International Journal of Pediatrics and Adolescent Medicine (2016) 3, 91—102

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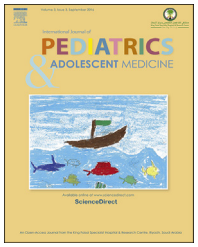

Review Article

Diagnosis and management of growth disorders in Gulf Cooperation Council (GCC) countries: Current procedures and key recommendations for best practice

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Received 5 April 2016; received in revised form 4 July 2016; accepted 4 July 2016
Available online 10 August 2016

KEYWORDS
Growth disorders;
Growth hormone;
Insulin-like growth factor-1;

Abstract Diagnosis and management of growth disorders comprises an important area of pediatric practice. Current procedures in the different stages of the identification, referral, investigation, and treatment of growth disorders in the Gulf Cooperation Council (GCC) countries have been summarized. Evidence-based procedures, relating specifically to height screening for identification of short stature, auxological criteria for patient referral from primary to secondary pediatric care, and general and endocrine investigations and diagnosis have

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Peer review under responsibility of King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia.

http://dx.doi.org/10.1016/j.ijpam.2016.07.002

Adherence;
Transitional care;
Height screening

been discussed and outlined. The management issues related to key disorders that are licensed for growth hormone (hGH) therapy, namely GH deficiency, Turner syndrome, short stature related to birth size small for gestational age (SGA), and idiopathic short stature are discussed with recommendations described for best practice. Finally, two key components of short stature management, namely transitional care for the transfer of patients from pediatric to adult endocrinology services and adherence to recommended therapy with hGH, have been addressed with current practice outlines and recommendations presented.

1. Introduction

Pediatric growth disorders are characterized by the heterogeneity of their pathogenesis. The quality of linear growth, expressed as normal growth rate or height velocity, is an index of the general health of a child. Classifications of growth disorders generally divide patients with short stature into groups of primary or secondary disorders [1,2] and those with so-called idiopathic short stature, a broad category that includes the healthy short child in whom no specific pathological cause has been identified [3].

Management of the child with a disorder of growth is a fundamental responsibility of pediatric healthcare professionals. Short stature may present clinically to any of the three levels of child health. In primary care, routine assessment of weight and height may detect insufficient growth and justify referral of the child for further assessment. In secondary care, the pediatrician needs to understand the differential diagnosis of short stature and be familiar with the key principles of clinical and laboratory assessment. Finally, the tertiary pediatrician, working in a specialist pediatric endocrinology unit to whom the child may ultimately be referred, needs to acquire experience in detailed endocrine assessment, consideration of therapeutic options, approaches to growth-promoting therapy, specifically with human growth hormone (hGH) and initiation and monitoring of hGH therapy.

The optimal management of the child with short stature in the GCC countries presents interesting challenges in terms of ethnic, socio-economic, and genetic diversity. Agreement exists that early diagnosis and treatment, particularly when hormone therapy is appropriate, leads to a greater benefit for the patient and will be linked to an improved adult height prognosis in subjects treated with hGH [4,5].

This article will review current clinical procedures, identify important challenges and, where possible, use evidence-based data to provide key recommendations for best practice in the management of growth disorders. The manuscript will be organized in the following way: A recent review of clinical practice in GCC countries [6] will be summarized, followed by sections that address issues that follow the child identified to have short stature by screening in primary care, criteria for referral to the secondary pediatrician, basic clinical and laboratory assessments, investigations of the GH-IGF-1 axis in a specialist unit and initiation and management of hGH therapy. Additional topics of adherence to hGH therapy and transitional care of the patient with GH deficiency will be covered.

2. Clinical practice in patients with GH deficiency (GHD) receiving hGH therapy in GCC countries

A meeting of experienced pediatric endocrinologists from four GCC countries was convened in 2011, and the proceedings, published in 2014 [6], concluded that most GCC experts adhered to international guidelines for hGH therapy in patients with GH deficiency (GHD) [7]. However, no agreement was reached on a single optimal approach to hGH therapy. Lack of clarity related to the diagnosis of GH deficiency, and the absence of a common approach to assessment of poor and good growth responses and their respective definitions was reported. Poor adherence to hGH was identified as a key area of concern. It was concluded that greater standardization of clinical practice with unification of protocols across the GCC countries was needed to optimize hGH therapy [6].

