the sum of IGF-1 plus IGF-2 exceeded IGFBP-3 in the three highest dosage treatment groups. Furthermore, there was a slight reduction in ALS concentration. These findings suggest that administration of IGF-1 results in the replacement of IGF-2 that is bound to the IGFBP-3/ALS complex, and that high levels of total and free IGF-1 may result in GH suppression and concomitant reduction in ALS, thus decreasing the overall binding capacity. Therefore, administration of the IGF-1/IGFBP-3 complex is useful to the extent that it prolongs the half-life of IGF-1 in serum, but even with the administration of this complex, an excessive increase in free IGF-1 will result in a reduction in the overall binding capacity of the complex. This potentially limits the highest dosage of IGF-I/IGBP-3 that can be given to 2 mg/kg.

Summary

In summary, administration of IGF-1/IGFBP-3 to diabetic subjects results in a substantial improvement in insulin sensitivity and a lowering of either endogenous C-peptide secretion or exogenous insulin requirements, with concomitant improvements in fasting and postprandial glucose levels, as has been noted previously following administration of IGF-1 alone. The reduction in fasting glucose is the most consistent change that has been noted with both treatment regimens and in both types of diabetes. The reduction in postprandial glucose in type 2 diabetics is less than that noted in patients with type 1 diabetes, possibly due to the fact that type 2 diabetics secrete minimal concentrations of GH and, therefore, GH suppression would be predicted to have less of an effect on insulin sensitivity. Whether IGF-1 suppresses renal glucogenogenesis in these patients has not yet been determined. Clearly, the effects of IGF-1 are mixed, and the postprandial effects may
be largely due to enhancement of insulin sensitivity in muscle; however, the effects on fasting glucose, and therefore endogenous overnight glucose production rates, appear to predominate. This suggests that the optimum utilization of IGF-1 in type 2 diabetes may be evening administration, in order to lower endogenous rates of glucose output.

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Disclosures: The author is a consultant for Insmed, Inc. who market IGF-1/IGFBP-3 (Iplex™) for the treatment of short stature due to IGF-1 deficiency.

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References


Leading Article

The Role of Growth Hormone and Insulin-Like Growth Factor-1 in the Treatment of Idiopathic Short Stature

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Idiopathic short stature (ISS) is a term that has been used to describe short stature in children who do not have growth hormone (GH) deficiency and in whom the etiology of their condition is not understood. In addition, all recognizable causes of short stature (i.e. intrauterine growth retardation, genetic or syndromic causes of short stature, and psychosocial deprivation) should have been ruled out before the diagnosis is made. Other terms have been used in the past to describe these children, some of which overlap with those describing ISS, for example, familial short stature, normal variant short stature, idiopathic growth failure, non-GH-deficient short stature, and nonendocrine short stature. Some patients with ISS have been diagnosed with GH neurosecretory dysfunction (i.e. low spontaneous GH secretion) as a means of justifying GH therapy. As a group, children with ISS do not achieve their adult height predictions, and many have adult heights that are quite short [1,2].

GH treatment of ISS
Between 1964 and 1971, there were a number of small studies that examined the treatment of non-GH-deficient short stature with GH [3]. In 1964, the National Institute of Child Health and Human Development sponsored an international conference that recommended analysis of GH treatment in non-GH-deficient conditions. In 1987, a Food and Drug Administration (FDA) advisory committee recommended a placebo-controlled study of GH treatment for ISS that would follow subjects to adult height.

In July 2003, the FDA approved the use of GH in children with ISS. They defined ISS as those children having a height that was >2.25 standard deviations (SDs) below the mean, open epiphyses, a growth velocity that makes it unlikely that the child’s adult height will be in the normal range (i.e. within 2 SDs of the mean), and a diagnostic evaluation that has excluded other causes associated with short stature, requiring observation or treatment by other means. One of the concerns has been the possibility of misdiagnosing and treating children for ISS who actually have constitutional delay in growth and maturation (CD), particularly if the child's bone age is delayed; certainly, there are such patients. However, if FDA guidelines are adhered to, a child who is >2.25 SDs below the mean, and has a predicted adult height that is >2 SDs below the mean, is probably more appropriately considered to have ISS than to be classified as having CD. There is evidence that adult height tends to be overpredicted, particularly in boys. Bramswig et al. compared the reliability of each of these three methods of height prediction with others, and with the target height in children with short stature, and CD [4]. The most accurate method for boys was the Roche–Wainer–Thissen (RWT) method, which underestimated adult height...
by –0.6 cm, while the TW-Mark 1 method (TWMI), and its refinement TWMII, used larger numbers of normal children (including children who were tall, short, and growth delayed), and underestimated adult height by –7.3 and –4.2 cm, respectively. The Bayley–Pinneau (BP) method, the most commonly used, overestimated adult heights in boys by 3.1 cm [5]. For girls, the mean prediction error was –0.8 cm, –2.1 cm, and –1.8 cm for BP, TWMI, and TWMII, respectively. RWT overpredicted height by 2.3 cm [6].

The relationship between a child’s expected adult height and their parents’ heights is represented as a bell-shaped distribution curve, with the peak of the distribution at the mid-parental height. When the adult heights are separated by gender, two distribution curves result, with the peaks separated by 12.7 cm (5 inches). A boy’s most likely adult height is the mid-parental height plus 6.35 cm (2.5 inches); a girl’s is the mid-parental adult height –6.35 cm (2.5 inches). This value represents the sex-adjusted mid-parental height, commonly referred to as the target height [7]. In the study by Bramswig et al., target height overpredicted adult height in boys by 1.7 cm and in girls by 1.2 cm [4].

**Efficacy of GH treatment in ISS**

Children with ISS who are treated with GH are as short at the beginning of GH therapy as children with chronic renal insufficiency, Turner syndrome, or children who are born small for gestational age; that is, their heights before treatment averages from –2.6 – –2.9 SDs [8–12]. In this group of children, insulin-like growth factor-1 (IGF-1) levels are often normal; however, approximately 25% of them are low, suggesting that some children in this group may have GH insensitivity. Many of the published studies of GH therapy in children with ISS have involved small sample sizes and did not have control groups. A meta-analysis of these studies suggested that the overall height gain may have been a height increase from –3.0 – –1.5 SDs with GH therapy [3], which represents a height increase of 4–6 cm. In studies with a control group, it appeared that the control group also had an increase in height (consistent with a previous report of spontaneous growth in children with ISS [13]), but the treated group exceeded the control group by approximately 0.78 SDs. Subsequent to this meta-analysis, results of a placebo-controlled study on the effect of GH therapy on adult height in peripubertal children with ISS demonstrated a height increase of 3.7–5.0 cm with GH therapy, despite a low dose of GH (0.22 mg/kg/week) and an injection schedule of three times per week [14]. A subsequent study evaluating two treatment protocols demonstrated a dose effect with a dosage of 0.37 mg/kg/week, resulting in an increase in adult height of 7.2 cm compared with 5.4 cm in the group receiving only 0.24 mg/kg/week [15]. An evaluation of data from children with ISS treated with GH, taken from a large GH database, showed that GH treatment resulted in an increase in height SD from –3.0 to –1.2 over the course of 7 years [9].

**Safety of GH treatment in ISS**

An evaluation by Quigley et al. [16] of safety data from the controlled trial of GH therapy of children with ISS [14] and the subsequent dose response study [15], as well as an evaluation of >8000 ISS patients followed in a large post-marketing database for children treated with GH [9], have shown that there are no safety issues in GH therapy different from those seen with treatment of GH deficiency.

**Psychosocial effect of treating ISS**

It is interesting that children with ISS have been treated with GH at least since the inception of the National Cooperative Growth Study (NCGS) in 1985, accounting for approximately 20% of those patients treated with GH [17]. Nonetheless, it has been difficult to demonstrate that an increase in height also results in increased quality of life. This is a particularly relevant question, as GH therapy is quite expensive – perhaps as much as US$52,634/inch [18]. A recent review of this issue concluded that parents and children retrospectively perceive
hormone therapy as beneficial; however, there is not enough evidence (mainly due to poor studies) from which we can conclude evidence-based positive effects.

