

British Society for Paediatric Endocrinology and Diabetes

**Submission of Evidence for the National Institute of Clinical
Excellence Health Technology Appraisal: The Use of Human
Growth Hormone in Children (review)**

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1.0 GROWTH HORMONE PRESCRIBING PRACTICE IN THE U.K.

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The British Society for Paediatric Endocrinology and Diabetes (BSPED) is the U.K. national society for professionals who coordinate the care of children with growth, endocrine and diabetes disorders. As such the aims of the society are to advance education in paediatric endocrinology, diabetes and related subjects by promoting research in such areas and disseminating the useful results of such research. The society is the largest U.K. society that represents clinicians and health professionals in this specialist area. It is the only U.K. society responsible for governing the training of doctors of the future in paediatric endocrinology and diabetes. The society also actively supports the ongoing training and education of allied health professionals in these specialist areas. The BSPED is also recognised by the Royal College of Paediatrics and Child Health (RCPCH) as the society responsible for this field of paediatric medicine.

The BSPED welcomes the opportunity to submit evidence to the National Institute for Clinical Excellence ahead of its forthcoming review of human growth hormone (GH) treatment in children. Each treatment category is dealt with fully, citing up-to-date evidence of treatment outcomes where applicable, and presenting our own critical appraisal of GH therapy where there is less evidence based research. This initial section covers the current GH prescribing practice in the UK.

1.1 INTRODUCTION

Human growth hormone (GH) has been used for the treatment of GH deficiency in children and adults, but is also used in conditions associated with short stature and normal endogenous GH secretion including, Turner syndrome and SHOX deficiency, children with poor growth related to chronic renal insufficiency (CRI), Prader-Willi syndrome and children born short for gestational age (SGA) who do not demonstrate spontaneous catch-up. In 2002 the National Institute for Clinical Excellence (NICE) appraised and approved GH for use in GH deficiency, Turner syndrome, CRI and Prader-Willi syndrome in children (NICE 2002). Since then a license for treating children with SGA and SHOX deficiency has also been approved in the UK. In most centres in the U.K. GH prescribing is performed on a shared care basis, with the lead centre taking responsibility for diagnosis and monitoring of GH therapy and the General Practitioner for prescribing. The BSPED have produced a shared care protocol which can be adapted for local usage (Kirk 2006).

The treatment of GH deficiency is, basically, a replacement therapy. To date, growth is the main parameter used to measure the efficacy of treatment; thus goals of therapy are defined in terms of growth:

- physiological catch-up growth if possible
- achievement of normal height during childhood

- timely and normal growth during puberty and
- normal height in adulthood.

Currently, the same set of major outcomes are used for the other recognised uses of GH. Other outcomes include changes in body composition, bone density, cardiovascular risk, respiratory function, behaviour, socialisation and self esteem.

To date there is a paucity of data on changes in quality of life (QoL) following instigation of GH therapy in any of the licensed conditions. Several centres in the U.K. are currently participating in a QoL study investigating outcomes in several treatment groups following implementation of GH therapy. Data is currently unavailable for this submission, but preliminary data maybe available towards the end of 2009. In 2002 the NICE appraisal used a cost/cm gained approach to calculate the cost effectiveness of GH utilising published RCT's at the time. The current review of GH therapy in children has indicated that a cost/QALY approach will be used. Given the limited QoL data in children receiving GH, the BSPED would endorse the fact that it is inappropriate to extrapolate any adult data on height and QoL to children. Hence, estimation of cost/QALY values must be viewed with caution.

1.2 AUDIT OF GH PRESCRIPTIONS

In 1998 an audit of GH prescriptions amongst mostly BSPED members showed a fairly uniform prescribing practice across regions and low levels (22%) of prescribing beyond licensed indications (SGA, bony dysplasia, Noonan's syndrome and other 'short normals' (Hilken 2001). As part of the submission to NICE for the first appraisal of GH in children the BSPED gave an undertaking to perform a longitudinal survey of new GH prescriptions and create an ongoing register (BSPED 2001). This began in autumn 2003 and has been monitored by the clinical trial unit (CTU) of the BSPED. From August 2003 to July 2008 there have been 1996 (1037 male) registrations from 56 consultants with an age range 0.04 – 28.1 years (mean 9.4) (Adelyn Thomason and Prof David Dunger, personal communication). Table 1 shows the comparison between the 1998 data which was a cross sectional survey of current practice at the time, compared to the BSPED register of new GH prescriptions 2003-2008. The degree of licensed to unlicensed usage of GH has remained unchanged at 78% and 22% respectively when comparing the 1998 audit to the 2003-2008 register. It is likely that the % of unlicensed usage in the current register is actually lower than this since Prader Willi syndrome is now a licensed indication but was grouped into the 'other' category for 2003-08 as it was in 1998 when it was unlicensed.