2.1. Height screening for short stature in primary care

2.1.1. Current procedures

Height screening currently exists to a variable degree in normal populations or in primary child health clinics across the GCC countries. This practice is consistent with the practice of population height measurement to identify short stature, which varies widely across countries and cultures [8,9]. Height screening is available in the majority of schools in the UAE and is mandated by the health authority in Abu Dhabi and the Ministry of Health in Dubai. Height and weight measurements were recorded during medical examinations as part of the Pediatric Kuwait Nutrition Surveillance System (PKNSS), providing data on stunting and wasting in children under the age of 60 months under the auspices of the Kuwait Ministry of Health. Measurements were performed during mandatory routine vaccination examinations. Primary care nurses were trained in measurement techniques, and lengths/heights were plotted on WHO growth charts published in 2006 [10], which are ideally suited for growth monitoring in children under five years of age in a multi-ethnic population [11]. A report

in 2012 from the PKNSS demonstrated that stunting (i.e., length/height ≤2 SDS) in 3860 subjects varied from 8.4% in infants under six months of age to 1.7% in one- to two-year-old children and 3.1% in four- to six-year-old children [12]. Length/height ≤2 SDs was used as an indication for referral to a general pediatrician. These data are clearly of value; however, further analysis is required to determine the percentage of the short children who were subsequently demonstrated to have a pathological cause for their short stature.

2.1.2. Recommendations

In GCC countries, WHO charts are considered to be best suited to detect children with failure to thrive or growth failure during the first two years of life. The Saudi growth charts established in 2007 [13] would generally be preferable to the WHO charts for use in Saudi Arabia. They are also preferable to the 2000 CDC charts, which, if used, would result in unnecessary referrals for short stature and undernutrition [14].

An ideal height screening program in primary care should have sufficient sensitivity to detect pathology and sufficient specificity to prevent the referral of completely healthy subjects [15]. Individual studies have measured populations of healthy pre-school or school children and reported a prevalence of pathological short stature in subjects with height ≤2 SDS to be approximately 5% [16—18]. However, the performances of most programs and particularly their economic consequences have not been critically appraised [8,9].

Auxological criteria are required for referral of short stature from primary to secondary care (Table 1). In Europe, studies in the Netherlands based on referral from routine child health clinics to secondary care have recommended evidence-based criteria. Grote et al published guidelines for a protocol including the performance of the best screening parameters in terms of sensitivity (true-positives) and specificity (false-positives) [15]. In 0—3-year-old children of normal birth weight, height SDS ≤3 or height SDS ≤2 on two or more occasions within one year gave the best sensitivity for a positive diagnosis with a low false-positive rate. For children aged 3—10 years, the combination of height, which is short for parental target height (TH), i.e., height SDS >1.6 below TH SDS and height SDS ≤2.5 and a change in height SDS >1 over an undetermined time interval, detected 85.7% of children with Turner syndrome and 76.5% of children with other growth disorders [15]. An updated definition of TH is used [19]; however, in primary and secondary care, the mid-parental height can be used. The false-positive rate was low. Analysis of these criteria was the basis for a recently updated algorithm for referral of children identified to be of short stature in primary care [20].

2.2. Investigation of short stature in secondary pediatric care

2.2.1. Current procedures

The responsibility for clinical assessment and initial investigations in children with short stature largely rests with secondary pediatricians, to whom infants or children identified as being short in primary care settings will be referred. There is current concern by GCC specialists that the education, knowledge, and experience of general pediatricians in the subject of childhood growth and growth disorders are insufficient. This deficiency should be identified as a priority in terms of medical education, which is needed for pediatricians to appreciate the importance of height as a biological index of general health. Pediatricians also have the responsibility to distinguish causes of poor growth such as failure to thrive, malnutrition, and chronic illness, e.g., gastrointestinal disorders, for which hormonal investigations are generally not required, from true endocrine disorders, which should be referred to pediatric endocrinology specialists.

2.2.2. Recommendations

Medical education is required to emphasize the basic disciplines of clinical assessment, i.e., history taking and physical examination, techniques of height measurement, and the use of growth charts together with knowledge of the differential diagnosis of short stature. In children with significant short stature, i.e., the auxological criteria for referral (see above), important baseline investigations should be performed to exclude non-endocrine pathology.

Recently, debates have taken place concerning baseline investigations contributing to the diagnosis of pathological short stature. In 2008, a consensus statement on the management of idiopathic short stature (ISS) patients recommended a panel of laboratory screening investigations for the short child [21]. A similar approach has been endorsed by other groups [2,22]. Regional differences in the incidence of certain disorders may alter the frequency of certain specific investigations. In 2013, a challenge to this principle of screening investigations in patients 'for whom the history and physical exam do not suggest a particular

Table 1 Criteria for referral of short children from primary to secondary care [15].

Infants from birth to three years of age
• Height SDS ≤3 or
• Height SDS ≤2 (3rd percentile) on two or more occasions within one year
Children aged three to 10 years
A combination of:
• Height that is short for parental target height (TH), i.e., height SDS >1.6 below TH SDS
• Height SDS ≤2.5
• Change in height SDS >1 over an undetermined time interval (minimum four months)

Note: For TH calculation, see Ref. [19] although mid-parental height SDS can be used.

diagnosis' was published [23]. Sisley et al from the Cincinnati Children's Hospital Endocrinology Clinic reported that screening tests in 'asymptomatic short patients' gave little diagnostic information and were not cost-effective, justifiably challenging the practice of 'blanket screening' in short children. However, in the context of secondary pediatrics in GCC countries, it is unlikely that pediatricians would have the experience to exclude disorders such as celiac disease, Crohn's disease, or mosaic Turner syndrome without performing baseline investigations. Our recommendations for clinical assessment and baseline investigations in short stature children are shown in Table 2.

