Treatment of children and adolescents with idiopathic short stature

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Abstract | Idiopathic short stature (ISS) is defined as shortness in childhood without a specific cause. ISS may be familial or nonfamilial and may be associated with or without delay of pubertal development. Treatment can be considered in an attempt to reduce the psychological burden caused by short stature in childhood and adult life. If counselling alone is not sufficient, medical modifications of the growth process can be attempted. In cases with pubertal delay, sex steroids, such as testosterone and oxandrolone, can favourably influence height velocity and growth tempo, although adult height is not affected. Medications that prolong the process of growth—for example, gonadotropin-releasing hormone agonists or aromatase inhibitors—might increase adult height, but findings to date are still experimental. Growth hormone therapy is approved for the treatment of very short children with reduced adult height expectation, as evidence has accumulated that this therapy can increase height in childhood and in adult life. Sensitivity to growth hormone is impaired in patients with ISS; therefore, doses higher than a replacement dose have to be applied. This treatment still needs to be optimized in terms of efficacy, cost-effectiveness and long-term safety. A debate is ongoing concerning the psychological benefit of height increase, with clinicians warning against the medicalization of a deviation in height.

Ranke, M. B. *Nat. Rev. Endocrinol.* **9**, 325–334 (2013); published online 23 April 2013; doi:10.1038/nrendo.2013.71

Introduction

For paediatricians, short stature is a very frequent diagnostic problem. A broad spectrum of disorders, some general in nature and others specifically related to the growth process, have to be considered during the diagnostic process. Whilst it has become possible to link short stature to specific causes in a great number of short children, for a substantial number a specific cause is not found. If no underlying cause can be determined, these children are considered to have so-called idiopathic short stature (ISS). The term is derived from Greek idios (one's own) and pathos (suffering).

Height development in humans is a complex process relating to the genetic growth potential of an individual. The process of height growth is divided into a prenatal phase (~ 25%), a prepubertal phase (~60%) and a pubertal phase (~15%), all of which are accomplished within a certain time frame (tempo). Deviations from the normal growth process may thus be caused by factors affecting the growth process itself and/or its tempo. The treatment of ISS and related topics have been reviewed in detail elsewhere,[1–4] and the results of an international consensus meeting have been documented.[3] This article discusses the best methods to alleviate the psychological burden that might be associated with short stature in ISS during childhood, adolescence or adult life. Furthermore, the development of various strategies to treat ISS is discussed and research to evaluate the efficacy and safety of these approaches is outlined.

Definition of ISS

Most experts accept that ISS be defined as a condition of short stature in which height is below –2 SD scores (SDS) (which is equal to the 2.3th percentile or often defined as <3rd percentile) for age, sex and the corresponding population, without evidence of a systemic disease, nutritional, psychological or chromosomal disorder, or overt hormonal abnormalities.[3,5] Specifically, children with ISS have a normal size at birth and no deficiency in growth hormone (GH), which is also known as somatotropin. Historically, a variety of other terms have been used for ISS, such as normal-variant short stature, constitutional short stature, constitutional delay of growth and adolescence (CDGA), constitutional delay of growth and puberty (CDGP), small/delay, familial short stature, and others. These terms are partly focused on short stature alone (for example, constitutional short stature) or on the combination of shortness and a retarded tempo of growth and puberty (for example, CDGA).

The term ISS includes both children whose height is below the normal range but inside the familial target range (termed familial ISS)[6] and children who are short but whose height is outside the familial target range (termed nonfamilial ISS). In addition, these two varieties can be further subdivided into those with normal and those with delayed timing of the onset of puberty (>13 years in girls and >14 years in boys).[7] As there is no definite method of predicting delayed onset of puberty

Competing interests
The author declares associations with the following companies: Ipsen, Novo Nordisk, Pfizer. See the article online for full details of the relationships.

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Key points

- Idiopathic short stature is defined as a condition of short stature after exclusion of specific causes
- Children with idiopathic short stature often remain short in adult life
- Shortness might cause a psychological burden, particularly in childhood
- Children with shortness and/or developmental delay can be treated with sex steroids, medications that prolongate growth or growth factors
- Therapy with recombinant human growth hormone is approved (in the USA) because of its potential to increase adult height
- Although growth hormone therapy is safe in the short term (for example, <10 years), long-term safety needs to be explored further

in a child with short stature—including the determination of bone maturation—a delay of puberty can only be defined when pubertal age has been reached and not before. Thus, ISS is exclusively defined on statistical grounds, and a numerical basis needs to be established empirically in respective populations and after exclusion of specific causes of shortness. An estimated ~80% of children presenting to a specialist because of short stature qualify for the diagnosis ISS.[1]

To date, it is unclear whether individuals with ISS represent the extremes within the normal distribution of height and/or the tempo of development or whether their developmental pattern is a reflection of distinct inborn deviations. Height and its developmental tempo are an expression of the genetic and epigenetic make-up of an individual's 'height' genes and presumptive 'tempo' genes and the interaction of these genetic factors with metabolic and environmental factors. Genome-wide association studies in the past few years have identified genes that are predominantly associated with the achievement of adult height.[8,9] The discovered genes and their polymorphisms are of relevance for general cellular or metabolic mechanisms, relate to growth-regulating systems (such as the GH/insulin-like growth factor 1 [IGF-1, also known as IGF-I] axis) or are of importance for mechanisms at the growth plate.[10]

Height is a phenotype that results from a multitude of genes (a classic polygenetic trait), which is even true for most of the extremes of height.[11] Likewise, there is an increasing understanding of the genetic and pathophysiological mechanisms leading to an activation of the hypothalamic core ('gonadostat'), which initiates and maintains an orderly and timely progression of pubertal events.[12–16] In addition, changes are occurring in anthropometric characteristics, such as height, weight and the timing of pubertal developments, in various populations worldwide. The 'secular' trend of an increase in height—foremost during childhood but also in adults—and the advancement of the timing of certain pubertal landmarks are assumed to be the consequence of dynamic socioeconomic and environmental influences.[17–20] The parallel changes in growth and puberty that are occurring in various populations underline the interdependence of these phenomena to height.[21]

Diagnostic evaluation

Only up-to-date reference data on the height and pubertal landmarks in the population that matches that of the individuals referred to physicians will enable an accurate definition of ISS into its various subgroups. If such references are not available, the WHO references for height are recommended as a compromise.[22] However, misleading conclusions based on comparison with such universal growth references must be avoided, particularly when children from other ethnic backgrounds than the indigenous population are concerned. As in any child with short stature, the diagnostic work-up for the definition of ISS is complex, as it requires the exclusion of a multitude of potential causes of shortness.[23] One of the predominant diagnostic efforts relates to the GH/IGF-1 axis, because idiopathic isolated GH deficiency (GHD) shares many of the clinical and anthropometrical characteristics of ISS. Similar to GHD, the basal levels of IGF-1 often tend to be subnormal in ISS.[24] Whether this subnormal level is the result of impaired GH secretion, impaired IGF production or other causes affecting the concentration of IGF-1 in blood is unclear.[25]

The endocrinological diagnosis of ISS is primarily made by excluding impaired GH secretion (Table 1). However, methodological problems and a diversity of assay types exist in the measurement of GH and GH secretion.[26,27] All of these methods of testing for GH secretion have a low level of reproducibility and, in addition, a lack of normative data exists in children and adolescents.[27] The cut-off value to distinguish between GHD and ISS was traditionally considered a GH level of 10 μg/l to standard stimulation tests, but when using modern international reference preparations for GH this figure corresponds to 6.7 μg/l. Whether the borders between the diagnoses ISS and GHD will be more strengthened or blurred if spontaneously secreted GH is evaluated requires further evidence.[28]

Rare disorders of the GH/IGF-1 axis that are not caused by impaired GH secretion but by primary IGF deficiency might also have to be considered as a possible cause of short stature. These rare disorders include those caused by defects in the GH receptor and its signalling cascade which result in impaired IGF-1 generation, IGF-1 receptor defects or an impairment of the IGF-binding protein complex acid labile subunit (ALS).[29,30] The discovery of a genetic defect in suspected cases *a priori* excludes the diagnosis of ISS. However, clinical symptoms that suggest genetic abnormalities may be absent or very subtle, such as in patients with SHOX deficiency,[31,32] and in individuals with mutations in the ghrelin receptor,[33,34] or in the natriuretic peptide or its receptor.[35,36] Thus an additional genetic work-up might need to be considered in these individuals.