Evidence that some ISS cases may be caused by GH resistance
In order to determine whether partial GH insensitivity was responsible for growth failure in children who were not GH deficient, data were analyzed from 773 children who were being treated with GH and were enrolled in a post-marketing surveillance project, the NCGS [19]. Patients enrolled in this study had their levels of IGF-1 and GH binding protein (GHBP) determined. In addition, these patients had been evaluated for GH deficiency by their response to provocative stimuli. Patients with a GH response of >10 ng/mL were classified as having ISS. Children with ISS had GHBP levels >2 SDs below the normal control patients, IGF-1 levels lower than controls (108–120 µg/L vs. 217–308 µg/L), but higher than in patients with GH deficiency (84–99 µg/L), and mean 12 h GH concentrations similar to controls (2.2 µg/L vs. 2.1–2.7 µg/L), but higher than in patients with GH deficiency (1.2–1.4 µg/L). A subset of 14 of these patients (height >2.5 SDs below the mean, normal GH secretion, IGF-1 levels >2 SDs below the mean, and serum concentrations of GHBP >2 SDs below the mean) were further studied [20]. Of the 14 patients, four had mutations in the GH receptor (none of the 24 control subjects had mutations). One of these patients was a compound heterozygote, with respect to the GH receptor. Due to these findings, it has been suggested that partial GH insensitivity may be a cause of growth failure in some children with ISS. It may be possible that they would respond to GH at higher doses, or it may be that these children should be treated with IGF-1 instead of GH.

IGF-1 treatment of ISS
In August and December of 2005, mercasermin IGF-1 (Increlex™, Tercica, Inc., Brisbane, CA, USA) and mecasermin rinfabate (Iplesh™, Insmed, Glen Allen, VA, USA), respectively, received approval from the FDA for the treatment of children with severe primary IGF deficiency or children with a GH gene deletion who have developed neutralizing antibodies to GH. These compounds have been shown to be effective in treating cases of GH insensitivity [21, 22] and IGF gene deletion [23]. However, there have been no published data regarding the treatment of ISS (or partial GH insensitivity), therefore the role of treatment of ISS with IGF-1 remains to be determined.

Treatment of GH-receptor deficiency with IGF-1 has resulted in a number of mild-to-moderate adverse events. Most commonly reported adverse events have included pain at the injection site and headaches. Data from a European study indicate that these events occur during the first month of treatment and then improve [22]. Other adverse events that have been reported following IGF-1 therapy have included lipohypertrophy at the injection site, papilloedema related to increased intracranial hypertension, and facial nerve paralysis [24,25]. With these events, symptoms resolved after interrupting treatment and re-starting with a lower dose [22].

A second concern has been hypoglycemia, which occurred in some of the patients receiving IGF-1, but only rarely resulted in seizures [21,26]. This problem was lessened by administering IGF-1 dose with meals, and hypoglycemia was usually a problem when there was an intercurrent illness resulting in loss of appetite.

Another effect of IGF-1 therapy has been the growth of lymphoid tissue, in particular, splenic enlargement and tonsillar hypertrophy. Renal size also increased, but renal function remained normal [21]. There were changes in facial appearance, with coarsening of features and an increase in hair growth, which were most noticeable during puberty.

Other approaches to treatment of ISS
LHRH agonists
It is well recognized that treatment of early-onset precocious puberty with luteinizing hormone-releasing hormone (LHRH) agonists
(gonadotropin-releasing hormone [GnRHa]) allows adult height to approach target height [27]. It has been postulated that GH may hasten progression of puberty, and that the addition of GnRHa treatment may permit further growth in children with ISS. Kamp et al. demonstrated that the addition of GnRHa to GH therapy in children with ISS or intra-uterine growth restriction resulted in an increase in predicted adult height of 8.0 cm in girls and 10.4 cm in boys [28]. A prospective study comparing treatment of normal short girls with GH alone or with GH plus GnRHa suggested that while GH alone resulted in an increase in predicted adult height, the addition of GnRHa combined with GH resulted in an even greater increase in predicted adult height [29]. The evaluation of two large GH registry databases and GH prediction models does not support the success of this treatment [30]. At present, there are no universally agreed upon guidelines for the use of GnRHa with (or without) GH in children with ISS; thus, this therapy is still considered experimental.

Aromatase inhibitors

A recent study has demonstrated a 5.9 cm increase in predicted adult height in boys with ISS using an inhibitor of aromatase (letrozole; without GH treatment) for 24 months [31]. The same group has reported a similar finding in boys with constitutional delay treated to near adult height with letrozole [32]; namely, the group receiving letrozole reached a near adult height which was 6.7 cm taller than those who did not. Although these reports appear quite promising, further studies carried out on adult height, with a careful evaluation of safety, are needed before this therapy can be adopted in a clinical setting [27].

Conclusion

ISS describes a group of children who are very short (>2 SDs below the mean) and who are not GH deficient. As early as 1983, there was interest in determining whether treating these children increased their adult height. Between 1985 and 2000 there were >40 studies published on the treatment of ISS. Most involved small patient populations, only 12 had adult height data, and only four were controlled. A controlled study was undertaken between the National Institutes of Health and Eli Lilly and Company, Indianapolis, IN, USA. Subsequently, that study demonstrated an increase in adult height from 3.7–7.5 cm with GH treatment [14,15]. The FDA approved the ISS indication in July 2003. An analysis of the data from a large registry of patients receiving GH demonstrated a similar response to therapy and no differences in safety than for the treatment of GH deficiency. There are few data regarding whether a psychological advantage is gained by patients with ISS treated with GH.

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References


Preliminary development of the new individualized HDQoL questionnaire measuring quality of life in adult hypopituitarism.

Editor's note: The effect of growth hormone (GH) therapy on quality of life (QoL) in adults with GH deficiency has been measured using different questionnaires, including the Nottingham Health Profile and the Psychological General Well-being Index. Studies have reported different outcomes, which may be due to the fact that the measures are patient-reported outcomes in addition to clinical outcomes. The present authors describe the preliminary development of a new, individualized Hormone Deficiency-dependent QoL (HDQoL) questionnaire. The design of this questionnaire is based on the Audit of Diabetes-dependent QoL. The current article discusses the development of the HDQoL and assesses the questionnaire’s psychometric properties for adults with hypopituitarism, including GH deficiency.

The evaluation of the HDQoL included consistency reliability, aspects of validity, and sensitivity to change, and was conducted in patients from two separate studies: a cross-sectional survey of 157 adults with treated or untreated GH deficiency, and a randomized, double-blind, placebo-controlled study with 21 severely GH-deficient patients, 12 of whom were allocated placebo for 3 months.

The study found that five of the original 18 items in the HDQoL were irrelevant; however, once removed, the resulting 13-domain questionnaire had excellent internal reliability (Cronbach’s alpha coefficient 0.914, n=109), and was sensitive to sex differences (cross-sectional study) demonstrating that women experienced a worse present QoL than men (p=0.021). The questionnaire’s sensitivity to change was confirmed in the GH-withdrawal study, which showed a significant difference in scores between patients receiving placebo and GH for the item “…things I can do physically…” (p=0.025), with the placebo group reporting greater negative impact of hormone deficiency on this item at the endpoint. To further improve the HDQoL, an additional seven items based on patient interviews and comments were added to the questionnaire, including energy, sleep pattern, and bodily pain.

Although the HDQoL proved a useful tool in identifying the expected changes following GH withdrawal, it needs to be assessed in additional trials and compared with other available QoL questionnaires to confirm its value.