2.3. Investigation of the growth hormone-IGF-1 axis

2.3.1. Current procedures

The GH-IGF-1 axis is the primary endocrine axis that regulates linear growth, and its investigation is indicated in any child in whom other significant causes of short stature have been excluded. In GCC countries, GH-IGF-1 axis investigations are generally performed in specialist or tertiary units under the care of a pediatric endocrinologist. The specialist has the responsibility to confirm the auxological status of the patient using WHO, CDC or Saudi growth charts as appropriate. General pediatric investigations also need to be checked, and disorders such as Turner syndrome, SGA, dysmorphic syndromes, and chronic illnesses must be excluded.

A report from GCC specialists has stated that no consensus was reached on the optimal procedure for assessing the functional integrity of the GH-IGF-1 axis [6]. Essentially two forms of investigation comprise this assessment; firstly, baseline measurements of the growth factors IGF-1 and IGFBP-3 and secondly GH stimulation tests. The IGF-1 generation test may be needed to assess peripheral sensitivity to GH.

For serum IGF-1 measurements, normal ranges for sex and age are provided by laboratories performing the assays. Values $\leq$2 SD are considered to be abnormal, but IGF-1 SDS calculations have not been equally adopted in clinical practice in the GCC region. The difficulty of interpretation of IGF-1 levels in infants under three years of age is recognized, and IGFBP-3 may be of greater value for diagnosis of GH deficiency in these subjects [24]. Interpretation of IGF-1 in children with low BMI may also be difficult. IGFBP-3 determination is performed sporadically throughout GCC countries. The IGF-1 generation test may be performed in children with low IGF-1 and normal or elevated GH secretion, although its interpretation may be problematic [25].

A range of GH stimulation tests is used, including clonidine, arginine, glucagon, and insulin. Priming of the GH stimulation test with sex steroids is performed variably, and determination of overnight physiological GH secretion is not performed. The cut-off GH level for diagnosis of GH deficiency is also variable between centers from 8 to 10 μg/L. In some centers, specialist pediatric endocrinology nurses support patient care; however, the GH tests are usually performed by medical staff. Pituitary MRI scans are performed in patients diagnosed with GH deficiency.

2.3.2. Recommendations

The assessment of the GH-IGF-1 axis to exclude or confirm GH deficiency is recognized to be problematic, and the approach to this investigation is controversial (Table 3) [3]. Detailed clinical and auxological assessment of the patient is essential, and in particular, a subnormal growth rate is a strong guide to GH deficiency or resistance. If available, baseline serum IGF-1 is then determined in a laboratory using a high quality standardized IGF-1 assay [26], ideally on 2–3 occasions to exclude nutritional variations. Normative IGF-1 [27] or IGFBP-3 [28]

Table 2 Clinical assessment and laboratory investigations recommended in children referred to secondary care for short stature [2,5].

Clinical assessment

- History: family history, inquiry about consanguinity, parental heights, birth weight, length of gestation, systematic inquiry for chronic symptoms
- Accurate height measurement using wall stadiometer, weight, BMI, plotting of height on growth chart compared with parental height percentiles
- Physical examination of systems
- Examination for dysmorphic features

Laboratory investigations

- Complete blood count
- Renal function
- Liver function
- ESR
- Calcium, phosphorus
- Alkaline phosphatase
- Bone age
- Skeletal X-rays (when body disproportion is present)
- Tissue transglutaminase
- IgA
- IGF-1 (when available)
- Free T4, TSH
- Karyotype or FSH (<2 and >9 years) if not available (in females only)

ESR, erythrocyte sedimentation rate; IgA, immunoglobulin A; IGF-1, insulin-like growth factor 1; Free T4, free thyroxine 4; TSH, thyroid-stimulating hormone; FSH, follicle-stimulating hormone.

Table 3 Recommended assessment of the GH-IGF-1 axis.

Clinical assessment
- Confirmation of auxological status
- Confirmation of investigations excluding non-GH deficient short stature, e.g., karyotype (in females)
- Exclusion of dysmorphic features of known short stature syndromes
- Exclusion of skeletal dysplasia

Laboratory assessment
- IGF-1 × 2—3 samples with comparison to normative data for age and sex
- IGFBP-3 (optional)
- GH stimulation test
  - Priming with sex steroids in boys > 11 years and girls > 10 years and not in established puberty
  - Cut-off for GH deficiency 6.7 μg/L using assay with IS 98/574
- Genetic sequencing of candidate genes or whole exome sequencing (when history and phenotype suggests genetic origin)

Hypothalamic-pituitary MRI scan in patients with GH deficiency

GH, growth hormone; IGF-1, insulin-like growth factor 1; IGFBP-3, Insulin-like growth factor binding protein 3; IS 98/574, International Recombinant Human GH Standard 98/574.

concentrations for age and sex taken either from the literature or from the local laboratory must be used for their interpretation. A plasma IGF-1 at or around the mean for age or in the upper half of the normal range would make a diagnosis of GHD very unlikely [3], and such a patient would not require a GH stimulation test. On the other hand, a low serum IGF-1 for age (≤2 SDS) in the presence of auxological abnormalities would indicate a relatively high likelihood of GH deficiency, which should then be confirmed by a GH stimulation test. A number of commercial assays are available to facilitate the conversion of serum IGF-1 values to SDS scores [29].