Table 1. Comparison of cross sectional survey of GH prescriptions in children in the UK 1998 with the BSPED register of new GH prescriptions 2003-2008.

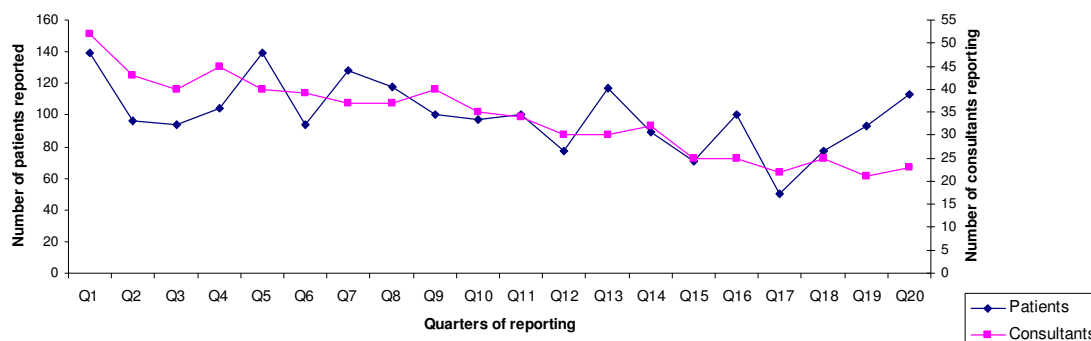
Category	1998—no. on GH	1998-% of total	BSPED 2003-08 new GH prescriptions	BSPED 2003-08 % of total
1. IGHD	656	27%	438	22%
2. Congenital GHD	225	9%	160	8%
3. Craniopharyngioma	91	4%	90	5%
4. Other acquired GHD	347	14%	368	18%
5. Turner syndrome	477	20%	286	14%
6. CRI	63	3%	55	3%
7. IUGR/SGA	<i>74</i>	<i>3%</i>	161	8%
8. Noonan syndrome	<i>44</i>	<i>2%</i>	<i>24</i>	<i>1%</i>
9. Bony dysplasia	<i>107</i>	<i>4%</i>	<i>29</i>	<i>2%</i>
10. Other	<i>311</i>	<i>13%</i>	<i>381</i>	<i>19%</i>
Total	2395	100%	1992*	100%

*1992 from 1996 registrations (no category data on 4 patients).

Numbers in bold represent licensed use and in italics unlicensed use of GH. IGHD – idiopathic GH deficiency, CRI – chronic renal insufficiency, IUGR/SGA – intrauterine growth retardation/small for gestational age.

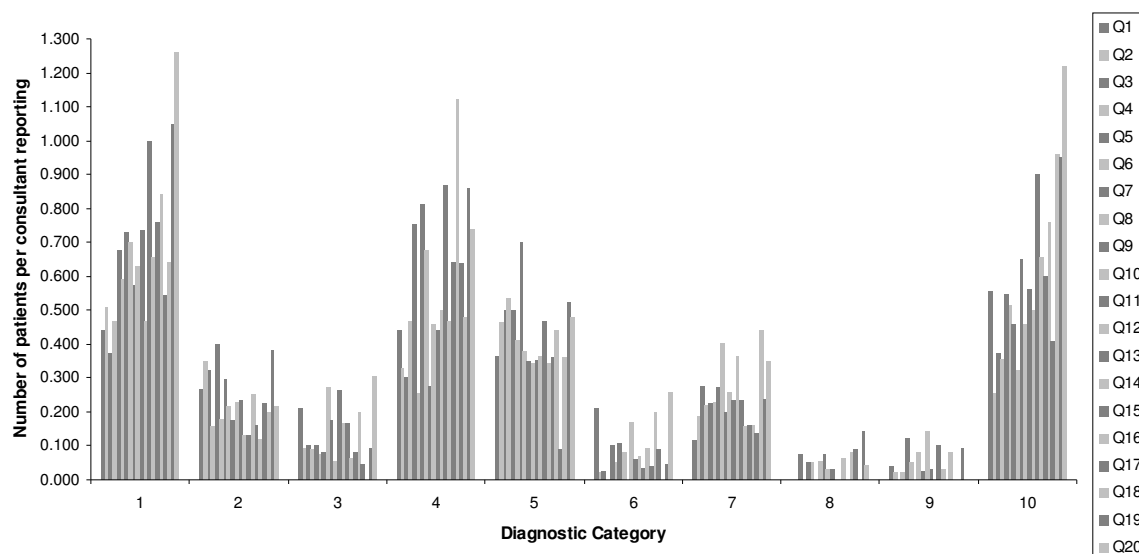
Over the 5 year data collection period the correlation between the number of consultants reporting and the number of patients reported has remained stable (Figure 1), and the number of patients per consultant reporting has stayed stable (Figure 2). Figure 2 clearly demonstrates that GH prescribing patterns appear to have stabilised even in more recent licensed indications such as SGA.