Spontaneous height achievement in ISS

A number of investigations have been conducted about the spontaneous adult height achievement in children with ISS.[37] In two of these studies, the children have been classified into those with familial and nonfamilial ISS.[38,39] Growth charts for children with ISS have also been devised.[39] All together, about half of all individuals with ISS remain short in adult life.[38,39] Children with familial ISS tend to reach their adult height target,

Table 1 | Distinctions between ISS, GHD and IGFD

Diagnostic features	Isolated GHD	ISS	IGFD
Height	<–2.0 SDS for age and sex	<–2.0 SDS for age and sex	<–2.0 SDS for age and sex
Body proportions	Normal	Normal or subtle deviations	Normal
Results of GH tests	Two tests below cut-off level (7–10 μg/l)	Any test above cut-off level (7–10 μg/l)	Any test above cut-off level (7–10 μg/l)
Basal serum level of IGF-1	<–1.0 SDS for age and sex	Variable	<–2.0 SDS for age and sex
sIGF-1 to rhGH treatment	Increase	Variable response	Insufficient
Growth with rhGH	Very good	Variable	Insufficient
Genetic cause	Rare	No (subtle anomalies)	Common

Abbreviations: GH, growth hormone; GHD, growth hormone deficiency; IGF-1, insulin-like growth factor 1; IGFD, IGF-1 deficiency; ISS, idiopathic short stature; rhGH, recombinant human GH; SDS, SD score; sIGF-1, serum IGF-1.

whereas children with nonfamilial ISS tend to reach an adult height that is ~0.5 SDS below the height target. In both types of ISS, adult height predictions made on the basis of bone age tend to predict height outcomes above those actually achieved, particularly if bone age is severely (>2 years) delayed.[40,41]

Presently, no method is available to predict the spontaneous height outcomes in an individual child accurately. Whether adult height predictions using automated bone-age reading will improve this situation for children with ISS needs further investigation.[42] Taken together, the studies suggest that children who present as very short (height <–3.0 SDS) at a very young age, have a low target height (<–1.0 SDS), and have no retarded bone age are the most likely to stay short. Whether the less favourable height outcomes observed in women compared with men who present with ISS in childhood is the consequence of biases or is based on physiological sex differences remains unclear.[38]

Psychological consequences

On the basis of the assumption that negative psychological consequences can arise from shortness alone or shortness combined with developmental delay in childhood and/or adolescence, investigations have focused on three domains: stress factors as an immediate consequence of shortness; consequences of adaptation processes to such stress factors (coping); and psychopathology as an outcome. In addition, investigations have been carried out concerning the psychological effect of short stature in adult life. Extensive literature exists on the subject but with divergent findings. The patient groups investigated vary with regard to their ethnic and socioeconomic backgrounds. Methodological approaches differ and are not always standardized. Foremost, however, the results of the investigations do not give a uniform or conclusive picture of what the psychological consequences of shortness in childhood and adulthood are. Excellent reviews are available on these topics.[2,43–45]

Within the context of discussing treatment options for children with ISS here, a few conclusions may be attempted. In general, short children are quite frequently exposed to stress factors as a result of their height, in terms of being teased by their peers and juvenilized by adults, which can have negative effects on self-perception, social adjustment and behaviour. Problems of psychosocial functioning are more frequent in individuals referred to physicians because of their short stature than in children with normal stature; however, psychosocial difficulties are not more frequent in children with short stature not referred to physicians than in children with normal stature.[46–48] Thus, a child's psychological situation is affected by a multitude of influences, not least by the parents' perception of shortness and the familial and socioeconomical conditions. Psychological factors and quality of life (QOL) measured in groups of children with ISS differ statistically when compared with those in children of normal height but are often not found to be outside the normal range.[49] Wide individual variation exists, and specific psychopathology can be attributable to shortness in some cases but not in others.

In adults with short stature, a significant correlation between height and QOL has been shown by Christensen and co-workers.[50] In this study, a significant reduction in QOL was found in individuals with a height <–2.0 SDS, and the researchers concluded that an increase in height of 1 SDS in these individuals would be expected to increase QOL. Whether psychological findings in adults with short stature are the reflection of their present height or the repercussions of potentially negative experiences during childhood and adolescence remains unknown. In the author's view, these investigations suggest that physicians who treat children with ISS need to attempt to get a comprehensive picture of the child's circumstances of life and their psychological situation. In the future, the measurement of validated QOL items may become an integral part of the decision-making process of growth-promoting treatments.

Treatment

The decision to embark on any form of treatment for ISS is made primarily on the basis of an exact diagnostic classification within the spectrum of ISS (namely, shortness with or without delay in development); an accurate as possible prediction of spontaneous adult height; the diagnosis and exclusion of specific psychopathology that would require therapy outside the somatic area (and might effect somatic treatment and the appraisal of its benefit); and full understanding by the patient

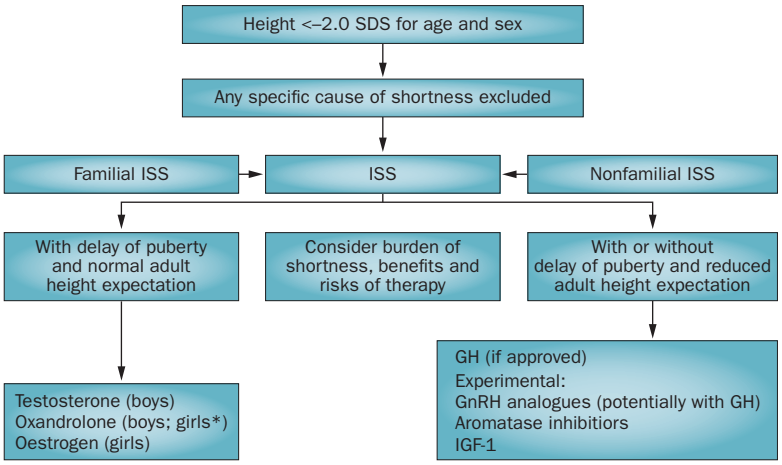

Figure 1 | Algorithm for the diagnosis and treatment of ISS. Before treatment can be considered, specific causes of shortness need to be excluded. The resulting diagnostic approach depends on the aims of treatment, which differ between an attempt to treat shortness alone or to also correct developmental delay in childhood. *Considering potential androgenic effects. Abbreviations: GH, growth hormone; GnRH, gonadotropin-releasing hormone; IGF-1, insulin-like growth factor 1; ISS, idiopathic short stature; SDS, SD score.

and parents of the aims of treatment, the modalities and duration of treatment, the expected efficacy and the potential risks and costs of therapy. This decision-making might occur as a step-wise process, and needs to be accompanied by empathy and cautious guidance by the treatment team. Figure 1 illustrates an algorithm for the diagnosis and treatment of ISS.