A GH stimulation test should ideally have high reproducibility, generate a strong stimulus for GH secretion, and have a favorable safety profile [7]. The exercise test has no adverse effects, but its positive predictive value is low. A traditional cut-off GH value of 10 μg/L for GH deficiency during the GH stimulation test has been used; however, an international consensus has recommended that if a GH assay using a polyclonal anti-GH antibody is calibrated against the international standard [IS] (IS 98/574), a cut-off of 6.7 μg/L is appropriate throughout childhood and early adolescence [26]. The Growth Hormone Research Society consensus statement recommends two GH stimulation tests to confirm the diagnosis of GH deficiency [7]. In our opinion, a single GH test combined with basal IGF-1 and interpreted together with clinical and auxological results will provide sufficient data to exclude or confirm GH deficiency.

Most pediatric endocrinologists use sex steroid priming immediately before the GH stimulation tests in boys who are older than 11 years of age and girls who are older than 10 years of age who are not in advanced puberty [7]. Choices for priming are a depot testosterone injection 100—125 mg five days before the GH test, ethinyloestradiol 100 μg daily for three days, or stilboestrol 1 mg twice daily for the two days before the test. An MRI scan of the hypothalamic-pituitary region should be performed in patients diagnosed with GH deficiency. This is particularly important in the infant presenting with congenital hypopituitarism [30]. In children with short stature who have a persistently low IGF-1 level, but GH secretion is normal, the IGF-1 generation test (IGF-1GT) may give information relevant to GH sensitivity. However, the IGF-1GT has been critically appraised and is likely only to be of benefit if the patient has extreme rather than partial GH insensitivity [25]. Genetic investigations may identify novel or established causes of GH deficiency, and both candidate gene and whole exome sequencing are available in specialist laboratories [31,32].

2.4. Growth hormone therapy

2.4.1. Factors influencing individualization of hGH therapy

2.4.1.1. Current procedures. In GCC countries, the growth disorders generally treated with hGH have been approved by Food and Drug Administration (FDA). Some disorders that are currently not approved such as achondroplasia and 3-M syndrome may also be treated. The doses of hGH used are usually doses recommended by the US Pediatric Endocrine Society [33]. GCC experts are generally satisfied with the range of therapies available; however, a common approach to the individualization of hGH therapy has not been developed, and the formal use of growth prediction models has not been adopted.

2.4.1.2. Recommendations. Growth hormone deficiency in children covers a wide range of GH secretory abnormalities, ranging from extreme deficiency in congenital hypopituitarism to mild or partial deficiency, which normalizes during exposure to sex steroids in puberty. A continuum model of GH-IGF-1 axis defects can be defined in which GH sensitivity on the X-axis scale ranging from high in the severely GH deficient subject to low or non-existent in the GH-resistant subject can be plotted against a range of GH secretion on the Y-axis [22,34] (Fig. 1). It is clear from the model that patients with severe GH deficiency have greater sensitivity and responsiveness to hGH therapy than patients with mild or partial deficiency. This variation in responsiveness is demonstrated in clinical practice, where

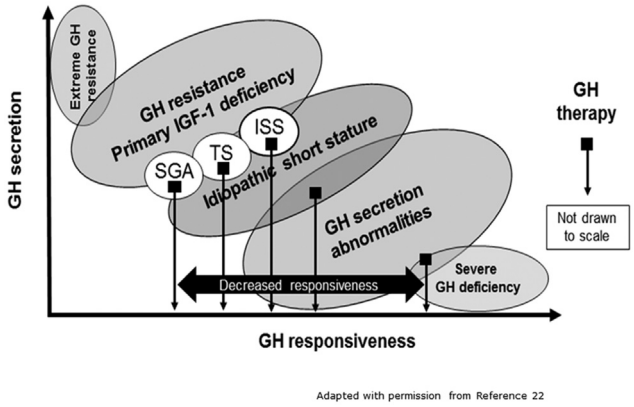

Figure 1 The continuum model of growth hormone-IGF-1 axis defects, showing variation in growth hormone responsiveness in different growth disorders compared to severe GH deficiency. Growth hormone (GH), idiopathic short stature (ISS), Turner syndrome (TS), short stature related to birth size small for gestational age (SGA).

severely GH-deficient subjects (peak GH <3 μg/L) have superior growth responses compared to milder cases (peak GH 3—10 μg/L) [35] and is also a key finding in analysis of data used to construct mathematical growth prediction models [36—38].