Discrepant results in the diagnosis of GH deficiency with the insulin-tolerance test and the GHRH plus arginine test in patients with traumatic brain injury.

Editor’s note: The recent focus on traumatic brain injury as a potential cause of occult growth hormone (GH) and other anterior pituitary hormone deficiencies has fuelled numerous studies that are currently reaching...
publication. Inevitably, they will reintroduce the established controversies with respect to the appropriate methods of assessing anterior pituitary function. It is clear that in such an area of debate, an assessment of GH secretory status requires concurrent assessment of other anterior pituitary hormone functions from a practical point of view (thyroid, adrenal, and gonadotroph function) in order to have meaningful interpretation of the clinical scenario. This current study highlights the problem of assessing acquired GH deficiency, where the clinical phenotype is of acute brain injury, without clues from the clinical history (growth, obesity, gonadal function, brain tumor management etc.) that might support a diagnosis of GH deficiency on the basis of one or two GH provocation tests.

As ever, high body mass index proved to be a confounding factor, but in this situation the serum insulin-like growth factor-1 level might be a better guide to true GH deficiency in the absence of any other apparent co-existing anterior pituitary hormone deficiency. The GH-releasing hormone test is unphysiological in the context of recent brain injury that it should only have a very limited role to play (if any). The authors of this paper did not address pituitary or hypothalamus magnetic resonance imaging, which certainly needs to be included in such studies if we are to define the relationship between trauma and pituitary dysfunction – acute, middle, or long-term.

**Genetic screening of combined pituitary hormone deficiency: experience in 195 patients.**


**Editor’s note:** These authors evaluated the prevalence of mutations in the transcription factors POU1F1, PROP1, LHX3, LHX4, and HESX1 in 195 patients with two or more pituitary hormone deficiencies, or one deficiency with a recognized intracerebral abnormality characterized by magnetic resonance imaging. The total prevalence of identified mutations was 13%, but this increased to 52% in the 20 patients with a family history of combined pituitary hormone deficiencies. Among the 16 patients with clinical features supporting a diagnosis of septo-optic dysplasia, no mutations of the *HESX1* gene were identified. Only one case of *LHX4* gene mutation (a previously described mutation) was identified in 39 patients with pituitary stalk interruption syndrome.

The most common transcription factor associated with an identified mutation in 20 of the 109 patients with extrapituitary abnormalities was PROP1. These included eight patients with a family history of combined pituitary hormone deficiencies. No *LHX3* and only one *POU1F1* gene mutation was identified – the latter was associated with postpubertal growth hormone and thyroid stimulating hormone deficiency. Thus, genetic causes of multiple pituitary hormone deficiencies are unlikely to be identified from existing ones, and in the absence of a family history of a similar phenotype, genetic studies currently hold limited value in the management of affected families.

**Mutations within Sox2/SOX2 are associated with abnormalities in the hypothalamo-pituitary-gonadal axis in mice and humans.**


**Editor’s note:** The transcription factor SOX2 can now be added to the list of regulatory factors associated with defective pituitary function through heterozygous mutations (*J Clin Endocrinol Metab* 2006;91:3329–36). In particular, the eight individuals reported in this current series, derived from a cohort of 235 patients with pituitary disorders, exhibited unilateral or bilateral developmental eye abnormalities (anophthalmia, microphthalmia, or bilateral optic nerve hypoplasia). Six of the mutations were *de novo* and were predicted to result in truncated protein products exhibiting partial or complete loss of function through altered DNA binding, nuclear translocation,
or transactivation. Hypogonadotrophic hypogonadism was common and midline defects affecting the corpus callosum, hypothalamic hamartomas, and mesial temporal structures were variable, with cases of sensorineural hearing loss and esophageal atresia observed clinically. An equivalent mouse model with targeted heterozygous disruption of the Sox2 gene showed abnormal pituitary development, but without eye defects.

**Adult height in patients with permanent growth hormone deficiency with and without multiple pituitary hormone deficiencies.**


Editor’s note: This retrospective study of patients treated in five Italian pediatric endocrine centers includes approximately 25% of patients who started growth hormone (GH) replacement with human pituitary GH >20 years ago, when the standard GH treatment was just three injections per week. Treatment for induction of puberty in those patients with gonadotrophin deficiency had, until then, often included an intentional delay beyond normal in order to achieve a better final height. However, this was achieved at the expense of body proportion (longer legs for sitting height) and the degree of psychosocial disturbance from the pubertal delay, which was never clearly quantified. The introduction of new clinical practices with the advent of commercial recombinant GH brought the use of GH injections to five or seven times a week and individual GH dose adjustments by supervising clinicians.

This multicenter collaborative report has appraised the final height and diagnostic outcome in 88 patients, 39 being assigned as having isolated GH deficiency (IGHD) as opposed to multiple pituitary hormone deficiency (MPHD). Magnetic resonance imaging scans of the underlying congenital central nervous system abnormality were obtained in all patients. Only five IGHD patients had no apparent abnormality, whereas all MPHD patients had abnormal scans; 40 with pituitary hypoplasia and ectopic posterior pituitary, and only two with septo-optic dysplasia. Pubertal induction for MPHD patients was with standard schedules of testosterone or estrogen and, more importantly, was introduced at a similar age to patients with IGHD (median age; males 14.0 years and females 13.5 years), i.e. it was not intentionally delayed for the potential future benefit of improved final height.

The final height outcome for both IGHD and MPHD groups was similar, and within parental height target ranges. Both groups showed similar growth increments from the onset of puberty to final height. The gain in height standard deviation score from the onset of treatment to final height outcome was also similar for both IGHD and MPHD groups. GH dosage was not specifically further increased (in respect of body weight) for treatment throughout puberty. This study is greatly reassuring in the respect that puberty should not be delayed in order to achieve normal final height in idiopathic or congenital MPHD patients, provided that physicians adhere to appropriate standard hormone replacement schedules in current practice.

**Growth hormone and IGF-I modulate local cerebral glucose utilization and ATP levels in a model of adult-onset growth hormone deficiency.**


Editor’s note: Growth hormone (GH) and insulin-like growth factor-1 (IGF-1) are important for normal brain development and for tissue recovery following brain injury. Their roles in the decline of brain function with age are unclear, although it has been suggested that decreases in circulating plasma IGF-1 levels that occur with age may contribute to the brain aging process. In an attempt to confirm this hypothesis, the authors of the current study used dwarf rats deficient in GH and IGF-1 to create a model.
of adult-onset GH/IGF-1 deficiency. In this model, a decrease in levels of plasma IGF-1 is similar to that observed with increasing age (e.g. 50% decrease), and replacing GH restores IGF-1 levels to those found in young animals with normal GH levels. GH/IGF-1 deficiency in these young animals was expected to produce a brain-aged phenotype, similar to that found in older animals.

Two groups of GH/IGF-1-deficient rats were reared and sacrificed at an age of 26 weeks. One group received only exogenous GH from age 4–14 weeks (GH/IGF deficient), whereas the other group received GH continuously from age 4–26 weeks (GH replete). The brain-specific phenotype in these animals was characterized by testing the effects of circulating GH and IGF-1 on local cerebral glucose utilization (LCGU). Analysis of LCGU indicated that GH/IGF-1 deficient animals exhibited a 29% decrease in glucose metabolism in many brain regions, especially those involved in the hippocampal-dependent processes of learning and memory. Similarly, a high correlation between plasma IGF-1 levels and glucose metabolism was found in these areas. The deficiency in LCGU was not associated with alterations in the glucose transporters GLUT1 or GLUT3, or in hexokinase activity. A 15% decrease in ATP levels was found in the hippocampus of GH-deficient animals, consistent with GH, providing compelling data that circulating GH and IGF-1 have significant effects on the regulation of glucose utilization and energy metabolism in the brain. Taken together, these results provide interesting data to support the conclusion that deficiencies in circulating GH/IGF-1 contribute to the genesis of brain aging.