An essential part of providing care to children and adolescents with ISS who are seeking medical help is to give advice as to the generally benign nature of their shortness and to create an understanding of the individual's situation. Advice and strategies to cope with psychological problems related to shortness were the only 'treatment' that physicians could offer before medical interventions became an option. In children and adolescents with less severe short stature, this psychological approach remains an effective way to help. In keeping with the ethical principle of Hippocrates *primum non nocere* (first, not to harm), interventions should not be justified by the 'medicalization' of physiologic variations, including short stature, as a defect or disease,[51] or by other considerations not exclusively in the interest of the affected child.

Medications that have an effect on height in ISS can be divided into those that increase height velocity without having a major effect on adult height, and those that also have the potential to considerably augment adult height. The medications used to treat ISS reflect our present understanding of the regulators of the postnatal growth process; statural growth is predominantly determined by cellular processes that occur at the epiphyseal growth plates of the long bones, and the growth of the long bones is characterized by chondrocyte proliferation. This process is associated with a multitude of structural and functional changes, for which GH and IGF-1 of systemic and/or local origin have a major role.[52,53]

Growth of long bones ends when the capacity of the cells involved to replicate is exhausted, as a result of an inherent programme or other factors, of which oestrogens are main factors in promoting growth-plate senescence.[54–56] Factors that augment the systemic or local production of GH and GH-dependent factors (such as IGF-1), and factors that stimulate the proliferation of growth-plate chondrocytes independently of the GH/IGF-1 system (such as androgens) promote longitudinal bone growth.[57] Oestrogens and androgens (by conversion into oestrogens) augment the secretion of GH from the pituitary gland but enhance the process of growth-plate senescence, which brings the growth process to an end.[58] Thus, the quantitative presence and the duration of action of these hormonal components determine the net effect on the growth process. These hormones, their derivatives and the factors influencing their secretion are, therefore, used in attempts to positively affect growth in patients with ISS.

Testosterone

In male individuals with ISS and delay in pubertal development (CDGA or CDGP), pubertal failure is often more of a burden than short stature. Testosterone esters are usually prescribed when puberty has not commenced after the age of 13–14 years, in order to stimulate growth and induce a masculine phenotype and body composition.[59,60] Treatment modalities in children with delayed puberty are principally identical to those in children with hypogonadism and vary according to national guidelines and the individual's circumstances.[61,62] Low doses of testosterone esters (50–100 mg by intramuscular injection per month) are effective in stimulating growth and puberty without affecting predicted or observed adult height.[63–66] Similarly, in girls, low-dose oestrogen does not negatively affect adult height outcomes.[67] In the experience of the author, a short course of treatment with testosterone (for example, 6 months) in boys, or a short course of oestrogen therapy in girls, may suffice to induce a spontaneous development of puberty and have a substantial psychological benefit.

Oxandrolone

Oxandrolone, an anabolic androgenic steroid, is a testosterone derivative, which has less androgenic effects than testosterone and does not aromatize to oestrogen. In the USA, oxandrolone is FDA-approved for the treatment of short stature in girls with Turner syndrome. Although the effect of oxandrolone on growth is not completely understood, it is probably not mediated through an augmentation of the GH/IGF-1 axis but is the result of direct effects at the level of the growth plate. Oxandrolone has been used and studied widely in children with growth delay.[68,69] In these children, oxandrolone increases height velocity without affecting expected adult height. As the androgenic effect of oxandrolone is small, this agent can be given to children of >9 years of age with presumed pubertal delay.[70] The dose given to patients with ISS is usually 2.5–5.0 mg orally per day restricted to a period <1 year. Although oxandrolone can also be

Table 2 | Effects of long-term GH treatment in patients with ISS

Study	Study characteristics								
	Groups	*n*	% male	Age at start (years)	Height at start (SDS)	Dose GH (mg/kg per week)	Final height (SDS)	Change in height (SDS)	Years on GH
Hindmarsh 1996[91]	GH	10	60	8.4	–2.2	0.22	–1.9	NR	9
	Control	6	16	7.6	–2.3	–	–2.0	NR	–
McCaughey 1998[96]	GH	8	0	6.2	–2.5	0.33	–1.1	1.4	6.2
	Control	6	0	6.1	–2.5	–	–2.4	NR	–
	Control	20	0	6.2	–2.3	–	–2.1	NR	–
Hintz 1999[97]	GH	80	71	10.2	–2.7	0.3	–1.4	1.3	5–7
Wit 2002[100]	GH	23	70	10.2	–3.6	0.2	–2.4	1.2	5.9
	GH	30	67	10.7	–3.2	0.3	–1.8	1.3	5.9
	Control	64	52	10.9	–3.0	–	–2.4	NR	–
Leschek 2004[101]	GH	11	82	12.9	–2.8	0.22	–1.8	NR	4.4
	Control	22	82	12.5	–2.7	–	–2.3	NR	–
Wit 2005[103]	GH	17	65	10.4	–3.3	0.24	–1.7	1.6	6.5
	GH	16	56	10.4	–3.1	0.24–0.37	–1.6	1.5	6.5
	GH	17	65	10.2	–2.9	0.37	–1.0	1.9	6.5
Ranke 2007[116]	GH	256	58	10.0	–2.5	0.19	–1.4	1.1	6.5

Abbreviations: GH, growth hormone; NR, not reported; SDS, SD score. Adapted with permission from S. Karger AG © Ranke, M. B. *et al*. *Horm. Res*. **68**, 53–62 (2007).

given to girls, its undesirable androgenic effects need to be considered.[71]

Gonadotropin-releasing hormone analogues

Gonadotropin-releasing hormone (GnRH) analogues are potent GnRH agonists, which by downregulation of gonadotropin (luteinizing hormone and follicle-stimulating hormone) receptors are able to reduce gonadal sex-steroid production. Treatment with a variety of available slow-release preparations is the standard therapy in girls and boys with central precocious puberty and has proven to be safe.[72] In precocious puberty, GnRH analogues prevent the loss of adult height, which is associated with a progression of the disorder. In ISS with normal timing of puberty, treatment with GnRH analogues is used in an attempt to slow bone-age progression and thus prolong the overall time for growth.[73] However, the effect is only marginal.[74] The psychological effects of delaying the developmental process artificially might also be viewed controversially. Whether the combination of GnRH analogues and GH has a beneficial effect on adult height in suitable cases with ISS, as it does in GHD,[75–77] needs to be evaluated further. In a controlled study in children with ISS, only a small (4 cm) increment in adult height was observed in the group who received GnRH analogues plus GH compared with the control group.[78]

Aromatase inhibitors

Males individuals with a mutation in the oestrogen receptor[79] or the aromatase enzyme CYP19A1, which is relevant for oestrogen synthesis from androgen precursors,[80,81] exceed their adult target height. Thus, inhibitors of oestrogen synthesis (for example, aromatase inhibitors) hold the potential to increase adult height in patients with ISS. A decrease in circulating oestrogens results in an increase in gonadotropin levels, which leads to an increase in testosterone levels in boys and to ovarian stimulation in girls. The latter effect precludes the use of aromatase inhibitors for growth disorders in girls.

In a placebo-controlled study, 15-year-old boys with CDGA received either placebo plus testosterone or the aromatase inhibitor letrozole for 2 years. At the end of the study, the cohort who received letrozole had a predicted adult height of 182.1 cm versus 175.2 cm in the placebo group.[82] Similar results were reported in another group with CDGA.[83] In this 2-year study, 31 boys with CDGA received 2.5 mg letrozole daily and 22 boys with CDGA received placebo. After 2 years, the predicted adult height in the treated group was 6.1 cm above that of the placebo group.

