Short and Tall Stature

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Key Words

Tall stature • Short stature • Height disorders • Growth disorders • Psychosocial problems

Abstract

Short or tall stature is primarily a normal variation of height. It is part of the continuum of the normal Gaussian distribution curve which defines the lower and upper limit of normal as the 3rd and 97th percentile. Within this context it is very important to differentiate normal variations in height and growth from pathological conditions. Normal variations in height are familial and idiopathic short or tall stature. Normal variations in growth are diagnosed as constitutional acceleration or constitutional delay of growth and puberty and are observed on all percentiles. Patients with pathological conditions of height usually have a syndromal, skeletal or chromosomal disorders such as Russell-Silver or Marfan syndrome, achondroplasia, Ullrich-Turner or Klinefelter syndrome. Many of the disorders with short stature have intra-uterine growth retardation. The (mean) final height does not necessarily follow the target height range, but reaches a height below or above the population 3rd or 97th percentile. Patients with pathological conditions of growth can have short, normal or tall stature. They have a reduced or increased growth rate caused by a wide variety of chronic organic or psychosomatic diseases. At present, treatment with growth hormone (GH) is available for patients with GH deficiency, Ullrich-Turner syndrome, chronic renal insufficiency, small for gestational age and Prader-Willi syndrome. The indication for GH treatment of idiopathic short stature is so far only approved in the USA. Adult height data indicate that patients with documented GH deficiency reach an adult

height within their target height range. For all other indications a statistically significant improvement in adult height has been documented. In the long-term follow-up of these patients not only a statistically significant but also a clinically relevant improvement in adult height should be demonstrated. Depending on the results, some of the indications for GH therapy might have to be reconsidered.

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Introduction

Normal height data are needed to define 'short' and 'tall' stature. Height data are specific for a certain population and vary widely, especially with ethnic background. They are collected within a defined population from cross-sectional, mixed cross-sectional and longitudinal height measurements or, rarely, from prospective longitudinal studies [1–5].

Short or tall stature means a length (birth to 2 years) or height (3–18 years) below or above the 3rd or 97th percentile. This corresponds to -1.8 or $+1.8$ standard deviations (SDs) of the mean height for chronological age. Alternatively, heights below or above 2 SD (2.3rd or 97.7th percentile) are used to define short or tall stature. This definition implies that a certain percentage of the population will always be short or will always be tall. It does not mean that short or tall stature is necessarily the result of disease.

Normal stature is the result of a complex growth process. Pregnancy, genetic and ethnic influences, nutrition, endocrine function, general health as well as psychosocial well being are involved in the normal process of

Table 1. Adult height (mean/median) in boys and girls of various countries

		Adult height in boys, cm				Adult height in girls, cm			
		mean/median	SD	+2 SD	-2 SD	mean/median	SD	+2 SD	-2 SD
The Netherlands	1985	182.0	6.70	195.4	175.3	168.3	6.20	180.7	162.1
Germany	1992	179.9	6.40	192.7	173.5	167.0	5.10	177.2	161.9
Sweden	1976	179.8	6.69	193.2	173.1	165.9	6.56	179.0	159.3
Belgium	1986	176.0	6.60	189.2	169.4	163.3	5.71	174.7	157.6
USA	1977	176.8	6.60	190.0	170.2	163.7	5.93	175.6	157.8
England	1995	176.6	6.95	190.5	169.7	163.7	6.02	175.7	157.7
France	1979	174.5	6.00	186.5	168.5	163.2	5.60	174.4	157.6
Spain	1988	175.6	6.04	187.7	169.6	161.3	5.72	172.7	155.6
Turkey	1978	173.5	6.30	186.1	167.2	160.0	5.93	171.9	154.1
Mexico	1975	172.8	7.19	187.2	169.5	160.6	7.39	175.4	153.2
Korea	1979	170.2	5.22	180.6	165.0	157.6	4.76	167.1	152.8
Japan	1990	170.4	5.60	181.6	164.8	157.9	5.00	167.9	152.9

growth [6–8]. The result of this growth process is a height within the range of the 3rd and 97th percentile or a height just deviating from normal as in short or tall stature. It is important to remember that in most instances normal height, short and tall stature are the result of normal growth.