Figure 1. Correlation between number of consultants reporting and number of patients reported by year quarters



Q = year quarter starting August 2003.

Figure 2. Change in number of prescriptions over time by diagnostic category (data expressed per consultant to account for differing numbers of consultants reporting over time).



Q- year quarter starting August 2003. For diagnostic category refer to Table 1.

1.3 GH CHOICE IN THE UK

In the UK there are now 7 pharmaceutical companies marketing GH in children. The profile of licensed indications for each company differs and is summarised below (Table 2).

Table 2. Marketing authorisation for GH for paediatric practice in the UK

Manufacturer (product)	GHD	TS	CRI	PWS	SGA	SHOX
Eli Lilly & Co Ltd (Humatrope)	✓	✓				✓
Ferring Pharmaceuticals (Zomacton)	✓	✓				
Ipsen Ltd (Nutropin Aq)	✓	✓	✓			
Novo Nordisk Ltd (Norditopin SimpleXx)	✓	✓	✓		✓	
Pfizer Ltd (Genotropin)	✓	✓	✓	✓	✓	
Sandoz Ltd (Omnitrope)	✓	✓	✓	✓	✓	
Merck Serono (Saizen)	✓	✓	✓		✓	

GHD – growth hormone deficiency, TS- Turner syndrome, CRI – chronic renal insufficiency, PWS - -Prader-Willi syndrome, SGA - -small for gestational age, SHOX – SHOX deficiency.

Approval for each individual diagnosis was granted after extensive studies on the efficacy and safety of the various products. Some studies required long term surveillance to reach adult height and many manufacturers were

required to document the efficacy and safety of their product in long-term prescription monitoring surveillance programmes such as KIGS (Pfizer international growth database, formerly the Kabi international growth study) and iNCGS (International cooperative growth study). These long-term post marketing surveillance programmes remain in existence to date and perform a vitally important role particularly when new indication for GH become licensed and approved. Hence, it is through these surveillance studies that we now know that recombinant GH preparations are remarkably safe. Recently, the European Medicines Evaluation Agency (EMA) relinquished this restrictive stance with regard to approval of medicines produced by recombinant technology. This change is based on the rationale that any recombinant GH can, in effect, be considered equivalent to the tried and tested preparations already in use, provided certain specifications are met. The term 'biosimilar' was coined to denote the similarities between products rather than their parity, as is the case with generic medicines. Although 'biosimilar GH' is being considered on equal grounds to previous recombinant GH in this appraisal, nevertheless the BSPED feel it is important to highlight that prescribing physicians need to have an informed choice when advising patients and their families and a full understanding of recombinant and 'biosimilar' technology is essential (Ranke 2008). The MHRA, in their guidance, have suggested that changing individual patients from one product to another is not advisable, and that substitution of a 'biosimilar' should not occur when a 'brand name' is prescribed (British National Formulary, Sept 2008). The BSPED fully support this recommendation.

There has been much discussion within the BSPED about patient choice of GH products. Much of this appears to hinge around the choice of delivery system as there is no evidence that any one GH product has efficacy or safety benefits over another, although no such study exists comparing long term outcomes between different products. However, in a one centre study, lower concordance with GH therapy appeared to be associated with lack of patient choice and lower height velocity (Kapoor RR et al 2008). However, although patient concordance may be improved by choice, there appear to be no specific features which determine what GH device a patient will choose (Wickramasuriya et al 2006). A survey of BSPED members has shown that 87% of 46 units prescribing GH now provide some degree of patient choice which includes demonstration of devices and/or use of instructional material such as DVD's (Jeremy Kirk, personal communication and published in abstract). More research is required into patient choice and outcome. Therefore until such data is available the BSPED would recommend that prescribers of GH are fully trained and informed to be able to advise their patients about appropriate choice of available products.