In another study, a group of boys with ISS and a mean age of 11 years received letrozole or placebo for 2 years. In the group who received letrozole there was an increase of 5.7 cm in predicted adult height over that in the control group.[84] No results on the effect of letrozole on actual adult height obtained are available for individuals in these three trials.[82–84] The author of two of these studies[82,83] has discouraged the use of aromatase inhibitors until issues relating to bone development, fertility, psychological development and other safety aspects are clarified.[85]

Growth hormone

After recombinant human GH (rhGH) was introduced in the 1980s, a number of reports about its short-term and long-term effects on height have been published (Table 2).[86–106] The reports vary in terms of the characteristics of the cohorts treated, the dose and duration of rhGH used and whether the studies were randomized controlled trials or not; therefore, the author refers the reader to reviews on the topic for a detailed account of the findings.[2,3,107,108] In 2003, the FDA approved the use

of rhGH in children with ISS in the USA. The evidence for the decision was derived from studies that reported the effects of rhGH treatment on adult height.[97,101] In these early studies, GH was frequently injected three times per week, a modality which is insufficient compared with the current practice of daily injections.

The prerequisites for the use of rhGH in ISS set by the FDA are that other diagnoses are excluded, that the presenting height is <–2.25 SDS (corresponding to the 1.2nd percentile) for age and sex, and that stature in adult life is expected to be below normal (<–2.0 SDS). The recommended daily dose of rhGH of 45 μg/kg of body weight is above the dose recommended for the prepubertal replacement in GHD, which reflects the relatively impaired sensitivity to GH in patients with ISS compared with patients with GHD. The approval of rhGH for the treatment of ISS by authorities has been accepted by most paediatric endocrinologists in the USA and has not altered the number of patients with ISS referred to specialists for treatment.[109]

Whether the short-term (first year) response in ISS to GH—usually expressed in terms of height velocity (cm per year) or change in height (Δ height SDS)[110]—is appropriate can be determined by comparison with empirically derived height velocity targets[111,112] or the results of prediction algorithms.[113,114] These algorithms have been developed on the basis of observations that during the first year of treatment, height velocity is a function (in order of importance) of age, rhGH dose, height distance to target height (height SDS minus target height SDS) and weight. A response of <–1 SDS in height change after 1 year of rhGH treatment is considered insufficient.[111,112] Other markers of sensitivity to rhGH have been reported that may become a part of future prediction models.[115]

Studies have also investigated the dose effect of rhGH on adult height outcomes. In studies from a Dutch group, the effect of a dose increase from 34 μg/kg to 53 μg/kg per day after 1 year on the lower dose resulted only in a small overall mean height gain (4 cm),[100,103] whereas in a Swedish study, the increase from 33 μg/kg to 77 μg/kg per day over the total treatment time to adult height resulted in a mean height gain of 8 cm (equivalent to a gain in Δ height of 1.3 SDS).[104] These studies suggest that the first year of treatment with rhGH is particularly important but also that, in a minority of patients, increased GH doses are probably needed to overcome the impaired sensitivity to GH in ISS.

Data from a pharmacoepidemiological study were analysed to understand the factors that influence adult height outcomes after rhGH treatment.[116] The cohort consisted of 148 boys and 108 girls who had been treated with rhGH from a mean age of 10 years (range 6–13 years), were prepubertal at rhGH therapy start and received a mean dose of rhGH of 27 μg/kg per day (range 19–43 μg/kg per day). In this study, adult height SDS was observed to be explained by an equation containing four predictive parameters (in order of importance): height at GH start (positive correlation); the responsiveness to GH during the first year of treatment calculated using the response prediction algorithm for the first year of treatment (positive correlation);[113] the age at GH start (negative correlation); and mid-parent height (positive correlation). The equation explains 64% of the variability of adult height, with an error of 0.63 SD. Thus, the taller and younger the children are when they receive rhGH and the better the initial responsiveness to rhGH is, the higher the adult height outcomes that can be expected. The fact that the proven dose dependence of short-term and long-term outcomes in response to rhGH[101,103,104] was not seen in this analysis was probably caused by the fairly narrow dose range in the study and the relatively minor importance of GH dose during puberty compared with that before puberty.[117]

Some uncertainty exists about the accuracy of the prediction of long-term height outcomes when using such an algorithm; however, a prediction can provide the patient and parents with a more realistic idea about the potential efficacy of rhGH treatment, rather than just referencing findings from research studies. The accuracy of predictive algorithms is increased when data after 1 year of treatment are included. A Cochrane review of studies on treatment with rhGH in ISS concluded that a mean gain in adult height of 7 cm can be expected.[108] The individual gain can of course vary considerable (0–20 cm). However, the effective dose range of rhGH needs further evaluation. Furthermore, unresolved issues still exist with regard to how doses should be varied over the course of treatment, and the duration of treatment.[2,118]

Some beneficial metabolic effects of rhGH treatment might occur in children with ISS.[119] The psychological effects of rhGH treatment are a subject of debate. Whilst some studies suggest that the treatment has a positive effect on adaptation, psychosocial function, or quality of life in children with ISS,[120,121] others do not support these conclusions.[122,123] The fact that rhGH treatment for short stature in ISS is approved in the USA but not in other countries is partly the reflection of different structures of the health systems. However, attitudes towards short stature may also differ between societies.

Safety of rhGH

The safety of rhGH, which has been used in children for various causes of shortness for more than 25 years, has been extensively investigated. Overall, rhGH has been concluded to be safe in the presently accepted indications and within the used dose ranges,[124–127] and also in patients with ISS.[124,128] In particular, concerns about an increase in the development of malignancies with rhGH treatment were not substantiated.[129]

Reports from three large pharmacoepidemiological studies, including children with various causes of short stature treated with rhGH, reported no increase in type 1 diabetes mellitus, but an increased rate in type 2 diabetes mellitus.[127,130,131] However, an increase in type 2 diabetes mellitus was not reported for children with ISS,[128] although this group of patients is still too small for final conclusions to be drawn. Hyperinsulinism tends to be the result of high doses of rhGH, such as in small-for-gestational age children, but appears to be reversible.[132]

Benign intracranial pressure as a result of water retention is a rare but serious risk of rhGH treatment. Publications from a still ongoing European study about the safety and appropriateness of GH (SAGhE) raised new concerns about the long-term safety of rhGH when given at supraphysiological doses.[133,134] The long-term surveillance of children who have received rhGH is, therefore, recommended by some investigators.[135]

IGF-1 treatment

In severe primary IGF-1 deficiency (IGFD),[136] replacement with recombinant human IGF-1 (rhIGF-1) is the pathogenically adequate form of therapy. In these patients, of which most have a GH receptor defect (Laron syndrome), IGF-1 replacement has been shown to increase height.[137,138] Compared with GH replacement in patients with severe early-onset GHD, the early catch-up growth during rhIGF-1 treatment in patients with IGFD is less pronounced.[137,138] However, severe primary IGFD is rare and the empirical basis of long-term treatment is narrow.

A discussion is ongoing about the definition of 'partial' IGFD, which could include cases primarily classified as ISS, in whom rhIGF-1 treatment might be a viable alternative to rhGH.[139] A randomized study of rhIGF-1 treatment in 136 children with short stature and very low IGF-1 levels was conducted in an attempt to prove the efficacy of this therapy in a subpopulation of children with ISS.[140] Height velocity was significantly increased in children who received rhIGF-1. In patients with primary IGFD, very severe adverse events (for example, hypoglycaemia) during rhIGF-1 treatment are reported with a fairly high frequency,[137,138] probably because the risk of free IGF-1 in the circulation after IGF-1 injections in severe primary IGFD is high. Adverse events or effects seem to occur with a lesser frequency in children with 'partial' IGFD or ISS than in those with total IGFD.[140] Presently, the use of rhIGF-1 for children with ISS is seen critically,[141] and further studies will be needed to prove its long-term efficacy and safety.