Turner Syndrome

Self-esteem and social adjustment in young women with Turner syndrome— influence of pubertal management and sexuality: population-based cohort study.
Carel JC, Elie C, Ecosse E et al.
Hôpital Robert Debré, Paris, France.
J Clin Endocrinol Metab 2006;91:2972–9.

Editor’s note: Within the last year we have had the opportunity to appraise the impact of growth hormone (GH) treatment on final height outcome in girls with Turner syndrome using a variety of controlled and open clinical management studies, specifically those from the US, The Netherlands, and Canada. The dominant message for clinical care seems to be that the greatest benefit of GH treatment on final height depends on initiation of treatment at an early age and the dose level used. This means the longer the duration of prepubertal treatment with GH, the greater the benefit it is likely to have on final height. However, an issue that is naturally raised in discussion is the concept of the timing of induction of puberty, and whether this should be delayed in order to achieve optimal final height in Turner syndrome girls. The current paper from the French multicenter study group includes a remarkable 566 young adult women at a mean age of 22.6 year (range 18–31 years), all of whom were treated with GH. A further 325 women were lost to follow-up or were unwilling or unable to respond to a questionnaire evaluating self-esteem and social adjustment.

Although it is potentially difficult to measure sensitive aspects of emotional development and psychosexual satisfaction, this study highlighted some major features of medical care in this group of young women. Age at first kiss and age at first sexual intercourse were, perhaps not surprisingly, related to age at induction of puberty, and this appeared to have significant impact on subsequent sex life. In this large cohort of Turner women that represented the first 2 decades of clinical management using GH as a supportive therapy, it was remarkable to note that height and height gain on GH
treatment had no significant association with psychological outcome, as assessed in this study.

While we are learning that the early treatment of Turner syndrome girls might negate the approach of inducing puberty later in order to enhance final height, it is clearly essential to keep the focus on the emotional needs and adult adjustments required for the teenage Turner girl.

**Free dissociable insulin-like growth factor I (IGF-I), total IGF-I and their binding proteins in girls with Turner syndrome during long-term growth hormone treatment.**


**Editor’s note:** This study reports the effects of recombinant human growth hormone (rhGH) therapy on circulating free insulin-like growth factor-1 (IGF-1) levels in a cohort (n=65) of girls with Turner Syndrome (TS), in an attempt to verify the relationship between free circulating IGF-1 levels and total IGF-1 and its principal binding proteins (BPs) IGFBP-1, 2, and 3. These biochemical parameters were determined at baseline (before onset of rhGH therapy), at 1–2 yearly intervals during therapy, and after discontinuation of treatment on attainment of final adult height. Subnormal levels of free IGF-1 were observed before the onset and after discontinuation of rhGH therapy. During therapy, increases in both circulating mean total IGF-1 and the IGF-1/IGFBP-3 ratio to well above the normal range (> +2 standard deviation score) were observed. In contrast, mean free IGF-1 levels were maintained within the normal range. The discrepancy in rhGH-induced longitudinal changes in circulating levels of free IGF-1 and total IGF-1 could not be accounted for, and the authors speculate that increased clearance of free IGF-1 from the circulation may be one explanation for their observation. The authors of the study also conclude that levels of total IGF-1 and the ratio of total IGF-1 to IGFBP-3 were not representative of free IGF-1 levels, as at best, they explained only 55% of the variation in free IGF-1 levels within the circulation. Free IGF-1 levels also showed no clear correlations with either height gained, final height, or height changes during the first few years of rhGH therapy. The authors suggest that, in terms of biological endpoints, free IGF-1 determination is of little predictive value in the evaluation of rhGH-treated patients with TS.

**Genomic imprinting in Turner syndrome: effects on response to growth hormone and on risk of sensorineural hearing loss.**


**Editor’s note:** This Canadian study of girls with Turner syndrome extends the developing concepts of individual patient management. We are already aware that girls with trisomy of Xq have an increased risk of autoimmune hypothyroidism (*Clin Endocrinol* 2001;55:223–26, *J Pediatrics* 1987;111:258–61), and that psychological skills are related to selective imprinting of parental alleles (*Nature* 1987;387:705–8).

This paper introduces two factors related to the parent-of-origin effect of the intact X chromosome, with respect to growth hormone (GH)-stimulated height gain and sensorineural hearing.

A cohort of 54 girls available for study from a larger national cohort of 154 Turner syndrome girls were evaluated. Microsatellite analysis was used to determine the origin of the intact parental X chromosome, with respect to growth hormone (GH)-stimulated height gain and sensorineural hearing.

A cohort of 54 girls available for study from a larger national cohort of 154 Turner syndrome girls were evaluated. Microsatellite analysis was used to determine the origin of the intact parental X chromosome (72% maternal in non-mosaic 45XO, 86% paternal in non-mosaic 46X, iXq). A linear regression analysis model found that maternal-derived X girls had a significantly greater response to GH (height standard deviation score gain from start of treatment) compared with those with paternal-derived X. This analysis represented final height for most patients. Furthermore, a lower incidence of sensorineural hearing loss in maternal-derived X (p<0.046) in young adulthood was observed.
Although it would be interesting to identify candidate genes that might account for these observations, the current study raises the issue of more extensive genetic analysis in Turner girls to help focus clinical management on target disorders at an earlier age.

**Pubertal height gain in Ullrich-Turner syndrome.**
Bechtold S, Dalla Pozza R, Schmidt H et al.
University Children’s Hospital, Munich, Germany.

Editor’s note: Ullrich-Turner syndrome (UTS) is characterized by short stature and ovarian failure. The reduced height has significant psychological and social implications. The use of growth hormone (GH) therapy has resulted in partial increase in final height, and thus improved self-image of these patients. Although GH and anabolic steroids improve the growth rate in patients with UTS, the final height outcome is less affected. Moreover, because estrogens accelerate bone maturation, further growth is limited once bone development is completed. Therefore, the timing of GH and anabolic steroid therapy initiation remains under debate.

In this study, the authors retrospectively analyzed the influence of age at initiation of puberty on final height in 77 UTS patients. A total of 65 girls receiving GH, 53 of whom were also given concomitant estrogen for initiation of puberty, reached an average final height of 150.6±5.7 cm. A control group of 12 girls, who did not receive GH treatment, had an average final height of 147.3±6.6 cm. A subgroup analysis of the estrogen-treated group demonstrated that there was no significant difference in final height between the patients who had puberty induced before and those who had it induced after the age of 13 years. Moreover, additional therapy with oxandrolone in nine girls had no impact on final height in this study.

The authors conclude that age of initiation of GH treatment, its duration, and height standard deviation score at the beginning of puberty influence final height. Thus, GH therapy should be started early in individuals with UTS, to allow estrogen-induction of puberty at the normal age of approximately 12 years.

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**Molecular Mechanisms of GH Resistance**

The d3/fl-growth hormone (GH) receptor polymorphism does not influence the effect of GH treatment (66 µg/kg per day) or the spontaneous growth in short non-GH-deficient small-for-gestational-age children: results from a two-year controlled prospective study in 170 Spanish patients.
Carrascosa A, Esteban C, Espadero R et al;
Spanish SGA Study Group.
Hospital Maternoinfantil Vall d’Hebron,
Barcelona, Spain.

Editor’s note: Following the initial observation by Dos Santos et al. (*Nat Genet* 2004;36:720–24) that the d3/fl-growth hormone (GH) receptor polymorphism was associated with a differential growth response to GH treatment there has been enormous interest in the subject. Several studies have now been reported that include the GH d3/fl genotype as an additional factor in the analysis of growth response, with conflicting results. Most studies had not been adequately designed with the GH receptor phenotype as a variable for analysis, and this report suffers from a lack of power by not addressing this issue. The main purpose of the study was as a multicenter trial comparing GH efficacy in short, non-GH-deficient children, with an untreated control group. To this end, the study was successful. However, there were only six children with d3/d3 homozygosity who had GH treatment and eight such homozygotes represented untreated controls, compared with approximately 30 children in
Clinical and biochemical characteristics of a male patient with a novel homozygous STAT5b mutation.