The variation in GH responsiveness is even more marked when non-GH deficiency disorders such as Turner syndrome and short stature secondary to SGA are treated with hGH [22] (Fig. 1). When GH-deficient patients are treated with a fixed dose of GH calculated for body weight or surface area, the mean response and stature at adult height may appear satisfactory, but a considerable variation in responses exists [39]. This variation is reduced when the hGH dose is individualized for each patient, depending on the variables predicting the likely response [40]. The key variables are diagnosis of the growth disorder, age at start of therapy, peak GH during a GH stimulation test in GH deficiency, height SDS compared with mid-parental height SDS, and dose of hGH. When hGH therapy is initiated, all of these factors should be taken into consideration to calculate the dose (Fig. 1).

2.4.2. Responses to hGH therapy in GH deficiency

2.4.2.1. Current procedures. General agreement exists in the GCC countries that GH deficiency is the most common indication for hGH therapy. International guidelines for initiation and monitoring of therapy were followed [7]. A starting hGH dose of 25 μg/kg/day was generally used, irrespective of the severity of the GH deficiency and might be increased to 50 μg/kg/day in patients with disappointing growth responses [6]. Patients were monitored every three or four months during the first year of therapy and thereafter every six months. A common approach was not available for the selection of the hGH dose and, in particular, an agreement was lacking on the definition of a good or poor response. The quality of growth response during the first year of hGH therapy was, however, recognized to predict long-term benefits in terms of adult height following completion of therapy.

2.4.2.2. Recommendations. Evidence-based data supporting the key factors predicting growth response during the first and second years of hGH therapy in GH deficiency should be considered when the starting dose of hGH is selected. Key predicting factors are severity of GH deficiency, age of the patient, and distance between the patient's height SDS and mid-parental height SDS [38]. Subjects with multiple pituitary hormone deficiencies experience better growth than individuals with isolated GH deficiency [41]. The starting dose of hGH should follow EMA and US Pediatric Endocrine Society guidelines of 23—39 μg/kg/day, i.e., 0.18—0.25 μg/kg/week [33,42]. Patients with severe GH deficiency, i.e., peak GH <3 μg/L, and patients with multiple anterior pituitary hormone deficiencies require hGH doses at the lower end of the recommended range, whereas patients with mild or partial GH deficiency require doses at the upper end of the range [38]. The increase of hGH dose during puberty is not recommended [33].

Following the initiation of hGH therapy, there is a need to define a poor or unsatisfactory response and to prevent or correct it by optimizing treatment within accepted guidelines. Poor responses to hGH are relatively common [35], and recognition of a poor response is an indication for action, either to modify the therapy or to review the primary diagnosis [43]. Unfortunately, no international consensus exists on the definition of a poor first-year growth response. Bakker et al suggested that GH-deficient patients with a first-year height velocity less than a mean HV -1.0 SD for that sex and diagnosis should be labeled as poor responders [44]. Similarly, Ranke argued that a poor response equals a gain in height SDS of <0.4 in a patient with severe GH deficiency and an increase in height SDS of <0.3 in patients with less severe GH deficiency, girls with TS or SGA subjects [38]. A change in height SDS >0.5 during the first year of therapy generally indicates that the patient is experiencing catch-up growth. In contrast, a change in height SDS <0.3 indicates a poor response [43]. Measurement of IGF-1 concentration is recommended for children with GH deficiency treated with hGH, with the aim of normalizing serum IGF-1 concentrations. However, evidence is lacking that supports the value of IGF-1 monitoring for safety in children and the lack of any data to indicate a safe upper limit for serum IGF-1 concentrations [45].

2.4.3. Responses to hGH therapy in Turner syndrome, short stature related to SGA and idiopathic short stature

2.4.3.1. Current procedures

2.4.3.1.1. Turner syndrome. In GCC countries, Turner syndrome is accepted as an indication for hGH therapy. In patients with the classical Turner syndrome phenotype and chromosomal abnormality, hGH therapy may be started as young as 1—2 years of age, with height SDS ≤ 2 being considered as an indication for therapy. A pharmacological dose of hGH 40—50 μg/kg/day is used, and the dose may be adjusted after six months if no change in height SDS is seen. The definition of a satisfactory response is an increase in height SDS of >0.5 during the first year of therapy. Growth

hormone therapy is usually continued on a long-term basis until adult height is reached. Estrogen replacement therapy is normally initiated at 11–12 years of age. Transitional care to adult services is implemented with multidisciplinary support. No specific adult Turner syndrome units have been reported.