Conclusions

ISS is a term used for children without definite causes of short stature. Whether these children just reflect the statistical extremes of the normal spectrum of height growth and tempo of development and/or have distinct but subtle inborn defects of growth and development is not clear. Shortness during childhood could be perceived as a disadvantage and might interfere negatively with normal psychological development. In children seeking advice for shortness, establishing a clear-cut relationship between height deviation and psychological distress is often difficult. Comprehensive counselling without medical treatment is often sufficient. Therefore, if shortness is to be treated effectively the aims, modalities, potential benefits and risks need to be considered. Treatment with rhGH has become an established approach that is approved by the FDA to increase height in patients with ISS, both in childhood and in adult life. However, further studies should be conducted to explore the optimal dose of rhGH for the treatment of ISS. In addition, extensive research is still needed to optimize the treatment modalities available and to understand the psychosocial implications of shortness and its correction.

Review criteria

A selective review of the literature was based on a PubMed search until December 2012 with the following search terms: "idiopathic short stature", "constitutional delay of growth", "constitutional delay of growth and puberty", "short stature genetics", "human height genetics", "short stature psychosocial", "short stature testosterone", "oxandrolone treatment", "short stature aromatase inhibitor", "short stature GnRH" and "ISS growth hormone".

1. Wit, J. M. *et al.* Idiopathic short stature: definition, epidemiology, and diagnostic evaluation. *Growth Horm. IGF Res.* **18**, 89–110 (2008).
2. Wit, J. M. *et al.* Idiopathic short stature: management and growth hormone treatment. *Growth Horm. IGF Res.* **18**, 111–35 (2008).
3. Cohen, P. *et al.* Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop. *J. Clin. Endocrinol. Metab.* **93**, 4210–4217 (2008).
4. Wit, J. M. Developments in idiopathic short stature (ed. Dunkel, L.). *Horm. Res. Pediatr.* **76** (Suppl. 3), 1–60 (2011)
5. Ranke, M. B. Towards a consensus on the definition of idiopathic short stature. *Horm. Res.* **45** (Suppl. 2), 64–66 (1996).
6. Hermanussen, M. & Cole, J. The calculation of target height reconsidered. *Horm. Res.* **59**, 180–183 (2003).
7. Delemarre-van de Waal, H. A. Secular trend of timing of puberty. *Endocr. Dev.* **8**, 1–14 (2005).
8. Weedon, M. N. *et al.* Genome-wide association analysis identifies 20 loci that influence adult height. *Nat. Genet.* **40**, 575–583 (2008).
9. Lettre, G. Genetic regulation of adult stature. *Curr. Opin. Pediatr.* **21**, 515–522 (2009).
10. Lui, J. C. *et al.* Synthesizing genome-wide association studies and expression microarray reveals novel genes that act in the human growth plate to modulate height. *Hum. Mol. Genet.* **21**, 5193–5201 (2012).
11. Chan, Y. *et al.* Common variants show predicted polygenic effects on height in the tails of the distribution, except in extremely short individuals. *PLoS Genet.* **7**, e1002439 (2011).
12. Ojeda, S. R. *et al.* The transcriptional control of female puberty. *Brain Res.* **1364**, 164–174 (2010).
13. Roa, J., García-Galiano, D., Castellano, J. M., Gaytan, F., Pinilla, L. & Tena-Sempere, M. Metabolic control of puberty onset: new players, new mechanisms. *Mol. Cell Endocrinol.* **324**, 87–94 (2010).
14. Gajdos, Z. K., Henderson, K. D., Hirschhorn, J. N. & Palmert, M. R. Genetic determinants of pubertal timing in the general population. *Mol. Cell Endocrinol.* **324**, 21–29 (2010).
15. Elks, C. E. *et al.* Thirty new loci for age at menarche identified by a meta-analysis of genome-wide association studies. *Nat. Genet.* **42**, 1077–1085 (2010).
16. Elks, C. E. & Ong, K. K. Whole genome associated studies for age at menarche. *Brief. Funct. Genomics* **10**, 91–97 (2011).
17. Cole, T. J. Secular trends in growth. *Proc. Nutr. Soc.* **59**, 317–324 (2000).
18. Delemarre-van de Waal, H. A. Secular trend of timing of puberty. *Endocr. Dev.* **8**, 1–14 (2005).
19. Bourguignon, J. P. & Juul, A. Normal female puberty in a developmental perspective. *Endocr. Dev.* **22**, 11–23 (2012).
20. Tinggaard, J. *et al.* The physiology and timing of male puberty. *Curr. Opin. Endocrinol. Diabetes Obes.* **19**, 197–203 (2012).
21. Ong, K. K., Ahmed, M. L. & Dunger, D. B. Lessons from large population studies on timing and tempo of puberty (secular trends and relation to body size): the European trend. *Mol. Cell Endocrinol.* **254–255**, 8–12 (2006).
22. World Health Organization. The WHO child growth standards. *World Health Organization* [online], http://www.who.int/childgrowth/standards/height_for_age/en/index.html (2008).
23. Johnston Rohrbasser, L. B. Genetic testing in short children. *Horm. Res. Pediatr.* **76** (Suppl. 3), 13–16 (2011).
24. Ranke, M. B. *et al.* Significance of basal IGF-1, IGFBP-3 and IGFBP-2 measurements in the