The ethnic variation in height is shown in table 1 for boys and girls. It demonstrates the large variability of height between populations. Normal adult height in the Netherlands is 168.3 cm for women and 182.0 cm for men [9, 10]. This height compares to a mean normal height of 157.9 and 170.0 cm in Japanese women and men, respectively. The difference in the normal mean adult height between these two populations is 10.4 cm for women and 12.0 cm for men. The mean height in the Netherlands is equivalent to tall stature in Japan. Short stature in the Netherlands is just below the mean normal height in Japan.

The data in table 1 demonstrate the need to obtain population-specific growth charts to define short and tall stature. In a very height-conscious global society the variation in height is of national and international importance with respect to psychosocial adaptation. The answers to ‘How tall is too tall’ and ‘How short is too short’ depend on the height data obtained in each ethnic group. Extremes of height can be defined and accepted only when the normal variance in height of the reference population is known. For the majority of children, adolescents and adults a height below the 3rd or above the 97th percentile should be seen as part of a continuum of a normal Gaussian distribution curve. Only very few will have a defined abnormality, i.e. a height or growth disorder.

Short Stature

Short stature is defined as a height below the 3rd percentile. This means that 3% of the population have short stature. Short stature is defined as familial short stature when one or both parents have a height below the 3rd percentile. Children and adolescents with idiopathic short stature have parents with a height in the lower range of normal, but not below the 3rd percentile. Their short stature probably represents the normal variation in height which can be observed in many families in which some children are taller or shorter than their siblings.

Familial and idiopathic short stature is best explained by estimating the target height according to Tanner [11]. Target height is the mean height of both parents adding 6.5 cm to obtain the target height for boys and subtracting 6.5 cm to define the target height for girls. The target height range is ± 8.5 cm, corresponding to 2 SD. The adult height of 94% of the patients with familial or idiopathic short stature should fall into this target height range. The majority of patients with familial short stature will have a final height below the 3rd percentile due to the short stature of their parents. The majority of patients with idiopathic short stature will have a final height above the 3rd percentile due to the normal stature of their parents [12]. Puberty should not be delayed but start within the normal age ranges that are known for the different stages of puberty [13, 14].

Familial or idiopathic short stature is diagnosed from previous height measurements which demonstrate growth below, but parallel to the 3rd percentile. Height measurements of both parents should be obtained and

documented on the child's growth chart together with the target height and the target height range. The physical examination and pubertal development should be normal and exclude pathological causes of short stature such as Russell-Silver syndrome, Ullrich-Turner syndrome, hypochondroplasia or other causes of syndromal, chromosomal or skeletal etiology [11, 15]. It is essential that the normal growth curves of the population are available (table 1). For the majority of children, adolescents and adults, a height below the 3rd percentile should be seen as a normal variation in height. Very few children will have a defined clinical abnormality.

One of the major differential diagnoses in so-called familial or idiopathic short stature is the variation in growth, i.e. constitutional delay of growth and puberty (CDGP). It is also part of a continuum of the normal Gaussian distribution curve with respect to the age at onset of puberty and the time of the pubertal growth spurt. Statistically, it also occurs with a frequency of 3%. A history of late pubertal development might be obtained from one or both parents or from older siblings. The diagnosis of CDGP is a preliminary diagnosis as long as puberty has not started. The already mentioned history of late puberty in the family and a retarded bone age of -2 or more years can point to the diagnosis. The final diagnosis of CDGP can only be made when the spontaneous onset of puberty occurs outside the $+2$ SD range of the reference population, i.e. 13.3 years for breast development Tanner stage B2 in girls and 13.6 years for spontaneous testicular growth of >3 ml in boys, referring to the data of the Zürich Longitudinal Growth Study [13, 14]. Growth delay and late pubertal development are the major reasons for referral of short patients. The Tanner growth curves for late onset of puberty as well as the data of Buckler and Wild [16] and Rikken and Wit [17] clearly demonstrate that boys and girls with CDGP will not follow their previous height or growth percentiles due to the late onset of their pubertal growth spurt. The already short adolescent will become even 'shorter' at a time when girls and boys with a normal onset of puberty have their pubertal growth spurt. A deviation from the growth curve is normal in these patients. It is necessary to explain this normal phenomenon of transient short stature combined with a late pubertal growth spurt in detail to the patient and his/her parents. The adult height will be within the target height range [12]. It is not necessary and usually confusing for the patients and parents, when an extensive workup is performed to confirm or exclude growth hormone (GH) deficiency (GHD) as the cause of this normal variation of growth. A large number of these patients have been test-

ed as 'transient GHD' [18–20]. Their correct diagnosis is most likely CDGP. It should be emphasized that CDGP is most often diagnosed in a patient with short stature but is also observed in adolescents with normal or tall stature and occurs, as already stated, with a frequency of 3%.