Editor’s note: This brief case report identifies the mutation in signal transducer and activator of transcription-5b (STAT5b) in an adult male with extreme short stature and a lack of growth response in childhood to a standard dose of growth hormone (GH). It represents only the fourth published case of such a disorder in the GH signaling pathways (N Engl J Med 2003;349:1139–47, JCEM 2004;89:1259–66, JCEM 2005;90:4260–66). This case differs from the previous two in so far as there were no associated pulmonary problems associated with immunodeficiency. When the patient was initially presented to a pediatric endocrinologist he was 16 years of age, having recently moved from the Dutch Antilles to The Netherlands. He was prepubertal with bone age delayed at 9 years. Height at that time was not reported, but investigations of his short stature revealed a peak GH level of 25 µg/l (50 mU/l) in response to GH-releasing hormone, with a normal 24-h plasma GH profile and a very low insulin-like growth factor-1 (IGF-1) level (-5.6 standard deviation score [SDS]). A presumptive diagnosis of GH neurosecretory dysfunction was made and a trial of GH treatment undertaken (GH 0.5mg/day for 25 months then GH 1.0 mg/day for 3 months), with minimal increase in growth velocity or IGF-1. Final adult height was –5.9 SDS. The patient returned to the Dutch Antilles shortly afterwards and was lost to follow-up until referred back aged 30 years at a final height of 141.8 cm (–5.9 SDS). The diagnosis of GH resistance was then considered in the context of the recent case reports of STAT5b mutations and a homozygous frameshift (nucleotide 1102-3insC, Q368fsX376), which results in an inactive truncated protein that lacks most of the DNA binding domain and the SH-2 domain.

Therefore, the phenotype of STAT5b mutations can clearly be wider than the initial cases identified, and clinicians should explore this diagnosis more extensively in patients with extreme short stature who lack the classical GH insensitivity (Laron) syndrome features, but have biochemical and clinical evidence of GH resistance (FEBS J 2006;273:3454–66).


Editor’s note: The resistance to growth hormone (GH) associated with post-receptor signal transduction pathways is likely to have a wider prevalence than has been recognized to date (J Clin Endocrinol Metab 2006; 91:3482–5). Short stature associated with low insulin-like growth factor-1 (IGF-1) and IGF binding protein-3 levels with apparently normal GH secretion is remarkably common. The potential causes for such “primary IGF deficiency” remain to be defined, and these include the signal transducer and activators of transcription (STAT) signaling pathways. These authors evaluated four short children in whom growth is responsive to increased doses of GH treatment, and their in vitro fibroblast studies show impaired STAT3 activation by both GH and interferon, with cell-cycle arrest at the G0/G1 phase. Molecular analyses showed no abnormality of STAT5 or STAT3 genes, and the basis for the impaired responsiveness remains unexplained.
A variable degree of intrauterine and postnatal growth retardation in a family with a missense mutation in the insulin-like growth factor I receptor.

Walenkamp MJ, van der Kamp HJ, Pereira AM et al.
Leiden University Medical Center, Leiden, The Netherlands.
J Clin Endocrinol Metab 2006;91:3062–70.

Editor’s note: The insulin-like growth factors (IGFs) are critical for fetal development as well as mediating the postnatal effects of growth hormone. This paper reports a mother and child carrying a missense mutation in the intracellular kinase domain of the IGF-1 receptor. Functional deficiency of receptor activity was demonstrated in maternal dermal fibroblasts. Mother and daughter exhibited prenatal and postnatal growth deficiency, with relatively high growth hormone and IGF-1 levels.

This phenotype is broadly similar to that reported for a mother and child with a heterozygous mutation in the cleavage site of the IGF-1 receptor (IGFR) proreceptor (JCEM 2005;90: 4679–87), and less severe than that observed in a girl with compound heterozygosity for two missense mutations in exon 2 of the IGF-1R and a boy with a heterozygous nonsense mutation, also in exon 2 (NEJM 2003;349:2211–22). No human homozygous IGF-1R mutations have yet been reported, and the knockout mouse model would predict intrauterine death or early neonatal lethality.

GH Treatment

Carel JC.
Hôpital Robert Debré and Faculté de Médecine René Descartes, Paris, France.

Editor’s note: Treatment with growth hormone (GH) has significantly improved the lives of children of short stature. The final outcome of height depends on nature and the level of defect in the GH axis, as well as the time of puberty onset. Pubertal growth represents 15–20% of adult height, and increasing the amplitude of the pubertal spurt has been a focus of many interventions.

Precocious puberty can lead to shorter “window in time” for GH therapy and, thus, a less optimal final height. Gonadotropin releasing hormone (GnRH) agonists have been used to suppress the gonadotropic axis and induce a delay in puberty onset, to allow a longer adolescent growth spurt and later closure of the epiphysis. Although several studies have shown that the use of GnRH agonists can induce a modest increase in height when used for an extended period of time, concomitant administration of these agents with GH is controversial and has not been approved for use in individuals with short stature. The database analyses and small uncontrolled trials conducted to date have produced contradictory results and lack conclusive data to show that additional GnRH agonists increases final height. The author of the current paper, therefore, rightly concludes that long-term and adequately powered clinical trials, focusing on efficacy, safety, and clinical significance, are required to fully evaluate combination therapy with GH and GnRH agonists in short adolescents.

Long-term primary medical therapy with somatostatin analogs in acromegaly.
Su DH, Liao KM, Chen HW et al.
Far Eastern Polyclinic, Taipei, Taiwan.

Editor’s note: Acromegaly is caused by excessive growth hormone (GH) secretion, and is associated with an increased morbidity and mortality rate. Pituitary adenoma is the most common cause of hypersecretion of GH.
Relief of symptoms can be achieved by surgical removal of the GH-secreting adenoma, radiotherapy, or pharmacotherapy using a somatostatin analog or a GH receptor-blocking agent (e.g. pegvisomant).

Surgical success depends on the size of tumor and the experience of the surgeon. Surgical removal of a microadenoma can cure the cause of hypersecretion of GH. Radiotherapy has generally been reserved for recurrent or locally invasive tumors. Both methods usually result in multiple hormone deficiency, requiring lifelong hormone replacement.

Several studies have indicated medical therapy as a primary treatment for acromegaly. However, it has the disadvantage of being chronic, which can be expensive and produce side effects; nevertheless, it can relieve symptoms and reduce tumor size.

In the current study, two patients with acromegaly were treated with somatostatin analogues for 10–14 years. Neither patient was a candidate for surgery. The treatment resulted in normalization of GH and insulin-like growth factor-1 levels, as well shrinkage of the tumors. This paper confirms that medical therapy can be used as primary treatment in a selected patient population with acromegaly.

**Growth hormone treatment and risk of second neoplasms in the childhood cancer survivor.**

Editor’s note: The roles of growth hormone (GH) and insulin-like growth factor-1 as potential triggers for stimulating tumor development continue to generate much speculation, research, and (inevitably) some degree of clinical concern. The patient population most at risk within the pediatric domain is of course the group of children who have suffered one previous tumor disorder for which treatment itself has resulted in the need for GH-replacement therapy. Most of these represent central nervous tumors. The risk of a second neoplasm (SN) in such patients can only be quantified by meticulous, long-term, follow-up studies of these “at risk” cohorts, with periodic review to produce the most recent analysis.