diagnostics of short stature children. *Horm. Res.* **54**, 60–68 (2000).
25. Walenkamp, M. J. & Wit, J. M. Genetic disorders in the growth hormone insulin-like growth factor-I axis. *Horm. Res.* **66**, 221–230 (2006).
26. Clemmons, D. R. Consensus statement on the standardization and evaluation of growth hormone and insulin-like growth factor assays. *Clin. Chem.* **57**, 555–559 (2011).
27. Ranke, M. B. in *Diagnostics of Endocrine Function in Children and Adolescents* 4th edn (eds Ranke, M. B. & Mullis, P. E.), 102–137 (Karger, Basel, 2011).
28. Binder, G. Growth hormone deficiency: new approaches to the diagnosis. *Pediatr. Endocrinol. Rev.* **9** (Suppl. 1), 535–537 (2011).
29. David, A. *et al.* Evidence for a continuum of genetic, phenotypic, and biochemical abnormalities in children with growth hormone insensitivity. *Endocr. Rev.* **32**, 472–497 (2011).
30. Forbes, B. E. Molecular mechanisms underlying insulin-like growth factor action: How mutations in the GH: IGF axis lead to short stature. *Pediatr. Endocrinol. Rev.* **8**, 374–381 (2011).
31. Rappold, G. *et al.* Genotypes and phenotypes in children with short stature: clinical indicators of SHOX haploinsufficiency. *J. Med. Genet.* **44**, 306–313 (2007).
32. Caliebe, J. *et al.* IGF1R and SHOX mutation analysis in short children born small for gestational age and short children with normal birth size (idiopathic short stature). *Horm. Res. Paediatr.* **77**, 250–260 (2012).
33. Pugliese-Pires, P. N. *et al.* Novel inactivating mutations in the GH secretagogue receptor gene in patients with constitutional delay of growth and puberty. *Eur. J. Endocrinol.* **165**, 233–241 (2011).
34. Inoue, H. *et al.* Identification and functional analysis of novel human growth hormone secretagogue receptor (GHSR) gene mutations in Japanese subjects with short stature. *J. Clin. Endocrinol. Metab.* **96**, E373–E378 (2011).
35. Olney, R. C. *et al.* Heterozygous mutations in natriuretic peptide receptor-B (NPR2) are associated with short stature. *J. Clin. Endocrinol. Metab.* **91**, 1229–1232 (2006).
36. Xiao, Y. *et al.* Measurement of amino-terminal propeptide of C-type natriuretic peptide in patients with idiopathic short stature or isolated growth hormone deficiency. *J. Pediatr. Endocrinol. Metab.* **24**, 989–994 (2011).
37. Price, D. A. Spontaneous adult height in patients with idiopathic short stature. *Horm. Res.* **45** (Suppl. 2), 59–63 (1996).
38. Ranke, M. B., Grauer, M. L., Kistner, K., Blum, W. F. & Wollmann, H. A. Spontaneous adult height in idiopathic short stature. *Horm. Res.* **44**, 152–157 (1995).
39. Rekers-Mombarg, L. T. *et al.* Spontaneous growth in idiopathic short stature. European Study Group. *Arch. Dis. Child*. **75**, 175–180 (1996).
40. Martin, D. D. *et al.* The use of bone age in clinical practice—part 1. *Horm. Res. Paediatr.* **76**, 1–9 (2011).
41. Topor, L. S., Feldman, H. A., Bauchner, H. & Cohen L. E. Variation in methods of predicting adult height for children with idiopathic short stature. *Pediatrics* **126**, 938–944 (2010).
42. Thodberg, H. H., Jenni, O. G., Caflisch, J., Ranke, M. B. & Martin, D. D. Prediction of adult height based on automated determination of bone age. *J. Clin. Endocrinol. Metab.* **94**, 4868–4874 (2009).
43. Noeker, M. & Haverkamp, F. Adjustment in conditions with short stature: a conceptual framework. *J. Pediatr. Endocrinol. Metab.* **13**, 1585–1594 (2009).
44. Bullinger, M. Psychological criteria for treating children with idiopathic short stature. *Horm. Res. Paediatr.* **76** (Suppl. 3), 20–23 (2011).
45. Mobbs, E. J. The psychological outcome of constitutional delay of growth and puberty. *Horm. Res.* **62** (Suppl. 1), 1–66 (2005).
46. Kranzler, J. H., Rosenbloom, A. L., Proctor, B., Diamond, F. B. Jr & Watson, M. Is short stature a handicap? A comparison of the psychosocial functioning of referred and nonreferred children with normal short stature and children with normal stature. *J. Pediatr.* **136**, 96–102 (2000).
47. Voss, L. D. Short normal stature and psychosocial disadvantage: a critical review of the evidence. *J. Pediatr. Endocrinol. Metab.* **14**, 701–711 (2001).
48. Visser-van Balen, H., Sinnema, G. & Geenen, R. Growing up with idiopathic short stature: psychosocial development and hormone treatment; a critical review. *Arch. Dis. Child*. **91**, 433–439 (2006).
49. Sandberg, D. E. & Colsman, M. Growth hormone treatment of short stature: Status of quality of life rationale. *Horm. Res.* **63**, 275–283 (2005).
50. Christensen, T. L., Djurhuus, C. B., Clayton, P. & Christiansen, J. S. An evaluation of the relationship between adult height and health-related quality of life in the general UK population. *Clin. Endocrinol. (Oxf.)* **67**, 407–412 (2007).
51. Allen, D. B. Clinical review: Lessons learned from the hGH era. *J. Clin. Endocrinol. Metab.* **96**, 3042–3047 (2011).
52. LeRoith, D. Clinical relevance of systemic and local IGF-I: lessons from animal models. *Pediatr. Endocrinol. Rev.* **5** (Suppl. 2), 739–743 (2008).
53. Wit, J. M. & Camacho-Hübner, C. Endocrine regulation of longitudinal bone growth. *Endocr. Dev.* **21**, 30–41 (2011).
54. Lui, J. C., Nilsson, O. & Baron, J. Growth plate senescence and catch-up growth. *Endocr. Dev.* **21**, 23–29 (2011).
55. Lui, J. C. & Baron, J. Mechanisms limiting body growth in mammals. *Endocr. Rev.* **32**, 422–440 (2011).
56. Emons, J., Chagin, A. S., Sävendahl, L., Karperien, M. & Wit, J. M. Mechanisms of growth plate maturation and epiphyseal fusion. *Horm. Res. Paediatr.* **75**, 383–391 (2011).
57. Ren, S. G. *et al.* Direct administration of testosterone increases rat tibial epiphyseal growth plate width. *Acta Endocrinol. (Copenh.)* **121**, 401–405 (1989).
58. Giustina, A. & Veldhuis, J. D. Pathophysiology of the neuroregulation of growth hormone secretion in experimental animals and the human. *Endocr. Rev.* **19**, 717–797 (1998).
59. De Luca, F. *et al.* Management of puberty in constitutional delay of growth and puberty. *J. Pediatr. Endocrinol. Metab.* **14** (Suppl. 2), 953–957 (2001).
60. Ambler, G. R. Androgen therapy for delayed male puberty. *Curr. Opin. Endocrinol. Diabetes Obes.* **16**, 232–239 (2009).
61. Kiess, W. *et al.* Induction of puberty in the hypogonadal girl-practices and attitudes of pediatric endocrinologists in Europe. *Horm. Res.* **57**, 66–71 (2002).
62. Drobac, S., Rubin, K., Rogol, A. D. & Rosenfield, R. L. A workshop on pubertal hormone replacement options in the United States. *J. Pediatr. Endocrinol. Metab.* **19**, 55–64 (2006).
63. Kelly, B. P., Paterson W. F. & Donaldson, M. D. Final height outcome and value of height prediction in boys with constitutional delay in growth and adolescence treated with intramuscular testosterone 125 mg per month for 3 months, *Clin. Endocrinol. (Oxf.)* **58**, 267–272 (2003).
64. Martin, M. M., Martin, A. L. & Mossman, K. L. Testosterone treatment of constitutional delay in growth and development: effect of dose on predicted versus definitive height. *Acta Endocrinol. Suppl. (Copenh.)* **279**, 147–152 (1986).
65. Zachmann, M., Studer, S. & Prader, A. Short-term testosterone treatment at bone age of 12 to 13 years does not reduce adult height in boys with constitutional delay of growth and adolescence. *Helv. Paediatr. Acta*. **42**, 21–28 (1987).
66. Arrigo, T. *et al.* Final height outcome in both untreated and testosterone-treated boys with constitutional delay of growth and puberty. *J. Pediatr. Endocrinol. Metab.* **9**, 511–517 (1996).
67. Wehkalampi, K., Päkkilä, K., Laine, T. & Dunkel, L. Adult height girls with delayed pubertal growth. *Horm. Res. Paediatr.* **76**, 130–135 (2011).
68. Stanhope, R., Buchanan, C. R., Fenn., G. C. & Preece, M. A. Double blind placebo controlled trial of low dose oxandrolone in the treatment of boys with constitutional delay of growth and puberty. *Arch. Dis. Child*. **63**, 501–505 (1988).
69. Wilson, D. M., McCauley, E., Brown, D. R. & Dudley, R. Oxandrolone therapy in constitutionally delayed growth and puberty. Bio-Technology General Corporation Cooperative Study Group. *Pediatrics* **96**, 1095–1100 (1995).
70. Tse, W. Y. *et al.* Long-term outcome of oxandrolone treatment in boys with constitutional delay of growth and puberty. *J. Pediatr.* **117**, 588–591 (1990).
71. Menke, L. A. *et al.* Efficacy and safety of oxandrolone in growth hormone-treated girls with turner syndrome. *J. Clin. Endocrinol. Metab.* **95**, 1151–1160 (2010).
72. Carel, J. C. *et al.* Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics* **123**, e752–e762 (2009).
73. Yanovski, J. A. *et al.* Treatment with a luteinizing hormone-releasing hormone agonist in adolescents with short stature. *N. Engl. J. Med.* **348**, 908–917 (2003).
74. Wit, J. M., Balen, H. V., Kamp, G. A. & Oostdijk, W. Benefit of postponing normal puberty for improving final height. *Eur. J. Endocrinol.* **151** (Suppl. 1), 41–45 (2004).
75. Reiter, E. O. A brief review of the addition of gonadotropin-releasing hormone agonists (GnRH-Ag) to growth hormone (GH) treatment of children with idiopathic growth hormone deficiency: Previously published studies from America. *Mol. Cell Endocrinol.* **254–255**, 221–225 (2006).
76. Mauras, N. Strategies for maximizing growth in puberty in children with short stature. *Pediatr. Clin. North Am.* **58**, 1167–1179 (2011).
77. Tanaka, T. *et al.* GH and GnRH analog treatment in children who enter puberty at short stature. *J. Pediatr. Endocrinol. Metab.* **10**, 623–628 (1997).
78. van Gool, S. A. *et al.* Final outcome after three years of growth hormone and gonadotropin-releasing hormone agonist treatment in short adolescents with relatively early puberty. *J. Clin. Endocrinol. Metab.* **92**, 1402–1408 (2007).
79. Smith, E. P. *et al.* Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. *N. Engl. J. Med.* **331**, 1056–1061 (1994).
80. Morishima, A. Grumbach, M. M., Simpson, E. R. Fisher, C. & Qin, K. Aromatase deficiency in male and female sibling caused by a novel mutation and the physiological role of estrogens. *J. Clin. Endocrinol. Metab.* **80**, 3689–3698 (1995).