It is one of the major challenges in pediatric endocrinology to differentiate normal variation in height, i.e. familial or idiopathic short stature, and normal variation in growth, i.e. CDGP from pathological causes of short stature and growth. Thus the pathology of short stature includes height and growth disorders.

Patients with short stature caused by height disorders have a short stature that follows a defined, disease-specific growth pattern. A typical example is the girl with Ullrich-Turner syndrome [21]. Her growth is clearly abnormal with respect to normal growth charts (fig. 1a), but exactly follows the specific and therefore normal growth pattern of Ullrich-Turner patients (fig. 1b). The same is true for many other diseases such as Down syndrome [22–25], Noonan syndrome [26], achondroplasia [22, 27, 28] and other skeletal disorders [29]. Disease-specific growth charts have been created for these and other diseases through the tedious efforts of interested and engaged physicians. Thus patients with height disorders have a pathological short stature, but a normal, disease-specific growth pattern. With these disease-specific growth charts adult height can be projected when a patient finds and follows his/her individual growth channel. Deviation from the disease-specific growth curve indicates disease and needs evaluation, perhaps even treatment.

The growth pattern is different for patients with pathological short stature caused by growth disorders. The height of these patients initially follows the normal, population-based growth channel indicated by the height of the parents and the target height range. Figure 2 demonstrates the height and growth pattern of twins and the height and target height range of their parents. The twins have an almost identical height and growth pattern for the first 4 years. Then twin B deviates from the previous growth channel whereas twin A continues growing along the 50th percentile. Unfortunately, no workup of this pathological growth pattern was initiated so that the diagnosis of craniopharyngioma was delayed until the age of 8 years.

Abnormal growth can present a height in the normal range of the 3rd and 97th percentile or as short or tall stature. Thus, normal height does not exclude a pathological growth process. Growth is the major component of normality and pathology in short, normal or tall stature.

Fig. 1. a Growth curve (●) of a girl with Ullrich-Turner syndrome which deviates from the height percentiles of the reference population. **b** Normal growth of the same girl using Turner-specific growth charts.

A large variety of mostly chronic diseases changes the previously maintained growth pattern. Height deviates from the normal growth channel when the specific disease becomes growth effective. Height can accelerate, as in patients with precocious puberty or congenital adrenal hyperplasia, or decelerate, as in hypothyroidism, GHD, craniopharyngioma or other mostly chronic diseases of various etiologies [15, 30, 31].

One of the major causes of pathological growth with or without short stature is GHD. The incidence varies from 1:4,000 [32] to 1:10,000 [30]. Very few studies have looked into the incidence of GHD in the general population [32]. Most reports are from pediatric endocrine clinics which probably overestimate the true incidence of GHD.

Fig. 2. Growth curves of twin A and twin B demonstrating parallel growth until the age of 4 years. Twin B's growth deviates thereafter from the growth curve of his brother. A diagnosis of craniopharyngioma was made at the age of 8 years.

Organic GHD has various causes. It includes tumors of the hypothalamic-pituitary area such as craniopharyngiomas or germinomas. It can also occur following pituitary surgery or cranial irradiation for brain tumors in localizations away from the hypothalamus and the pituitary as in medulloblastoma or in nasopharyngeal carcinoma. GHD becomes evident usually during childhood and adolescence, and in some cases much later, i.e. in adulthood, a long time after radiation therapy [33].

During the last several years our knowledge about the etiology of GHD in combination with other pituitary hormone deficiencies has greatly expanded. Several genetic defects of pituitary development and the GH-releasing hormone (GHRH)–GH–insulin-like growth factor-1 (IGF-1) axis have been described [34, 35]. Most defects are associated with multiple pituitary hormone deficiencies, some affect GH secretion only. Low GH and IGF-1 levels lead to the diagnosis of GHD which could be called ‘GH-dependent growth failure’. The treatment of choice would be a substitution therapy with GH.