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2.0 RECOMBINANT HUMAN GROWTH HORMONE FOR CHILDHOOD GROWTH HORMONE DEFICIENCY (GHD) - CLINICAL ASPECTS OF TREATING A CHILD WITH GHD

Prepared by Dr Leena Patel and Professor Peter E Clayton, The University of Manchester, and Central Manchester & Manchester Children's University Hospitals

2.1 INTRODUCTION

The 2002 NICE Guidance recommended recombinant human growth hormone (somatropin)(rhGH) treatment for children with a clinical diagnosis of growth hormone (GH) deficiency (GHD) and included the following:

- auxological (measurements of height), biochemical and neuroimaging findings to confirm the clinical diagnosis with two GH provocation tests in suspected isolated GHD and one test in those with defined CNS pathology, history of irradiation, multiple pituitary hormone deficiencies (MPHD) or a genetic defect affecting the GH axis
- arbitrary peak GH concentrations below 20 mU/litre ($\approx 7.5 \mu\text{g/L}$) as the cut-off to support the diagnosis
- dose 25–35 $\mu\text{g/kg/day}$
- treatment to be initiated and monitored by a paediatrician with special expertise in the management of children with GH disorders
- a paediatrician with special expertise in the management of children with GH disorders to consult with patient and carers about (1) stopping treatment at near final height when height velocity is less than 2 cm/year or (2) continuing treatment until transition to adult care and re-evaluation by an adult endocrinologist

This report provides an update from published literature since 2000 [Appendix A]. A number of trials pertain to management during the transition period. These along with consensus opinion from internationally recognised experts provide the best available evidence for continuing rhGH treatment beyond final height [Clayton 2005; Ho 2007]. The goals of rhGH treatment for children with GHD are to (1) normalise height during childhood, (2) attain normal adult height which is within the parental target and (3) reach mature somatic development around age 25 years.

2.2 FINAL HEIGHT (cm or SDS (standard deviation score)¹)

(height at completion of growth expressed in cm or relative to adult norms)

Adult height reported in untreated GHD is -6.1 to -4.8 SDS (134-146 cm) in males, -5.9 to -3.9 (128-134 cm) in females [Frindik 1999]. Recent observational studies of children treated with GH, which include a multicentre study of patients characterised to have severe GHD [Maghnie 2006] and the large KIGS international database [Reiter 2006], have reported:

¹ A standard deviation score is derived by subtracting the population mean from an individual measurement and then dividing the difference by the population standard deviation. This process allows standardizing or normalizing so that children of different ages and genders can be considered together.

- final height SDS -0.4 to -0.9 (when HV (height velocity) <1cm/y) [Maghnie 2006] and near-final height -0.7 to -1.1 (when HV <2cm/y, CA (chronological age) >15y in females and >17y in males, or BA (bone age) >14y in females and >16y in males) [Reiter 2006]
- near-final height -0.2 to -0.8 SDS below target height [Reiter 2006]
- no significant differences in height attained by patients with isolated GHD and spontaneous puberty compared to those with MPHD and induced puberty (at 13.5y in females and 14y in males) [Maghnie 2006; Reiter 2006]

2.3 DOSE DURING CHILDHOOD AND ADOLESCENCE

The KIGS international database reflects management and outcomes in a large number of children in routine clinical practice since 1987. Replacement doses of rhGH reported from it range from 17 to 41 µg/kg/day [Reiter 2006]. Individually titrating the dose of rhGH to maintain IGF-I and IGFBP-3 levels in the normal range while normalising growth approximates physiological replacement [Ranke 2001; Scirè 2008] and is considered to be the most effective strategy. Therefore monitoring during childhood includes:

- growth measurements and evaluation of growth response at 3 to 6 monthly intervals
- serum IGF-I and IGFBP-3 levels at least annually
- assessment of compliance at every visit.

Available evidence does not suggest substantial benefit from higher doses during puberty when balanced against potential adverse effects of high IGF-I levels and cost [Coelho 2008; Mauras 2000]. Maximising growth before the onset of puberty with early diagnosis and initiation of treatment at the youngest possible age remains crucial for optimising final height. Children with GHD born small for gestational age (SGA) attain final height which is comparable to those born appropriate for gestational age (AGA) and with similar doses of rhGH [Di Cesare Merlone 2005]. Thus, unlike short non-GHD SGA children, they do not require treatment with higher doses.

2.4 ADDITION OF GNRH ANALOGUE

Addition of gonadotrophin-releasing hormone (GnRH) analogue to rhGH does not appear to enhance final height [Reiter 2003], and therefore such treatment should only be considered in patients with a poor final height prediction where precocious or early onset of puberty is thought to compromise it further.