81. Rochira, V. *et al.* Tall stature without growth hormone: four male patients with aromatase deficiency. *J. Clin. Endocrinol. Metab.* **95**, 1626–1633 (2010).
82. Wickman, S., Sipilä, I., Ankarberg-Lindgren, C., Norjavaara, E. & Dunkel, L. A specific aromatase inhibitor and potential increase in adult height in boys with delayed puberty: a randomised controlled trial. *Lancet* **357**, 1743–1748 (2001).
83. Salehpour, S. *et al.* A double-blind, placebo-controlled comparison of letrozole to oxandrolone effects upon growth and puberty of children with constitutional delay of puberty and idiopathic short stature. *Horm. Res. Paediatr.* **74**, 428–435 (2010).
84. Hero, M., Wickman, S. & Dunkel, L. Treatment with the aromatase inhibitor letrozole during adolescence increases near-final height in boys with constitutional delay of puberty. *Clin. Endocrinol.* (*Oxf.*) **64**, 510–513 (2006).
85. Dunkel, L. Treatment of idiopathic short stature: effects of gonadotropin-releasing hormone analogs, aromatase inhibitors and anabolic steroids. *Horm. Res. Paediatr.* **76** (Suppl. 3), 27–29 (2011).
86. Hopwood, N. J. *et al.* Growth response of children with non-growth-hormone deficiency and marked short stature during three years of growth hormone therapy. *J. Pediatr.* **123**, 215–222 (1993).
87. Loche, S. *et al.* Final height after growth hormone therapy in non-growth-hormone-deficient children with short stature. *J. Pediatr.* **125**, 196–200 (1994).
88. Barton, J. S. *et al.* The growth and cardiovascular effects of high dose growth hormone therapy in idiopathic short stature. *Clin. Endocrinol.* (*Oxf.*) **42**, 619–626 (1995).
89. Lanes, R. Effects of two years of growth hormone treatment in short, slowly growing non-growth hormone deficient children. *J. Pediatr. Endocrinol. Metab.* **8**, 167–171 (1995).
90. Wit, J. M., Kamp, G. A. & Rikken, B. Spontaneous growth and response to growth hormone treatment in children with growth hormone deficiency and idiopathic short stature. *Pediatr. Res.* **39**, 295–302 (1996).
91. Hindmarsh, P. C. & Brook, C. G. Final height of short normal children treated with growth hormone. *Lancet* **348**, 13–16 (1996).
92. Bernasconi, S., Street, M. E., Volta, C. & Mazzardo, G. Final height in non-growth hormone deficient children treated with growth hormone. The Italian Multicentre Study Group. *Clin. Endocrinol.* (*Oxf.*) **47**, 261–266 (1997).
93. Kawai, M. *et al.* Unfavorable effects of growth hormone therapy on the final height of boys with short stature not caused by growth hormone deficiency. *J. Pediatr.* **130**, 205–209 (1997).
94. Zadik, Z. & Zung, A. Final height after growth hormone therapy in short children: correlation with siblings' height. *Horm. Res.* **48**, 274–277 (1997).
95. Buchlis, J. G. *et al.* Comparison of final heights of growth hormone-treated vs. untreated children with idiopathic growth failure. *J. Clin. Endocrinol. Metab.* **83**, 1075–1079 (1998).
96. McCaughey, E. S., Mulligan, J., Voss, L. D. & Betts, P. R. Randomised trial of growth hormone in short normal girls. *Lancet* **351**, 940–944 (1998).
97. Hintz, R. L., Attie, K. M., Baptista, J. & Roche, A. Effect of growth hormone treatment on adult height of children with idiopathic short stature. Genentech Collaborative Group. *N. Engl. J. Med.* **340**, 502–507 (1999).
98. López-Siguero, J. P., Garciá-Garcia, E., Carralero, I. & Martínez-Aedo, M. J. Adult height in children with idiopathic short stature treated with growth hormone. *J. Pediatr. Endocrinol. Metab.* **13**, 1595–1602 (2000).
99. Coutant, R. *et al.* Growth and adult height in GH-treated children with nonacquired GH deficiency and idiopathic short stature: the influence of pituitary magnetic resonance imaging findings. *J. Clin. Endocrinol. Metab.* **86**, 4649–4654 (2001).
100. Wit, J. M. & Rekers-Mombarg, L. T. Final height gain by GH therapy in children with idiopathic short stature is dose dependent. *J. Clin. Endocrinol. Metab.* **87**, 604–611 (2002).
101. Leschek, E. W. *et al.* Effect of growth hormone treatment on adult height in peripubertal children with idiopathic short stature: a randomized, double-blind, placebo-controlled trial. *J. Clin. Endocrinol. Metab.* **89**, 3140–3148 (2004).
102. Kemp, S. F. *et al.* Efficacy and safety results of long-term growth hormone treatment of idiopathic short stature. *J. Clin. Endocrinol. Metab.* **90**, 5247–5253 (2005).
103. Wit, J. M. *et al.* Growth hormone (GH) treatment to final height in children with idiopathic short stature: evidence for a dose effect. *J. Pediatr.* **146**, 45–53 (2005).
104. Albertsson-Wikland, K. *et al.* Dose-dependent effect of growth hormone on final height in children with short stature without growth hormone deficiency. *J. Clin. Endocrinol. Metab.* **93**, 4342–4350 (2008).
105. Lee, P. A. *et al.* Comparison of response to 2-years' growth hormone treatment in children with isolated growth hormone deficiency, born small for gestational age, idiopathic short stature, or multiple pituitary hormone deficiency: combined results from two large observational studies. *Int. J. Pediatr. Endocrinol.* **2012**, 22 (2012).
106. Hughes, I. P. *et al.* Growth hormone regimens in Australia: analysis of the first 3 years of treatment for idiopathic growth hormone deficiency and idiopathic short stature. *Clin. Endocrinol.* (*Oxf.*). **77**, 62–71 (2012).
107. Finkelstein, B. S. *et al.* Effect of growth hormone therapy on height in children with idiopathic short stature: a meta-analysis. *Arch. Pediatr. Adolesc. Med.* **156**, 230–240 (2002).
108. Bryant, J., Baxter, L., Cave, C. B. & Milne, R. Recombinant growth hormone for idiopathic short stature in children and adolescents. *Cochrane Database of Systematic Reviews,* Issue 3. Art. No.: CD004440. http://dx.doi.org/10.1002/14651858.CD004440.pub2
109. Hardin, D. S., Woo, J., Butsch, R. & Huett, B. Current prescribing practices and opinions about growth hormone therapy: results of a nationwide survey of paediatric endocrinologists. *Clin. Endocrinol.* (*Oxf.*). **66**, 85–94 (2007).
110. Bang, P. *et al.* A comparison of different definitions of growth response in short prepubertal children treated with growth hormone. *Horm. Res. Paediatr.* **75**, 335–345 (2011).
111. Bakker, B., Frane, J., Anhalt, H., Lippe, B. & Rosenfeld, R. G. Height velocity targets from the national cooperative growth study for first-year growth hormone responses in short children. *J. Clin. Endocrinol. Metab.* **93**, 352–357 (2008).
112. Ranke, M. B., Lindberg, A. & KIGS International Board. Observed and predicted growth responses in prepubertal children with growth disorders: guidance of growth hormone treatment by empirical variables. *J. Clin. Endocrinol. Metab.* **95**, 1229–1237 (2010).
113. Ranke, M. B. & Lindberg, A. Growth hormone treatment of idiopathic short stature: analysis of the database from KIGS, the Kabi Pharmacia International Growth Study. *Acta Paediatr. Suppl.* **406**, 18–23 (1994).
114. Ranke, M. B. & Lindberg, A. Predicting growth in response to growth hormone treatment. *Growth Horm. IGF Res.* **19**, 1–11 (2009).
115. Kamp, G. A. *et al.* Biochemical markers of growth hormone (GH) sensitivity in children with idiopathic short stature: individual capacity of IGF-I generation after high-dose GH treatment determines the growth response to GH. *Clin. Endocrinol.* (*Oxf.*). **57**, 315–325 (2002).
116. Ranke, M. B. *et al.* Age at growth hormone therapy start and first-year responsiveness to growth hormone are major determinants of height outcome in idiopathic short stature. *Horm. Res.* **68**, 53–62 (2007).
117. Ranke, M. B. & Lindberg, A. Observed and predicted total pubertal growth during treatment with growth hormone in adolescents with idiopathic growth hormone deficiency, Turner syndrome, short stature, born small for gestational age and idiopathic short stature: KIGS analysis and review. *Horm. Res. Paediatr.* **75**, 423–432 (2011).
118. van Gool, S. A. *et al.* High-dose GH treatment limited to the prepubertal period in young children with idiopathic short stature does not increase adult height. *Eur. J. Endocrinol.* **162**, 653–660 (2010).
119. Dahlgren, J. Metabolic benefits of growth hormone therapy in idiopathic short stature. *Horm. Res. Paediatr.* **76** (Suppl. 3), 56–58 (2011).
120. Stabler, B. *et al.* Behavior change after growth hormone treatment of children with short stature. *J. Pediatr.* **133**, 366–373 (1998).
121. Chaplin, J. E. *et al.* Improvements in behaviour and self-esteem following growth hormone treatment in short prepubertal children. *Horm. Res. Paediatr.* **75**, 291–303 (2011).
122. Theunissen, N. C. *et al.* Quality of life and self-esteem in children treated for idiopathic short stature. *J. Pediatr.* **140**, 507–515 (2002).
123. Ross, J. L. *et al.* Psychological adaptation in children with idiopathic short stature treated with growth hormone or placebo. *J. Clin. Endocrinol. Metab.* **89**, 4873–4878 (2004).
124. Allen, D. B. Safety of growth hormone treatment of children with idiopathic short stature: the US experience. *Horm. Res. Paediatr.* **76** (Suppl. 3), 45–47 (2011).
125. Cook, D. M. & Rose, S. R. A review of guidelines for use of growth hormone in pediatric and transition patients. *Pituitary* **15**, 301–310 (2012).
126. Ross, J. *et al.* Growth hormone: health considerations beyond height gain. *Pediatrics* **125**, e906–e918 (2010).
127. Bell, J. *et al.* Long-term safety of recombinant human growth hormone in children. *J. Clin. Endocrinol. Metab.* **95**, 167–177 (2010).
128. Quigley, C. A. *et al.* Safety of growth hormone treatment in pediatric patients with idiopathic short stature. *J. Clin. Endocrinol. Metab.* **90**, 5188–5196 (2005).
129. Wilton, P., Mattsson, A. F. & Darendeliler, F. Growth hormone treatment in children is not associated with an increase in the incidence of cancer: experience from KIGS (Pfizer International Growth Database). *J. Pediatr.* **157**, 265–270 (2010).
130. Child, C. J. *et al.* Prevalence and incidence of diabetes mellitus in GH-treated children and adolescents: analysis from the GeNeSIS observational research program. *J. Clin. Endocrinol. Metab.* **96**, E1025–E1034 (2011).