Before the initiation of GH therapy, an MRI of the hypothalamic-pituitary area should be obtained. The MRI should exclude tumors such as craniopharyngiomas and germinomas or demonstrate structural lesions such as an interrupted pituitary stalk, an ectopic neurohypophysis or a small or absent adenohypophysis. Detection of congenital abnormalities in the hypothalamic-pituitary area on MRI is important in explaining and confirming the diagnosis of GHD [36–38].

The long-term results of patients treated for GHD have greatly improved in recent years. The adult heights in proven GHD are usually close to target height or within the target height range [39, 40]. One of the major improvements in handling the injections of GH was the introduction of daily subcutaneous GH injections instead of three-weekly intramuscular injections by Kastrup et al. [41].

In other cases the GH receptor and the IGF-1 system are affected [34, 35]. GH levels are elevated with low IGF-1 serum levels. This form of GHD would be an ‘IGF-1-dependent growth failure’. Other pituitary hormones are usually normal. The treatment of choice would be substitution therapy with IGF-1, an option that is not widely available so far.

In recent years the diagnosis of true GHD has become increasingly difficult. These difficulties have become evident when the diagnosis of GHD could not be confirmed during the long-term follow-up of pediatric patients with isolated GHD. GH stimulation tests were normal in a very high percentage of patients who were retested for GHD after the end of GH therapy [42, 43]. It is so far un-

explained why this change in GH secretion occurs. Transitory GHD [19] is one possible explanation, a wrong diagnosis the other reason. These patients are still prepubertal at a chronological age of 11–13 years when the diagnosis of GHD is made. They have very low, but ‘normal’ growth rates – very similar to patients with CDGP [16, 17]. During this period GH secretion is obviously reduced in response to GH stimulation tests. The patients usually have isolated GHD, experience a late but normal pubertal growth spurt and reach an adult height within the target height range. When GH stimulation tests are repeated after the end of GH therapy normal results are frequently obtained. Thus, to avoid a ‘wrong’ diagnosis of GHD in this particular group of patients it might be necessary to lower the normal cutoff values for stimulated GH serum levels to <10 ng/ml or perform estrogen or testosterone priming before the GH stimulation test.

The cutoff levels for GH following GH stimulation tests have changed since 1965. When only a limited amount of pituitary GH was available, a maximum stimulated GH level of <5 ng/ml was chosen. This somewhat arbitrary level was changed to <7 ng/ml in 1975 and to <10 ng/ml in 1985 [44]. There were no obvious reasons for this change and as prospective randomized controlled trials documented that GH levels between 5 and 10 ng/ml also indicated GHD.

Today, GH treatment is also possible for short patients who do not have GHD. GH therapy has been approved for girls with Ullrich-Turner syndrome since 1991, for patients with Prader-Willi syndrome since 2001, for children born small for gestational age since 2003, and for children with chronic renal insufficiency since 1995. GH secretion is generally normal, sometimes even increased as in chronic renal insufficiency, suggesting GH insensitivity as the possible cause of growth failure. In addition, the growth response to GH treatment is extremely variable and usually not comparable to the growth response seen in children with proven GHD.

The mean height gain over projected height in girls with Ullrich-Turner syndrome varies in different studies from 3.6 to 16.9 cm above projected height [45–47]. Height gains above 10 cm have been reported in studies that used considerably higher doses than the recommended therapeutic dose of 0.035 mg/kg/day. Some of the authors have stated that the higher doses are not justified for the small additional gain in height [45, 48–51].

The effects of GH in patients with Prader-Willi syndrome are not only height-, but also weight-related [50, 51]. The initial reports have been promising, but long-term data are needed to evaluate the benefits of GH therapy.

Children born small for gestational age can be treated with GH as approved by the Food and Drug Administration in 2001 and the European regulatory agency, EMEA, in 2003. A recent analysis of long-term GH therapy suggests an increase in adult height by 1 or more standard deviation scores (SDS) which is approximately 5–7 cm depending on the population standard [52, 53]. Children with the greatest parental height-adjusted height deficit and children treated at a younger age have a better response to GH. Height gain is about 0.4 SDS, roughly 2.4 cm greater when a higher dose of GH is used. Here, the same question arises: can the additional costs and the possibly increasing side effects justify the higher dose of GH? The recommended dose in Europe is 0.035 mg/kg/day.