2.5 HEIGHT VELOCITY AND HEIGHT VELOCITY STANDARD DEVIATION SCORES

(change in height over given time period, eg. cm/year) (height velocity relative to norms for children of same age)

Reports from the KIGS database provide information about height velocity during the catch-up phase after starting rhGH replacement in prepubertal children with idiopathic GHD [Ranke 2007]. Median height velocities (range) in first, second and third year of treatment were 8.6 (6.2-12.7), 7.1 (5.1-9.6) and 6.3 (4.5-8.6) cm/year respectively (pretreatment 4.7 cm/y). First year height velocity (13.3 vs 8.6 cm/year) and maximum change in height SDS after the first year (1.7 vs 0.6 SDS) have been found to be greater in children

with idiopathic GHD who started treatment before age 3 years compared to those who started treatment at age 7-8 years [Ranke 2005]. However, the younger patients were on higher doses of rhGH (0.83 vs 0.66 IU/kg/day, equivalent to 0.28 vs 0.22 mg/kg/day).

2.6 BODY COMPOSITION AND BIOCHEMICAL MARKERS

(group of measures that assess obesity and amount of fat relative to other body tissues)

Untreated children with GHD, before and during puberty, have abnormal body composition with reduced lean, muscle and bone mass, and greater fat mass [Boot 1997; Roemmich 2001; Högler 2005]. With rhGH replacement, body composition normalises within 24 months [Boot 1997; Roemmich 2001; Högler 2005] and improvements in bone architecture and bone mineral density continue over 5 years [Schweizer 2007; Gonc 2007].

2.7 LIPID METABOLISM AND CARDIOVASCULAR RISK

Prepubertal children and adolescents with moderate or severe GHD have dyslipidemia [Lanes 2001; Gleeson 2002]. There is some evidence that this risk factor for future cardiovascular morbidity is modified with childhood rhGH replacement [Salerno 2004; Boot 1997] but stopping treatment at final height has an adverse impact on lipid profile [Colao 2005]. Reduced cardiac size but not function in prepubertal children and adolescents with GHD [Salerno 2004; Lanes 2005], and vascular abnormalities in untreated patients but better endothelial function with rhGH replacement have also been reported [Lanes 2005].

2.8 QUALITY OF LIFE

Some difficulties with psychosocial functioning, mood, behaviour and cognitive ability have been reported in children and adolescents with GHD [Lagrou 2001; Sandberg 2000]. These are more so in those who have MPHD, who start treatment in the teenage years and who are exceptionally short at the start of treatment. There is limited evidence that rhGH replacement enhances quality of life in children with GHD [Stabler 1998]. However, a U.K. study is currently underway to address this issue but results will not be available until the end of 2009.

2.9 MANAGEMENT DURING THE TRANSITION PHASE OF DEVELOPMENT

Effects of rhGH

The transition phase is the post-pubertal period from near-final height in mid to late teens until 6 to 7 years after reaching adult stature (around age 25 years). In addition to achieving psychosocial maturation, it is a critical phase of somatic development characterised by attainment of adult height, maximal muscle mass and peak bone mass. Despite paediatric rhGH replacement until final height, young persons with childhood-onset GHD (CO-GHD) have deficits in somatic development with lower lean mass and bone mass, and impaired muscle performance compared to healthy peers [Hulthen 2001] and patients with adult-onset GHD [Attanasio 2002]. These deficits are partly attributed to the traditional practice of stopping treatment when final height is

reached. Restarting rhGH treatment in those patients who have persistent and severe GHD results in improvement in body composition and bone accrual [Shalet 2003; Attanasio 2004; Vahl 2000]. Seamless continuation of rhGH treatment but with reduced dose after final height is reached allows sustained acquisition of lean mass and bone mass [Carroll 2004; Drake 2003]. In addition, stopping treatment has an adverse impact on body fat and lipid profile while continuing rhGH has a positive effect on reducing cardiovascular risk [Underwood 2003]. Evaluation of quality of life suggests that psychological problems in young persons with GHD are worse than in healthy peers but respond positively to rhGH treatment in the transition phase [Wiren 2001; Attanasio 2005].

Thus there is compelling evidence to continue rhGH treatment in patients with severe GHD after final height and until age 25 years. Further re-evaluation thereafter will direct whether ongoing adult rhGH replacement is required.

Re-evaluation at near final or final height

Re-evaluation at the end of linear growth is essential to redefine GH status and identify patients with severe persistent GHD who warrant rhGH treatment during transition [Clayton 2005; Ho 2007]. Initial clinical assessment helps to group patients according to the likelihood of severe GHD:

- I. Isolated GHD with an identified mutation (eg. GH-1, GHRH-R), transcription factor mutation (POU1F1, PROP-1, HESX-1, LHX-3, LHX-4) and congenital or acquired panhypopituitarism with 4 to 5 hormone deficiencies implies profound GHD and rhGH should be continued without interruption
- II. Severe GHD in childhood, with or without 2 or 3 additional hormone deficiencies, due to a defined genetic cause, structural hypothalamic-pituitary abnormalities, CNS tumours or cranial irradiation suggest a high likelihood of severe persistent GHD.
- III. The remaining patients including those with idiopathic GHD, either isolated or one additional hormone deficiency, have a low likelihood of GHD.