2.4.3.1.2. Small for gestational age. Short stature related to birth size small for gestational age (SGA), defined as birth weight and/or length ≤2 SD for gestational age, is a licensed indication for hGH therapy approved by both the FDA and EMA. In GCC countries, it appears that many children with short stature related to SGA are missed, and relatively few receive hGH therapy. However, this is a global finding with far fewer subjects presenting and receiving therapy than are statistically eligible [46]. The average age for starting hGH therapy was reported to be between seven and nine years [47]. The population of SGA subjects in GCC countries is of particular interest related to an increased prevalence of genetic causes such as 3-M syndrome [48] and IGF-1 and IGF-1 receptor mutations [49]. No consensus currently exists on the approach to the management of short stature related to SGA.

2.4.3.1.3. Idiopathic short stature. Idiopathic short stature (ISS) is not a specific diagnosis. It is a descriptive term used to define children who are short, i.e., height ≤2 SD, with normal birth weight, absence of chromosomal defects, no dysmorphic features or chronic illnesses, and no identified endocrine abnormality [50]. The term ISS, therefore, describes a heterogeneous group of children with many unidentified causes of short stature [21]. The approach to the management of ISS and specifically hGH therapy in ISS subjects remains controversial, with FDA approval for hGH being granted in 2003. In contrast, approval has not been given by the EMA despite numerous applications by pharmaceutical companies [21]. Although a consensus approach to the diagnosis or treatment of ISS in GCC countries has not been established [6], it appears that FDA rather than EMA guidelines are generally followed, with approximately 20% of hGH-treated children having ISS as reported from Kuwait [51] and the UAE [52].

2.4.3.2. Recommendations

2.4.3.2.1. Turner syndrome. As a specific disorder, albeit with a range of X-chromosome defects and significant phenotypic heterogeneity, Turner syndrome is a licensed indication for hGH therapy. The beneficial pharmacological effect of hGH therapy on growth in Turner syndrome patients is now established [53], and a general agreement exists that the hGH dose of choice should be approximately 50 μg/kg/day [54]. Key factors predicting the growth response to hGH are the dose of hGH, a young age at initiation, and the duration of therapy [53–55] (Table 4). Children started on hGH before the age of four years are particularly responsive [56]. A small additional gain in adult height (2.3–4.6 cm) has been reported if the mild androgen oxandrolone (0.03–0.05 mg/kg/day) is given starting at 8–10 years of age in addition to hGH [57].

Debate remains concerning the optimal regimen for estrogen replacement in girls or adolescents with Turner syndrome. Quigley et al [58] have recently presented compelling results showing advantages in terms of growth, pubertal development, and cognitive function when very low-dose estrogen replacement was commenced from the age of five years. Whether a regimen such as this or estrogen commencement at the physiological age of puberty is chosen, agreement exists that delaying sex steroid replacement until the mid-teen years, with the aim of prolonging and improving hGH-induced height gain, is

Table 4 Recommended approach and hGH treatment regimens for patients with Turner syndrome, SGA and idiopathic short stature (ISS).

	Turner syndrome	SGA (birth weight/length ≤ −2 SD)	ISS
Factors predicting response [55]	• hGH dose • Age • Weight SDS • Oxandrolone	• hGH dose • Age • Weight SDS • MPH SDS	• Age • hGH dose • Weight SDS • Height − MPH SDS
hGH dose (μg/kg/day)	50	35[a] 67[b]	50
Starting height (SDS)	–	−2.5[a] −2.5[b]	−2.25[b]
Starting age (years)	–	4[a] 2[b]	–
Key comments	• Early diagnosis • Oxandrolone <0.06 mg/kg from 8 to 10 yr • Sex steroids at physiological age • Transition essential	• Early diagnosis • Increased catch-up with higher hGH dose • Start hGH >2 yr before puberty	• Response unpredictable • If no response (Δ height SDS <0.5) after year 1, stop hGH

SGA, Small for gestational age; SDS, Standard deviation score; MPH, Mid-parental height.
[a] UK National Institute for Health & Care Excellence (NICE)/European Medicines Agency guidance.
[b] FDA, (US Food and Drug Administration (FDA) guidance.

disadvantageous for the patient [59]. A discussion of the detailed management of gonadal dysgenesis is beyond the scope of this review.

2.4.3.2.2. Small for gestational age. The criteria for hGH therapy in SGA subjects differ between the FDA and EMA approval guidelines (Table 4). However, there is agreement that hGH can induce significant gain in adult height. Research data has demonstrated rapid height gain in young, pre-school SGA subjects treated with hGH [60], and early diagnosis and initiation of therapy is strongly recommended [47]. Catch-up growth occurs more rapidly when an hGH dose of approximately 67 μg/kg/day is used [61] and maintained for up to four years [62,63]. However, the dose of hGH recommended in the EMA license is 35 μg/kg/day, which also induced significant adult height gain [46] (Table 4). This was further increased marginally by the addition of a GnRH analogue to suppress puberty [64]. Convincing evidence is available suggesting that a delay in hGH treatment until less than two years before the physiological onset of puberty compromises adult height gain [65].