Children with chronic renal insufficiency have benefited from GH therapy in the initial treatment years. Limited data from long-term follow-up reports describe height gains of approximately 7–11 cm [54–56].

After these initial and some long-term data in patients with non-GHD short stature became available, it was not surprising that studies were initiated to document the growth response to GH in children with idiopathic short stature who were not GH deficient [57–60]. With the results of these studies and a reported gain in adult height of approximately 7 cm, the Food and Drug Administration in the United States saw some evidence for the effectiveness of GH in the treatment of children with idiopathic short stature. Children with a height of more than 2.25 SDS (or less than the 1.2 percentile) below the mean for age and sex can be treated with GH after exclusion of other causes of short stature, and when they have a normal GH response on provocative testing, open epiphyses with a bone age within 2 SD of chronological age, and a growth rate showing that it is unlikely that the child will attain an adult height within the normal range. The lower limit of normal adult height is defined as 160.0 cm in men and 149.9 cm in women. It is not stated what method should be used to reliably predict this adult height, especially in children with a history of CDGP.

Final height data for GH treatment of idiopathic short stature have been published [59, 61, 62]. The mean gain in height over predicted height or a control group varies between 3.7 [59] and 5.4 or 7.2 cm when GH was administered at a dose of 34 or 53 µg/kg/day [58, 61].

The psychosocial impact of short stature has been evaluated in several studies with controversial results [63–68]. Some authors describe social, school and behavioral problems and low self-esteem, especially in patients referred to medical centers for evaluation of short stature

[63–68]. Others state that there is no evidence for major psychosocial problems in the general group of children, adolescents or adults with short stature [63–68]. The question whether we should offer GH therapy or psychosocial treatment for short stature is therefore open for further research. The effects of GH therapy on adult height, even if statistically significant, do not necessarily solve the psychosocial problems. It would therefore be appropriate to initiate and conduct prospective randomized controlled studies to examine the effects of medical versus psychosocial treatment on psychosocial functioning during GH treatment and during an observational follow-up period in adulthood. Foreseeing the difficulties of such a study, investigators should retrospectively evaluate the psychosocial functioning of GH-treated patients. The results should be compared to a carefully selected control group of short adolescents and adults. It might be wise to delay large scale treatment of patients with non-GHD-deficient short stature, until the results of such a study are available.

Tall Stature

Tall stature is defined as a height above the 97th percentile. This means that 3% of the population have tall stature. Tall stature is called familial tall stature, when one or both parents have a height above the 97th percentile. Children and adolescents with idiopathic tall stature have parents with a height in the upper range of normal, but below the 97th percentile. Their tall stature probably represents the normal variation in height within a family or the positive secular trend in height.

The diagnosis of familial or idiopathic tall stature can generally be made from previous height measurements which demonstrate growth above but parallel to the 97th percentile, and a normal physical examination. For this diagnosis of a normal variant of height, reference growth curves of the population are needed (table 1).

The differential diagnosis includes overgrowth syndromes such as Sotos syndrome or sex chromosome disorders such as Klinefelter syndrome [69, 70]. Rarely is tall stature due to an excess of GH secretion caused by a pituitary adenoma or by an ectopic GHRH-producing tumor. Transient tall stature is observed in patients with true precocious and pseudo-precocious puberty. When untreated, these patients have a final height below their target height, sometimes even a height below the 3rd percentile.

Girls are more often referred for evaluation of familial or idiopathic tall stature than boys. Being already tall

they would like to know how tall they will be as adults. Thus predictions of adult height play an important role in the management of tall stature. Whenever height predictions exceed a certain height, usually 3 SD above the population mean, treatment of tall stature might be considered by patients, parents and physicians.

Several height prediction methods are available. They are generally based on the assessment of bone age and some height-related variables. For the evaluation of bone age the Greulich-Pyle Atlas [71] and the Tanner-Whitehouse method of bone age determination [72] are most commonly used. The height prediction tables of Bayley and Pinneau [73] and Roche and Wettenhall [74] refer to the Greulich-Pyle Atlas, and the Tanner-Whitehouse Mark I or Mark II methods [72, 75] to the Tanner-Whitehouse method of bone age determination. Apart from bone age-related height predictions target height according to the method of Tanner [11] can be used. This is mid-parent height +6.5 cm for boys and -6.5 cm for girls with a range of ± 8.5 cm.