The consensus is that patients in the latter two groups should have biochemical tests after stopping rhGH for at least 1 month [Clayton 2005]. IGF-I level ≤ -2 SDS for patients in group II supports the clinical suspicion of severe GHD. Patients with an IGF-I level > -2 SDS and those in group III require GH stimulation tests. Severe GHD during the transition phase is defined as a peak GH level <5 $\mu\text{g/L}$.

Dose of rhGH and monitoring during the transition phase

The dose of rhGH reported in various trials ranges from 12.5 to 25 $\mu\text{g/kg/day}$. In clinical practice, the dose should be titrated to maintain IGF-I levels between 0 to $+2$ SDS [Clayton 2005; Ho 2007]. The following monitoring is recommended:

- weight, weight, BMI and BP at least 6-monthly
- IGF-I at least annually
- quality of life annually (using adult validated AGDHA scoring)
- waist circumference annually
- body composition by DXA at baseline and every 2 to 5 years

- fasting glucose and HbA1C annually
- total and LDL cholesterol every 2 to 5 years

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Appendix A. Summary of key publications since 2000

FINAL HEIGHT (cm or SDS)

	Study and subjects	Final height definition	Results of final height
Maghnie 2006	Multicentre observational. Permanent severe childhood onset GHD (peak GH <10 µg/L to 2 tests at diagnosis; <3 µg/L to insulin test or <5 µg/L to other stimulation tests at re-evaluation). 39 IGHD vs 49 MPHD (sex steroids at 13.5y and 14y in F and M). rhGH 0.16-0.21 mg/kg/wk (5-7 doses).	HV<1cm/y	FH -0.4 to -0.9 SDS Total pubertal height gain and adult height <ul style="list-style-type: none"> • similar in IGHD and MPHD • not different if puberty spontaneous or induced Ht at onset of puberty has major impact on adult ht; early diagnosis and treatment to optimise prepubertal growth are important
Reiter 2006	Observational. KIGS international database. Idiopathic IGHD or MPHD (peak GH <10 µg/L to 2 tests at diagnosis). 1258 at near-adult ht. rhGH 0.12-0.29 mg/kg/wk for at least 4y (range 4.4-12.1y) and included minimum 1y prepubertal treatment.	near-adult ht HV<2cm/y, CA >15y F and 17y M, or BA >14y F and 16y M	Caucasian: Near-adult ht IGHD: F and M -1.0 and -0.8 SDS MPHD: F and M -1.1 and -0.7 SDS. Increase in ht SDS: IGHD 1.6, MPHD 2.3. NA ht -0.2 to -0.8 SDS below target height.
Thomas 2001	Observational. 61 Idiopathic GHD (peak GH <10 µg/L to 2 tests at diagnosis). rhGH 0.5-0.7 (mean 0.63 ± 0.1) IU/kg/wk - daily inj, until FH. 49 most IGHD and spontaneous puberty (SP), 12 MPHD and induced puberty (IP). Only 24% had severe GHD (<5 µg/L) on re-evaluation	HV<2cm/y	Pre-treatment HV 3.8 (1.3) cm/y SP 3.9 (1.3), IP 3.5 (1.4). HV 1 st y treatment cm/y. SP 9.5 (2.2), IP 8.9 (3.2). HV 2 nd y treatment cm/y SP 7.9 (2.1), IP 8.0 (2.3) FH -0.7 (1.0) SDS SP -0.8 (1.0) SDS 157.3 (6.2) cm F, 169.0 (7.1) cm M IP 0 (0.9) SDS 161.7 (6.4) cm F, 175.5 (5.1) cm M FH minus MPH SDS: SP 0 (0.9), IP 0.1 (1.6)
Radetti 2003	Observational, 13 pts in each group selected and matched		FH SDS A -0.45 (0.36), B -1.07 (0.7)

	for age, sex, ht SDS before treatment Gp A.0.3 mg/kg/wk vs Gp B. 0.15 mg/kg/wk NB: small no. in each group		Ht gain SDS A 1.81 (0.58), B 1.23 (0.62)
Rachmiel 2007	Observational 96 GHD (GH <8µg/L to 2 tests) rhGH 0.18mg/kg/wk started at age 11.9y, ht -2.9 (1.04) SDS NB: 6 pts had GnRH _a , 20 pts had sex steroids	HV<2cm/y, CA>15y F and 17y M, BA>14y F and 16y M	HV 1st year 9.0 (2.4) cm Total ht gain 1.8 (1.2) SDS FH -1.04 (1.0) SDS FH 165.7 (8.9)cm all, 156.2 (6.6) F, 168.7 (7.3) M