2.4.3.2.3. Idiopathic short stature. In 2003, the FDA approved ISS as a licensed indication for hGH therapy for patients with height ≤2.25 SD and a reduced adult height expectation. No agreement exists on the optimal therapeutic approach to such patients; however, because these patients do not have GH deficiency, a pharmacological dose of approximately 50 μg/kg/day has been recommended [21,50,66] (Table 4). In a recent Nordic study [35], no difference was observed in the first-year growth response to hGH in patients with mild GH deficiency (peak GH 3–7 μg/L) and with ISS (peak GH >7 μg/L). Age at the start of therapy and dose of hGH are the two key factors predicting growth response [4]. However, as the quality of response in ISS is unpredictable, and the rate of poor response is 30%–40% [35], an approach to the family explaining this information is important. The first-year response will correlate with long-term benefits; therefore, assessment of change in height SDS at the end of the first year of hGH therapy is essential [66]. In patients who show a change of height <0.3 SDS, discontinuation of treatment is recommended [43]. Some slight additional gain in pubertal growth may be achieved by the addition of a GnRH analogue to hGH. In this case, the analogue should be commenced in early puberty and continued for a minimum of two years [67].

2.5. Transitional care of the GH-deficient patient after completion of linear growth

2.5.1. Current procedures

In the GCC countries, the concept of transitional care for the transfer of patients with GH deficiency from pediatric to adult endocrine care is recognized to be important. Agreement exists with the guidelines published by the American Association of Clinical Endocrinologists [68]; however, their implementation has proven to be difficult in practice. The establishment of transitional care services is recognized as an unmet clinical need. Currently, clinical care is organized on the basis of 'transfer' to adult endocrinology, rather than through a process of 'transition' involving collaboration of pediatricians and adult specialists. Two obstacles that have been identified for optimal care are first, the relatively young age, for example 12–14 years of age, when a patient is required to leave pediatric care and secondly, the reluctance of some adult endocrinologists to take over the care of a patient receiving hGH therapy because of the administrative load linked to this treatment. Joint transition clinics have not been established, and endocrine specialist nurses are generally not involved in the care of adolescent patients. Patients with diabetes mellitus are considered to have priority over patients with other endocrine disorders.

2.5.2. Recommendations

Transitional care of the adolescent and young adult patient at completion of linear growth was brought into focus by the establishment of the adult GH deficiency syndrome as a distinct clinical and endocrinological entity [69]. Randomized studies on the effects of discontinuation of hGH replacement in the GH-deficient adolescent demonstrated unequivocally that bone mineral content [70] and body composition [71] became impaired. Continued hGH replacement until the age of acquisition of peak bone mass and full physical maturity, i.e., at approximately 25 years of age, is necessary to complete physiological somatic development. Studies of quality of life (QoL) during the transitional period indicated that although overall baseline QoL was not compromised in severely GH-deficient patients, dimensions related to age-specific psychological problems were significantly worse than in healthy subjects and appeared to positively respond to hGH treatment [72].

Following these studies, it became clear that a structure of care was required to manage the endocrine requirements of the GH-deficient patient between pediatric and adult services. This need was recognized by a dedicated consensus statement that set out the principles, requirements and practical details of a transitional care service [73]. Following completion of linear growth, GH secretion needs to be reassessed, ideally using an insulin or glucagon stimulation test. Growth hormone replacement will be limited to patients with severe GH deficiency, i.e., a peak GH level <3–5 μg/L. Further results on the implementation of transitional care have been published [74]. These results are summarized in Table 5.

2.6. Adherence to hGH therapy: prevention and management of poor adherence

2.6.1. Current procedures

Adherence to hGH therapy and the prevention of poor adherence were topics that have been clearly prioritized by GCC specialists. Poor adherence was considered to be the most likely cause for a suboptimal growth response in GCC countries [6]. The link between poor adherence and poor growth responses to hGH, now well documented in the literature [75,76], were clearly identified. The most frequently advocated steps to improve adherence were first, the initiation of a motivational conversation with the patient and secondly, the use of an electronic injection device that would record the number of doses administered. A strategy to address the issue of adherence to hGH remains to be implemented.

Table 5 The principles and requirements of transitional care to meet the needs of the GH-deficient patient following completion of linear growth.

Requirements:
- Development of an amicable and collaborative working relationship between the pediatric and adult endocrinologist
- Clinical and academic interest of the adult endocrinologist to take responsibility for the young adult patient with severe GH deficiency
- Understanding that somatic and skeletal development is not complete until the age of 25 years and that the GH-IGF-1 axis is necessary to achieve this

Organization:
- Joint consultations in either the pediatric or adult setting to agree on priorities for investigations, e.g., DEXA scan, reassessment of GH secretion
- Following demonstration of GH deficiency, an agreed protocol for reintroduction of hGH therapy
- Assessment of pituitary function, both hormonal and imaging, to ensure optimal puberty, thyroid and adrenal function
- Ideally, close liaison between pediatric and adult endocrinology specialist nurses

Benefits:
- Seamless patient care with transfer to the adult service at an agreed age and following an agreed protocol of care
- Educational advantages for both pediatrician and adult specialist with opportunities for productive collaborative research

GH, growth hormone; hGH, human growth hormone; IGF-1, insulin-like growth factor 1.