Most height prediction methods are derived from height data on children growing within the 3rd and 97th percentile. No special attempt has been made to include children with tall or short stature. Therefore, when applied to untreated children with tall stature, the value of each prediction method has to be critically appraised. The accuracy of various prediction methods in untreated boys and girls with tall stature has been evaluated by different authors [70, 76], the results of which have been summarized by Drop et al. [69]. There are major differences among the three methods. Some overestimate and others underestimate final height. For some methods there is no consistent tendency to over- or underestimate adult height. Whereas the Bayley-Pinneau method tends to overestimate adult height in all bone age groups in boys with tall stature, the Tanner-Whitehouse Mark I method overestimates adult height at younger and underestimates adult height at older bone ages, thus presenting the best result for the total group [69, 70]. The Roche-Wainer-Thissen method [74] underestimates adult height with the exception of 13-year-old boys. Generally and not surprising, height prediction methods become more accurate with increasing age. The largest error in height prediction occurs when the target height method is performed. Tall girls and tall boys exceed their target height on average by 9.36 or 13.37 cm, respectively [70].

There are no established and generally accepted criteria for the treatment of an adolescent with tall stature. On the contrary, a long-lasting controversy has accompanied the treatment of tall stature [77]. Thus, treatment should

be initiated only after the patient and her/his parents have been thoroughly informed about the accuracy of the height prediction method and the results and side effects of treatment.

A gender bias regarding treatment exists in the US. Treatment of tall stature is acceptable in girls, but rarely done in boys. In addition, treatment of tall stature is rarely performed in populations with a lower average height, though the phenomenon of tall stature is the same as well as the number of children with a height above the 97th percentile or above 3 SD.

The criteria for tall stature and thus the indication for treatment are different from author to author and have changed with time. The published predicted adult heights used as an indication for treatment vary between 175 cm in Swiss girls [78, 79] to 185 cm in German or Dutch girls [69, 70]. In boys the reported heights are as low as 195 cm [80] and as high as 205 cm. Most reports originate from Europe, Australia or the US.

High doses of estrogens or testosterone are generally used for the treatment of tall stature. The therapeutic regimen for boys varies only slightly in different publications. Testosterone enanthate is given at 500 mg i.m. every 2 weeks. Treatment continues up to a bone age of 17 years, when 99% of the adult height is reached according to the Bayley-Pinneau prediction model. Ethinyl estradiol and conjugated estrogens are the basis of treatment in tall girls. Whereas the dose for conjugated estrogens remained the same with 0.625 mg/day, the doses for ethinyl estradiol were reduced from 0.5 to 0.3 mg and now to 0.1 mg/day [69, 70]. Estrogens are taken continuously without interruption. A gestagen is added, e.g. norethisterone acetate at a dose of 10 mg/day or medroxyprogesterone acetate at a dose of 5 mg/day, from day 19 to 28 of each cycle followed by menstrual bleeding.

The effect of treatment, i.e. the difference between predicted height and adult height, varies with the age at onset and the duration of therapy, the height prediction method used and the age when final height is measured. A longer, 2- to 3-year follow-up after the end of therapy is generally recommended until 'true' final height can be measured.

The mean height reductions vary from 4.8 to 12.7 cm in boys and from 3.6 to 5.3 cm in girls [69, 70]. Bone age-specific data demonstrate that the height reduction clearly depends on the bone age at the start of therapy. At a younger bone age height is markedly more reduced. It amounts to 21.3 or 16.6 cm in the youngest and to 2.8 or 2.9 cm in the oldest bone age groups in boys and girls, respectively [70]. Heights in most of these patients were

measured at the end of therapy when the bone age in boys was 17 years and in girls 15 years. Some additional growth has to be expected which will probably increase adult height by 1–2 cm in girls and 2–3 cm in boys. The reduction in adult height at the end of therapy is approximately 50–70% of the difference between the height before treatment and the predicted adult height using the Bayley-Pinneau method of height prediction [70]. Since some additional growth has to be expected the reduction in adult height amounts to approximately 40–50% of the predicted height gain without therapy. This height reduction as a percentage of the predicted height gain is obviously independent of the bone age at which treatment is initiated. It can serve as a 'rule of thumb' for patients and parents to describe the extent of the height reduction which can be achieved through therapy. Large individual variations will persist as indicated.