This brief report introduces approximately 3 years of additional follow-up data to the authors’ previous published data in this field (*J Clin Endocrinol Metab* 2002;87:3136–41). The observation of a further five new SN cases, for a total of 20 out of 361 5-yr survivors of childhood cancer patients on GH treatment, yields a calculated increased risk ratio of 2.15 (95% confidence interval = 1.3–3.5) compared with a risk ratio of 3.21 in their previous analysis. This suggests that the risk of SN decreases with duration of follow-up and that SNs are more likely to develop relatively early after the diagnosis and treatment of primary cancer. The occurrence of meningiomas as the most common SN (nine of twenty cases) bears some similarity with the experience of adults under surveillance for tumor development during GH treatment, and most likely relates to common mechanisms, although not necessarily to GH treatment itself.

Continued surveillance of these patient populations will be essential to clarify links between these tumors and GH treatment, and hopefully provide progressive reassurance of the safety of GH replacement therapy for these disorders.

**Comparative pharmacokinetics and pharmacodynamics of a new sustained-release growth hormone (GH), LB03002, versus daily GH in adults with GH deficiency.**

Editor’s note: This small study (nine adult patients) demonstrates the efficacy and tolerability of weekly injections of a depot growth hormone (GH) preparation over a 5-week period. Sustained-release GH has
been formulated by incorporating GH with sodium hyaluronate and dispersing the product in an oil base compound of medium-chain triglycerides. Delivered subcutaneously after a 4-week washout period from standard GH treatment, daily injection of the selected dose was able to mimic peak levels of GH and sustain serum insulin-like growth factor-1 levels equivalent to those on daily GH treatment. Although well-tolerated over this short treatment period, sustained-release GH will require further substantial, extensive investigation in a wider population and an extension to children in order to assess whether such a depot treatment would be a feasible and appropriate replacement alternative to current, more physiological, daily GH treatment.

Recurrence of brain tumours in patients treated with growth hormone: analysis of KIGS (Pfizer International Growth Database).

Editor’s note: The KIGS (Pfizer International Growth Database) pharmacovigilance database has proven to be a valuable resource for monitoring the side effects and treatment outcomes of children and adolescents receiving recombinant human growth hormone (rhGH) therapy. In this paper by Darendeliler et al., the KIGS database was analyzed in an attempt to confirm the view that rhGH therapy given to childhood brain tumor survivors with GH deficiency does not result in an increased risk of tumor recurrence. There has always been a hypothetical concern that rhGH given to cancer survivors may increase the risk of tumor recurrence. This is largely based on observations made in animal and in vitro study settings, where GH administration has been shown to increase the risk of malignancy, particularly when administered at supraphysiological doses.

In this study, data for tumor recurrence were analyzed retrospectively in 2503 patients who had previously received treatment for intracranial tumors. The recurrence-free-survival varied significantly between the different intracranial tumor categories, and ranged from 63% after a follow-up period of 10 years for craniopharyngiomas to 92% after 4.6 years for medulloblastomas.

Overall, the frequency of recurrence was:

- 11.7% for craniopharyngiomas (n=1038).
- 4.7% for medulloblastoma (n=1655).
- 8.8% for ependymomas (n=113).
- 4.0% for germinoma (n=297).
- 9.8% for astrocytoma or glioma (n=400).

These data are similar to previously reported studies carried out on fewer patients, and are reassuring in that the recurrence rates are no higher than those reported in the literature for the natural follow-up of these tumors in patients not receiving rhGH therapy.

Growth hormone treatment and adverse events in Prader-Willi syndrome: data from KIGS (the Pfizer International Growth Database).

Editor’s note: This report by Craig et al., on behalf of the KIGS (the Pfizer International Growth Database) pharmacovigilance survey, provides data on growth outcomes and adverse events from the largest cohort (n=675) of children treated with recombinant human growth hormone (rhGH) with Prader–Willi syndrome (PWS) to date. These are welcomed data given the increasing numbers of children with PWS being prescribed rhGH therapy, and because of the concerns that rhGH may be associated with significant adverse events, including reports of sudden death in a small number of children after a relatively short duration of rhGH treatment. Longitudinal data on growth parameters were collated from all those PWS patients who had completed at least 1 year of therapy (n=328) and data on adverse events from all
other PWS patients receiving rhGH entered onto the KIGS database (n=675).

Height standard deviation score (Ht SDS) and height velocity increased significantly during treatment with responses greater in pre-pubertal patients (Ht SDS –0.7 vs. –1.8 pre-treatment) compared with those patients already in puberty (Ht SDS –1.5 vs. –1.8). Growth velocity during the first year of treatment was determined by rhGH dose, body weight (positive correlation), height SDS minus mid-parental height SDS, and chronological age (negative correlation). However, this only accounted for 40% of the variation in rhGH response. Unfortunately, data relating to more sensitive assessments of body composition (e.g. total body fat or fat-free mass) were not available and were limited to measurements of body mass index (BMI). BMI was reduced by a small, but not statistically significant, extent after 1 year of rhGH therapy, and did not change after 2 years of treatment.

Of the 675 rhGH-treated patients in KIGS, scoliosis was the most commonly reported adverse event and was observed in 24 patients. Scoliosis is a recognized feature of PWS, and in 10 out of the 24 cases, pre-existing scoliosis had been noted that progressed with rhGH therapy. Nine obese PWS patients (all age >11 years) developed abnormalities in glucose metabolism (four with impaired glucose tolerance and five with type 2 diabetes) with rhGH therapy. Finally, there were five reported cases of sudden death (three males; age range 3–15 years; duration rhGH therapy range 2–95.5 weeks). Three of the children were obese males (weight SDS 2.4, 3.1, and 5.7) in whom the circumstances of death were attributed to bronchopneumonia, respiratory insufficiency, and sleep apnea, respectively. Unfortunately, no data were available to determine whether rhGH therapy specifically resulted in a deterioration of respiratory function and contributed to their death.

Overall, this analysis of the KIGS database provides a degree of reassuring evidence that rhGH therapy is effective in improving linear growth over the relatively short-term period of 1–2 years. Clearly, further data are required to determine whether rhGH improves final height, long-term body composition, and metabolic outcomes. In terms of adverse events and safety of rhGH therapy, ongoing caution and vigilance are required when embarking on this treatment. Current recommendations that ear, nose, and throat assessment and sleep studies should be performed before starting rhGH therapy in PWS patients seem justified, and those with extreme obesity or disordered breathing should be closely monitored for adverse events.

**Miscellaneous**

**Increased atherosclerotic lesion area in apoE deficient mice overexpressing bovine growth hormone.**

Andersson IJ, Ljungberg A, Svensson L et al.
Göteborg University, Göteborg, Sweden.
*Atherosclerosis* 2006;188:331–40.

Editor’s note: Growth hormone (GH) and insulin-like growth factor-1 (IGF-1) have important effects on the cardiovascular system. In conditions of excess GH, for example, acromegaly increases cardiovascular morbidity and mortality. The mortality has generally been attributed to the development of cardiomyopathy and to the concomitant effects of hypertension and dyslipidemia on blood vessels. However, surprisingly, there are few data on the vascular pathological changes associated with GH excess that support this hypothesis.

In the current study, an elegant series of animal experiments are described, in which the effects of high GH concentrations on atherosclerotic lesion formation were studied. The authors developed a novel transgenic mouse model by crossing a bovine GH (bGH)
overexpressing mouse with an apolipoprotein E deficient (apoE−/−) mouse that spontaneously develops hypercholesterolemia and atherosclerotic lesions similar to those observed in humans. The atherosclerotic lesion area of the thoracic aorta was determined in the new mouse model (apoE−/−/bGH) and in apoE−/− littermates after feeding with either a low-fat standard diet or high-fat content (Western) diet for 22 weeks. The crossbred apoE−/−/bGH mice showed significantly larger atherosclerotic lesions compared with apoE−/− mice, both on the standard and Western diets. ApoE−/−/bGH mice also had significantly higher blood pressure and evidence of increased inflammatory markers (serum amyloid and hepatic C-reactive protein messenger RNA expression). The markedly disturbed serum lipoprotein profile characteristically seen in the apoE−/− mice was not worsened by the GH over-expression present in apoE−/−/bGH mice. The authors conclude that excess GH accelerates the development of atherosclerosis seen in apoE−/− mice. The lack of any change in serum lipid profile leads to speculation that the mechanism behind this effect may be due to either the direct consequence of GH on the vascular atherosclerotic process that occurs in the blood vessel wall, or indirectly due to concomitant increases in blood pressure in the general inflammatory state.