DOSE OF rhGH DURING PUBERTY

	Study and subjects	Final height definition	Results of final height
Coelho 2008	Randomised, no placebo controls, not blind, no reasons given for withdrawal 57 prepubertal GHD (2 tests), rhGH 15 IU/m ² /wk at least 1y, spontaneous puberty Randomised to rhGH 15 IU/m ² /wk or 30 IU/m ² /wk	HV <0.5cm/y &/or BA ≥ 15.5y F, 16.5y M	-0.87 (1.1) SDS No difference between 2 doses during puberty
Mauras 2000	Multicentre, randomised, no placebo controls, not blind 48/97 completed study - GHD (2 tests, GH <10 ng/ml), rhGH at least 6m, in puberty (BA >12y F, 14y M; age 8-16y F, 10-18y M) std dose 0.04mg/kg/d - 42 pts high dose 0.10mg/kg/d - 41 pts drop-out - 14 pts	Near-adult ht: HV<2 cm/y, & BA >14y F, 16y M Adult ht: HV <1 cm/y, epiphyses closed on BAXR	Near-adult ht: std dose -0.7 (0.9) SDS high dose 0 (1.2) SDS HV cm/y (pre-study 8.5): std dose 8.2, high dose 9.8 High dose vs std dose gain in cm: 4.6 cm for 3y and 5.7 cm for 4y treatment But IGF-I higher and >+2 SD in significant no. of patients

ADDITION OF GnRH ANALOGUE

	Study and subjects	Final height definition	Results of final height
Reiter 2003	Observational KIGS International Database, IGHD 1893 rhGH alone vs 39 rhGH+GnRH _a rhGH dose 0.2 mg/kg/wk	near-adult ht HV<2cm/y, CA >14y F and 16y	Near-adult ht SDS: F -1.3 vs -1.6, M -1.1 vs -1.1 Total change in ht SDS: M +1.1 vs +1.6 F +1.1 vs +1.4 No substantial ht gain with addition

		M, or BA >13y F and 14y M	of GnRHa
Saggese 2001	24 girls GHD on rhGH 0.1 IU/kg/d before puberty and no improvement in ht prediction at start of puberty: 14 self-selected for GnRHa vs 10 not on GnRH controls, BA 10.9 vs 10.7y		FH SDS -0.39 (0.5) vs -1.45 (0.2) Better FH with addition of GnRHa at start of puberty if poor ht prediction
Mericq 2000	21 GHD (GH<7µg/L, low IGF-I, low IGFBP-3), treatment naive, pubertal, CA 14.3 (1.6)y, BA 11.3 (1.1)y Randomised: 7 rhGH+GnRHa vs 10 rhGH alone 0.1 U/kg/d	BA 14y F, 16y M	FH SDS -1.3 (0.5) vs -2.7 (0.3) Better FH with addition of GnRHa if treatment started after onset of puberty

EFFECT OF BIRTH WEIGHT

	Study and subjects	Final height definition	Results of final height
Di Cesare Merlone 2005	Prepubertal isolated GHD: 14 SGA (BW <-2SD) and 21 AGA Dose 23-32 vs 23-28 µg/kg/d Duration 3.5-8y vs 3.9-5.8y	HV <1cm/y	Final ht SGA -1.1 vs AGA -1.0 SDS no difference between 2 groups

HEIGHT VELOCITY AND HEIGHT VELOCITY STANDARD DEVIATION SCORES

	Study and subjects	Outcomes	Results
Ranke 2007	KIGS International Database 4802 idiopathic GHD rhGH 0.21 mg/kg/wk started at median age 6.7y	HV 1 st , 2 nd , 3 rd year	median 8.6 (6.2-12.7), 7.1 (5.1-9.6), 6.3 (4.5-8.6) cm/y (pretreatment median 4.7 cm/y)
Ranke 2005	KIGS International Database Idiopathic GHD I. 265 age 0-3y and II. 509 age 7-8y at treatment start Dose 0.83 vs 0.66 IU/kg/wk	1st year HV Max change in ht SDS after 1y	13.3 vs 8.6 cm/y 1.7 vs 0.6 SDS