Individual patients have discontinued therapy for various reasons before reaching the recommended bone age of 17 years in boys. In a long-term follow-up we were able to demonstrate that the reduction in adult height was similar in these patients when compared to those treated until a bone age of 17 years. For this reason we initiated a short-term 6-month study in tall boys with a long-term follow-up and compared the results with the historical long-term therapy group [81]. Boys usually received high-dose testosterone treatment for an average of 14 months. We compared treatment outcome in this group with the results in the 6-month study group. Height reduction was similar between the 2 groups with 7.5 and 7.555 cm in each group respectively. It is important to know that these results were not confirmed by another group with a smaller number of patients [82].

Short-term and some long-term side effects of treatment have been reported for boys and girls. Whereas acute side effects are sufficiently known, less is known about long-term side effects in women and men 30–40 years after therapy. High doses of estrogens and testosterone suppress the hypothalamic-pituitary-gonadal axis, well known from women using anti-conceptive therapy. Recovery of the hypothalamic-pituitary-gonadal axis was demonstrated by several investigators [83]. Spontaneous menstrual periods occurred from 3 to 6 months after the end of therapy in most patients. In men, sperm concentration and other ejaculate parameters were in the normal range or only slightly subnormal when compared to a control group with untreated tall stature [84] or a randomly selected group of men with normal stature [85].

Pregnancy and paternity are the 'final' proof of complete recovery of the suppressed hypothalamic-pituitary-

gonadal axis. This has been documented, but less often. In a recent report from Australia [86, 87] the pregnancy rates between 371 treated and 409 untreated women were 77.4 and 76.5%, and the rate of live births was 66.9 and 65.3%, respectively. Additional data were obtained from study participants demonstrating that treated women were more likely to have tried for 12 or more months to become pregnant without success, that they were more likely to have seen a doctor because they were having difficulty becoming pregnant, and were more likely to have taken fertility drugs. The results of this report and the limited number of other reports make it necessary to add further information from previously treated women and men. The changing pattern of partnerships, marriages and child bearing has to be kept in mind when interpreting the forthcoming results.

Some patients experience different side effects during therapy. Most of these are mild and are reported only by a small number of patients. Acne in men and considerable weight gain in women are among the most frequently documented side effects. At the beginning of therapy peripheral edema can develop in girls and boys. They usually disappear when therapy is interrupted and restarted after a few weeks with the same or an initially lower dose that is increased to the recommended dose after a few weeks.

The weight gain in girls amounts to 5–10 kg or even more during the first 6 months of therapy. This is a problem especially for those patients who already have a tendency to be overweight before therapy. It should be known that the weight gain is considerably less during the following months of therapy. The total weight gain probably does not exceed the normal weight gain during puberty, but is concentrated at the beginning of therapy.

Psychosocial aspects of tall stature lead patients and parents to get information and treatment for their children. The impact of tall stature on girls or boys is fairly well documented for those patients who seek information or treatment for tall stature [88]. Very few data exist in an unselected patient group, a similar situation for patients with short stature. Fortunately, the acceptance of this treatment is high even several years after therapy. Among 91 men and 202 women, 91.2 and 89.6% accepted their treatment when they were 21.2 ± 2.2 and 20.2 ± 2.3 years old, respectively. Treated women and men had a height of 180.6 ± 4.1 or 197.5 ± 4.4 cm. When asked what height they would like to have the answer was 175.3 ± 3.8 cm in girls and 190.5 ± 5.9 cm in boys which corresponds to approximately the 75th percentile indicating that the actual height for most treated patients is still somewhat too tall.

Conclusion

Treatment of tall stature is and will remain a controversial issue. The indication for treatment, the accuracy of height predictions, the effects of therapy with respect to a reduction in adult height or long-term side effects are only some of the many issues of debate. Ethical problems related to tampering with normal growth and excessive height can be added to the list of controversies. Some of the problems such as gonadal function and fertility could be solved by obtaining long-term follow-up data in later adulthood; others probably need prospective random-

ized controlled studies when the question of height reduction between treated and untreated patients requires a definite answer.

The tall adolescent and her/his parents therefore need full information before therapy is initiated. Written informed consent should be obtained from the patient and her/his parents. Treatment of tall stature is performed for psychosocial and only rarely for medical reasons. Therefore, patients and parents should know that treatment of tall stature can be discontinued at all times when patients no longer want treatment or experience untoward side effects.

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