131. Cutfield, W. S. *et al.* Incidence of diabetes mellitus and impaired glucose tolerance in children and adolescents receiving growth-hormone treatment. *Lancet* **355**, 610–613 (2000).
132. Hokken-Koelega, A. C., De Waal, W. J., Sas, T. C., Van Pareren, Y. & Arends, N. J. Small for gestational age (SGA): endocrine and metabolic consequences and effects of growth hormone treatment. *J. Pediatr. Endocrinol. Metab.* **17** (Suppl. 3), 463–469 (2004).
133. Carel, J. C. *et al.* Long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or childhood short stature: preliminary report of the French SAGhE study. *J. Clin. Endocrinol. Metab.* **97**, 416–425 (2012).
134. Sävendahl, L. *et al.* Long-term mortality and causes of death in isolated, GHD, ISS, and SGA patients treated with recombinant growth hormone during childhood in Belgium, The Netherlands, and Sweden: preliminary report of 3 countries participating in the EU SAGhE study. *J. Clin. Endocrinol. Metab.* **97**, E213–E217 (2012).
135. Rosenfeld, R. G. *et al.* Long-term surveillance of growth hormone therapy. *J. Clin. Endocrinol. Metab.* **97**, 68–72 (2012).
136. Rosenfeld, R. G. The IGF system: new developments relevant to pediatric practice. *Endocr. Dev.* **9**, 1–10 (2005).
137. Ranke, M. B. *et al.* Long-term treatment of growth hormone insensitivity syndrome with IGF-I. Results of the European Multicentre Study. The Working Group on Growth Hormone Insensitivity Syndromes. *Horm. Res.* **51**, 128–134 (1999).
138. Chernausek, S. D. *et al.* Long-term treatment with recombinant insulin-like growth factor (IGF)-I in children with severe IGF-I deficiency due to growth hormone insensitivity. *J. Clin. Endocrinol. Metab.* **92**, 902–910 (2007).
139. Savage, M. O. *et al.* Idiopathic short stature: will genetics influence the choice between GH and IGF-I therapy? *Eur. J. Endocrinol.* **157** (Suppl. 1), 33–37 (2007).
140. Midyett, L. K. *et al.* Recombinant insulin-like growth factor (IGF)-I treatment in short children with low IGF-I levels: first-year results from a randomized clinical trial. *J. Clin. Endocrinol. Metab.* **95**, 611–619 (2010).
141. Rosenbloom, A. L. Is there a role for recombinant insulin-like growth factor-I in the treatment of idiopathic short stature? *Lancet* **368**, 612–616 (2006).