2.6.2. Recommendations

Adherence to any chronic therapy is a challenge for the patient and the treating physician. Treatment with hGH is both invasive and psychologically demanding because of its long-term time frame. Evidence suggests that poor adherence to hGH is common; however, this topic is frequently ignored by the medical team responsible for the patient [77]. It is simpler to pretend that poor adherence does not exist than to take steps to address it. The most common reasons have recently been reviewed [78] and are summarized in Table 6.

Addressing the topic of adherence requires that a basic organizational structure be introduced into the growth disorders outpatient clinic. Clearly the head of the clinic needs to be fully committed to this activity. A single health care professional (HCP), who could be a nurse, doctor or psychologist, should assume primary responsibility for issues related to adherence and develop an initial and ongoing relationship with the patient before and during hGH therapy. The technique of non-confrontational interviewing and encouragement of the patient that will be carried out by this HCP requires training and, once implemented, adds time to the outpatient consultation, which is an additional reason why adherence is frequently ignored. A summary of the key steps involved in the implementation of an adherence program is shown in Fig. 2.

The establishment of such a program will be of considerable value to patients receiving hGH therapy and will

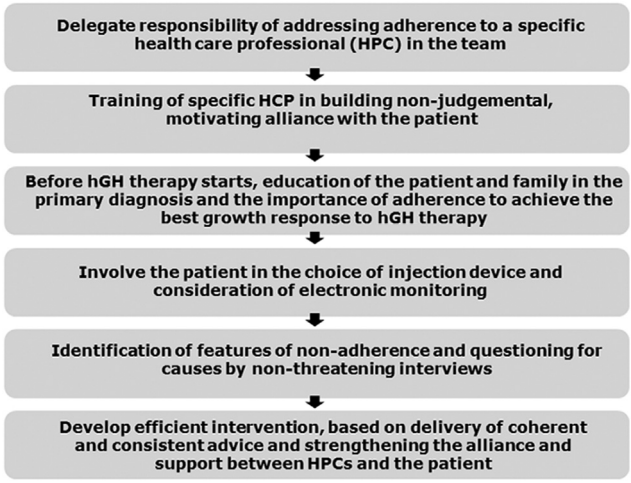

Figure 2 Key stages in the implementation of a program to address the subject of adherence to pediatric hGH therapy.

Table 6 The most common reasons for poor adherence to hGH therapy.

- The child's and care-giver's lack of understanding of the primary disease
- Adolescence
- The length of treatment anticipated
- Implications of poor adherence regarding growth response
- Inadequate support and monitoring by healthcare providers including inconsistent contact
- Pain and discomfort of injections
- Fear of needles
- Lack of choice of injection device and/or complicated devices
- Parental lifestyles and inadequacy of support of the child
- Inconvenience of injection schedule
- Dissatisfaction with the growth response

bring rewards to the medical and nursing team involved in their management. A program which addresses communication skills of HCPs, adherence and the delivery of consistent advice may well be beneficial outside the field of hGH therapy. The introduction of such programs can contribute to cost-effective services, especially in the current climate of value-based health care (Fig. 2).

3. Conclusion

The diagnosis and management of growth disorders is a challenging field, particularly in the context of a wide and multi-ethnic geographical area, such as what exists in the GCC countries. This review aimed not to be critical, but constructive. A widespread commitment exists extending from primary to tertiary pediatric health care to address the current gaps in clinical procedures and to work toward the goal of best practice. The recommendations for diagnosis and treatment of growth disorders that have been described in the review are attainable, but by definition, they are also challenging. The authors, representing four key GCC countries, have demonstrated their determination to show leadership through clinical example and education to achieve optimal standards in this rich and exciting field of clinical pediatrics.

Disclosure statement

M.O.S. has served as a consultant to Merck KGaA, Darmstadt, Germany, Ipsen, Sandoz, and OPKO and has received speaker honoraria from Novo Nordisk. A.S.A.H. has served as a local principal investigator for the ECOS study conducted by Merk Serono Middle East FZ-LLC and has received speaker honoraria from Merck Serono, Novo Nordisk, Lilly and Medtronic.

Ethical clearance

We believe that Ethical clearance isn't relevant to this manuscript, as it is a review of current procedures and not a clinical study.

Author contribution

We confirm that all authors made substantial contributions to the analysis and interpretation of data, and to the drafting of the manuscript or revising it critically for important intellectual content. In addition, all authors provided final approval of the manuscript.

Conflict of interest

The authors have no conflicts of interest relevant to this article to disclose.

Acknowledgments

This publication followed an Advisory Board Meeting entitled '*Gaps in Diagnosis of Growth Disorders and Optimization of GH Therapy*' organized in Dubai in December 2015 by Merck KGaA, Darmstadt, Germany. The authors contributed to the Advisory Board Meeting and to this publication.

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