Central and opposing effects of IGF-1 and IGF-binding-3 on systemic insulin action.
Muzumdar RH, Ma X, Fishman S et al.
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Editor’s note: The insulin sensitizing effects of insulin-like growth factor-1 (IGF-1) are mediated partly through its ability to suppress growth hormone (GH) (an insulin antagonist) and partly through GH independent effects on peripheral glucose uptake (which is increased) and hepatic glucose production (which is decreased). The hepatic effects of IGF-1 on glucose metabolism are intriguing given that the reported paucity of IGF receptors in the liver has raised questions as to how these GH independent effects of IGF-1 may be mediated. There is some evidence that the metabolic effects of insulin could partly be mediated via the central nervous system (CNS) acting through the hypothalamus. Given the relative abundance of IGF-1 receptors in this area of the brain, there is a possibility that the IGF-IGF-binding protein (IGFBP) system in the CNS may also be physiologically relevant.

In the current study, the CNS-mediated effects of IGF-1 and IGFBP-3 on insulin sensitivity were examined. Using a rat model, the authors’ experimental protocol involved giving intracerebroventricular (ICV) infusions of either IGF-1, IGFBP-3, or artificial cerebrospinal fluid (CSF) immediately before and during a hyperinsulinemic (3 mU/kg·min−1) and euglycemic (7–8 mmol/L) clamp in order to assess effects on hepatic and peripheral insulin sensitivity. ICV IGF-1 administration resulted in significant improvements in hepatic insulin action (50%, p<0.05) when compared with controls receiving ICV infusions of artificial CSF fluid. In contrast to this, ICV infusion of IGFBP-3 significantly impaired insulin action in the liver (45% increase in hepatic glucose production, p<0.01). When compared with controls, ICV IGF-1 marginally increased peripheral glucose uptake, whereas ICV IGFBP-3 significantly decreased peripheral glucose uptake (approximately 30%; p<0.01). In order to clarify whether the effects of IGFBP-3 were IGF-1 independent or not, a mutant form of IGFBP-3 that binds to IGF-1, but which lacks any intracellular activity, was given via the ICV route. Mutant IGFBP-3 administration minimally inhibited both hepatic and peripheral insulin action, suggesting that IGF-1 binding alone is insufficient to mediate the ICV effects of IGFBP-3.

The authors conclude that IGF-1 and IGFBP-3 have opposing effects on glucose metabolism that may in part be mediated through the hypothalamus. Furthermore, the effects of IGFBP-3 on the hypothalamus may involve activity that is mediated by interfacing with other molecules in addition to IGF-1.
An IGF-I gene polymorphism modifies the risk of diabetic retinopathy.

Editor’s note: It remains unclear whether insulin-like growth factor-1 (IGF-1) is involved in the pathogenesis of microvascular complications of type 1 and type 2 diabetes (TD2M). Controversy exists as to whether it is the endocrine effects of circulating free IGF-1 or the autocrine or paracrine effects of locally produced tissue IGF-1 that are important for the development of diabetic microangiopathy.

In humans, a Cαn polymorphism in the promoter region of the IGF-1 gene has been identified and has been associated with lower serum total IGF-1 levels, lower height, and a higher risk of developing TD2M. This polymorphism can be used as a proxy for genetically determined IGF-1 expression in the body. In this study, the presence or absence of this particular polymorphism was determined in a large cohort of subjects with either impaired glucose tolerance (IGT; n=775), T2DM (n=394), or healthy controls (n=4366). Subjects were recruited from a single-center, prospective, follow-up study of all residents aged >55 years living in a suburb area of Rotterdam, The Netherlands. Ophthalmic assessments, in the form of retinal photography, were carried out in this population at initial baseline assessment on recruitment, on to the study, and after a follow-up period of 6–7 years. This was carried out in order to determine retinal vessel diameter and to detect incident diabetic retinopathy. The wild-type IGF-1 genotype was found in approximately 73% of the population, whereas approximately 27% were variant carriers with the Cαn polymorphism. Variant carriers with IGT or T2DM appeared to have larger retinal arteriolar and venular blood vessel diameters at baseline compared with wild-type carriers. This was particularly evident in those variant carriers with IGT or T2DM who went on to develop incident retinopathy during the follow-up period. Variant carriers with IGT or T2DM had an increased risk (odds ratio 1.8 [95% confidence interval 1.0–3.2]; p=0.04) of retinopathy compared with subjects with the wild type IGF-1 gene.

The authors speculate that larger retinal blood vessel diameter is associated with increased progression of retinopathy, and that IGF-1 gene polymorphisms may modulate susceptibility and subsequent progression of diabetic retinopathy.

Insulin-like growth factor binding protein (IGFBP-1) involvement in intrauterine growth retardation: study on IGFBP-1 overexpressing transgenic mice.

Editor’s note: Severe intrauterine growth retardation (IUGR) in humans is characterized by disturbances in normal growth and bone maturation. The insulin-like growth factor (IGF) system is thought to have important pleiotropic effects on bone and cartilage development, and disturbances to the equilibrium of this system may play a key role in the development of the IUGR phenotype. The IGF-binding proteins (IGFBPs) are important in regulating the metabolic and mitogenic effects of IGFs, and in humans IUGR is associated with high levels of the inhibitory binding protein IGFBP-1. In the current study, the authors assess the in vivo impact of circulating IGFBP-1 on fetal growth, bone development, and tissue carbohydrate resources in a transgenic mouse model that overexpressed IGFBP-1 in the liver from embryonic day (E)14.5 through to adulthood.

Growth retardation was observed as early as E17.5 in homozygous (HM) transgenic mice, who were 20% smaller at birth compared with non-transgenic (NT) mice. Anatomical analysis of the skeletons showed that HM mice exhibited several skeletal abnormalities, including smaller dysmorphic bones and reduced bone mineralization. IGFBP-1 overexpression in the HM mouse also resulted
in decreased fetal hepatic glycogen, and blood glucose levels in newborn HM mice pups were significantly lower compared with NT pups. Maternal IGFBP-1 expression was also clearly associated with neonate growth retardation (newborn weights from HM mothers were 20% smaller than newborns from NT mothers) and reduced fetal carbohydrate resources.

Overall, these experiments suggest that fetal growth retardation and delayed bone mineralization in HM mice are related to the overexpression of fetal and maternal circulating human IGFBP-1. The authors speculate that excess IGFBP-1 may be one of the principal factors contributing to growth retardation and skeletal abnormalities seen in severe cases of human IUGR.

**Insulin-like growth factor I: a predictor of long-term glucose abnormalities in patients with acute myocardial infarction.**

**Editor’s note:** During admission with myocardial infarction, it is now recommended that all subjects should undergo an oral glucose tolerance test (OGTT) to identify patients with previously undiagnosed diabetes and other degrees of dysglycaemia. This study examines associations between levels of fasting insulin-like growth factor-1 (IGF-1), IGF binding proteins (IGFBPs), and newly detected abnormal glucose tolerance in patients with acute myocardial infarction, and repeats the assessment at 12 months. The authors of the current study found that patients with newly detected abnormal glucose tolerance had lower levels of IGF-1 and IGFBP-3 compared with controls and patients with normal glucose tolerance, and IGF-1 predicted the glucometabolic state at 12 months. They conclude that IGF-1 may be a clinically useful tool for the classification of patients with myocardial infarction; however, they do not consider that this test is not available in many local biochemistry laboratories, and that a repeat OGTT is a simple and well validated method of determining glucometabolic status.

**Chromium picolinate supplementation attenuates body weight gain and increases insulin sensitivity in subjects with type 2 diabetes.**

**Editor’s note:** Lifestyle modification and pharmacological intervention are the recommended strategies for improving metabolic control in subjects with type 2 diabetes, but patients frequently use nutritional supplementation including chromium picolinate (CrPic). Although it has been suggested that CrPic supplementation improves glycemia, there are conflicting reports on its efficacy. The authors of the present article provided a comprehensive clinical evaluation of CrPic by conducting a randomized, double-blind, placebo-controlled trial in 25 patients with type 2 diabetes. The study design consisted of a 4-week washout period, when oral agents were discontinued, a 12-week period when treatment with sulfonylurea (glipizide gastrointestinal therapeutic system [GITS], 5 mg/day) was introduced and maintained, and a 24-week period of either glipizide GITS with placebo or glipizide GITS with 1000 µg of CrPic. At the end of each period (4th, 16th, and 40th weeks), the patients were assessed at the clinic for:

- Body composition (computer tomography and dual-energy-X-ray absorptiometry scans).
- Glucose tolerance (75 g glucose oral tolerance test) and insulin sensitivity (hyperinsulinemic–euglycemic clamp).
- Urinary chromium excretion.
- Levels of insulin, GHb, adiponectin, free fatty acids, and triglycerides.

Subjects randomized to sulfonylurea/CrPic had significant improvements in insulin
sensitivity (glucose disposal in mg/min per fat-free mass: 28.8, p<0.05 vs. 15.9, p=0.4), GHB (−1.16%, p<0.005 vs. −0.4%, p=0.3), and free fatty acids (−0.2 mmol/L p<0.001 vs. −0.12 mmol/L, p<0.03) compared with subjects randomized to sulfonylurea/placebo. Unexpectedly, the subjects randomized to sulfonylurea/placebo had a greater change of body weight (2.2 kg, p<0.001 vs. 0.9 kg, p=0.11), percent body fat (1.17%, p<0.001 vs. 0.12%, p=0.7), and total abdominal fat (32.5 cm², p<0.05 vs. 12.2 cm², p<0.10) compared with those randomized to sulfonylurea/CrPic. These data suggest a beneficial effect of CrPic on the body composition and fat distribution. The underlying mechanisms of these findings are not known but clinical research studies addressing dietary intake, skeletal muscle fat oxidation, and insulin signaling have been undertaken. However, these results do not agree with another study utilizing the same dose of CrPic, which found no effect on insulin sensitivity. (Diabetes Care 2006;29:521–5). Explanations for this different result suggested by the authors were that the participants in the other study were heavier, on insulin therapy, and more advanced in their disease. Therefore, controversy still remains and further studies are necessary to validate the beneficial effect of CrPic observed in this study.

The gender insulin hypothesis: why girls are born lighter than boys, and implications for insulin resistance.
Wilkin TJ, Murphy MJ.
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Editor’s note: The classic fetal origins hypothesis states that low birth weight is an indicator of poor fetal nutrition and results in gestational programming that predisposes the offspring to subsequent insulin resistance (fetal insulin hypothesis). This hypothesis is valid within both sexes. The facts that female birthweight is generally lower than male birthweight and that insulin is the principle growth factor in utero prompted the authors to hypothesize that female fetuses are more insulin resistant than male fetuses due to sex-specific genes (gender insulin hypothesis). The authors provide the following data suggesting that female subjects are intrinsically more insulin resistant than male subjects:

- Despite the lower birth weight of female babies, their insulin levels in the cord blood (essentially fetal) are higher than in their male counterparts.
- Before puberty, girls have higher fasting insulin levels than boys after adjustment for potential covariates (subcutaneous fat, body mass index [BMI], weight, height, visceral fat, waist circumference, and physical activity).
- The seeming switch in sex differences in adulthood (fathers in the same study were more insulin resistant than the mothers) reverses after adjustment for waist circumference, a proxy measurement of visceral fat mass associated with acquired insulin resistance.
- The regression analysis of the relationship between (log) insulin resistance and waist circumference shows that the slope between sexes is similar but the intercepts on the y axis (indicating insulin resistance that is independent from the waist circumference) are higher in women than in men.
- Type 2 diabetes is more predominant in young girls than boys, but this trend does not continue into adulthood due to the potential for greater accumulation of visceral fat in men. However, women are more prone to developing type 2 diabetes for any given BMI, suggesting that although men may be at greater risk, women are more susceptible.
- Female fetuses are predicted to be less responsive to the exaggerated trophic effects of fetal hyperinsulinemia associated with the mother’s gestational or type 2 diabetes.

The authors suggest that the hunt for insulin resistance genes should focus on those genes that account for the sex difference in birth weight. This search should begin with analysis of the XY chromosome pair.
Investigation of global developmental delay.
McDonald L, Rennie A, Tolmie J et al.
Royal Hospital for Sick Children, Glasgow, UK.
Arch Dis Child 2006;91:701–5.

Editor’s note: The stimulus to develop these evidence-based guidelines was the observation that four child development centers in Glasgow, Scotland each had different practices with regard to the use of laboratory investigations in preschool children presenting with global developmental delay (GDD).

The authors of this study recognize the difficulty facing all specialties, where the subject does not lend itself to multicenter, randomized controlled trials e.g. neurodisability. Although the evidence base was well searched, the protocol that was ultimately developed derived from level IV evidence i.e. a consensus of expert opinion. The discussion presented here is a comparison between guidelines developed in North America and those derived in this paper.

Guidelines were developed to assist in the assessment and management of children with GDD presenting to secondary level services. Evidence was found supporting the use of genetic and biochemical investigations on a screening basis, but there was no evidence to support the use of metabolic investigations or neuroimaging in the absence of other positive findings on history or examination. Detailed history and examination are paramount in the assessment of children with GDD and investigations can be a useful adjunct in determining etiology.

An easy-to-follow flowchart with a succinct explanation accompanies the guidelines.

Are adolescent boys with Klinefelter syndrome androgen deficient? A longitudinal study of Finnish 47, XXY boys.
Wikstrom AM, Dunkel L, Wickman S et al.
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Editor’s note: Klinefelter syndrome is a common form of male hypogonadism. Affected males have an increase in height velocity, tend to be long-legged, have a slightly lower than normal testicular volume, and tend to become centrally obese before puberty. Prepubertal boys with Klinefelter syndrome may have delayed speech development, learning difficulties, and problems with relationships. They are described as being quiet and have an unassured manner. All of these symptoms are related to androgen deficiency. Adults with Klinefelter syndrome are treated with testosterone substitution therapy.

The aim of this study was to consider whether adolescent boys with Klinefelter syndrome should be considered as candidates for testosterone therapy. To answer that question, the authors sought to find out whether the boys were actually androgen deficient or not.

They investigated 14 non-mosaic 47,XXY boys who were between the ages of 10 and 13.9 years. They were followed up for 4–37 months and stage of puberty and reproductive hormone measurements were checked repeatedly. Androgen activity was studied by measuring serum sex-hormone binding globulin (SHBG), leptin, and prostate-specific antigen (PSA) levels.

Interestingly, the onset and progression of puberty according to Tanner stages were normal in these boys, while serum testosterone concentrations increased as expected and were normal throughout follow-up. Indices of androgen action (decreases in serum SHBG and leptin and an increases in serum PSA levels) occurred as normal, except that the average leptin levels were higher in boys with Klinefelter syndrome.

Even though these boys had normal testosterone concentrations, they did have raised follicle stimulating hormone and luteinizing hormone levels and an exaggerated gonadotropin response to gonadotropin releasing hormone. Putting all the results together, the authors were unable to demonstrate unequivocal androgen deficiency and thus, androgen supplementation is not required during early puberty.