BODY COMPOSITION AND BIOCHEMICAL MARKERS

	Study and subjects	Outcomes	Results
Schweizer 2007	Prepubertal GHD, mean age 7.2y, ht -2.9 SDS, rhGH 30 µg/kg/d vs non-GHD SGA	muscle strength, pQCT at	muscle mass and bone characteristics lower than normal at rhGH start, improved with

	Observations at 0,6,12,24m (n=74 at 12m, n=55 at 24m)	65% proximal forearm at	rhGH treatment
Gonc 2007	35 IGHD, 15 MPHD mean age 11.26 and 11.46y mean ht SDS -3.3 and -4.4 mean BMD z-score -2.92 and -3.49 rhGH 0.6 U/kg/wk Followed for 1-5y	BMD lumbar Bone turnover	rhGH had positive effects on bone mass over 5y; greater effect in IGHD than MPHD
Högler 2005	20 GHD, 57 ISS 13 GHD, 42 ISS receiving rhGH followed over 24m	DXA BMC, body comp	Femoral neck BMD reduced in GHD. During treatment, % body fat decreased in GHD
Roemmich 2001	6 GHD vs 6 healthy control matched for gender, wt, BA	Body comp	rhGH reduced % body fat in 1 st 3m, FFM increased 3-fold, FM unchanged, abdominal visceral fat reduced
Boot 1997	40 GHD, mean age 7.9y – bone study 17 GHD – lipid metabolism	DXA BMD, bone metabolism, body comp, lipid metabolism	BMD variables decreased at baseline, increased during rhGH LM increased and FM decreased during treatment Lipid profile normal at baseline, rhGH had beneficial effect on lipid metabolism

LIPID METABOLISM AND CARDIOVASCULAR RISK

	Study and subjects	Outcomes	Results
Salerno 2004	12 prepubertal GHD, age 8.1y (± 1.7) Before and after 6 and 12m of rhGH 30 $\mu\text{g}/\text{kg}/\text{d}$ vs 12 healthy children, matched for sex, ht, wt, BSA	LV mass, lipid profile	GHD affects heart morphology, by inducing a significant decrease in cardiac size, but does not modify cardiac function and lipid profile. 12 m of rhGH normalizes cardiac mass, and reduces the atherogenic index
Colao 2005	23 GHD adolescents: re-evaluation 15 GHD 8 non-GHD vs 23 healthy controls matched for age, sex and BMI	risk of early atherosclerosis from cardiovascular risk factors and intima media thickness in common carotids	Before stopping rhGH, HDL cholesterol reduced, increased LDL cholesterol and glucose Stopping rhGH in confirmed GHD adolescents not followed by changes in common carotid arteries, despite the profound negative alterations of the lipid profile In adolescents found to be non-GHD, IMT was increased while on GH therapy and normalized when they were taken off GH

Lanes 2005	10 GHD on rhGH, CA 14.6y (± 1.7) vs 12 untreated GHD, CA 15y (± 3)	ECHO cardiac & vascular function	untreated GHD: reduced LV mass and vascular abnormalities, increased epicardial adipose tissue – good indicator of abdominal/visceral fat rhGH treatment associated with better endothelial function and reduction in arterial stiffness
Lanes 2001	12 GHD untreated, age 14.2y (± 2.8), ht 140.6 (± 17.9)cm, -2.6 (± 0.3) SDS: 6 treated with rhGH but off treatment several years + 6 not treated vs 7 GHD on rhGH vs 19 healthy adolescents	ECHO cardiac mass +function, carotid artery intima-media thickness, lipid + lipoprtA levels	untreated GHD: increased LDL cholesterol, total cholesterol, triglycerides, lipoprtA ie. have dyslipidemia as a risk factor for future cardiovascular morbidity no alterations in cardiac mass and function or early atherosclerotic changes in GHD regardless of rhGH treatment
Boot 1997	40 GHD, mean age 7.9y – bone study 17 GHD – lipid metabolism	DXA BMD, bone metabolism, body comp, lipid metabolism	BMD variables decreased at baseline, increased during rhGH LM increased and FM decreased during treatment Lipid profile normal at baseline, rhGH had beneficial effect on lipid metabolism

QUALITY OF LIFE

	Study and subjects	Outcomes	Results
Lagrou 2001	36 patients, age 20y (± 1.3), FH -0.5 SDS (± 0.9) rhGH started before age 12y vs after age 12y	Retrospective perception of ht and effect of rhGH with semi- structured interviews	more difficulties with psychosocial functioning especially in patients with rhGH started after age 12y, height deficit below -3 SDS at start of treatment and MPHD
Sandberg 2000	GHD pts vs same sex sibs		IGHD functioned better than MPHD FH and growth during rhGH unrelated to QoL outcomes

OUTCOMES DURING THE TRANSITION PHASE

	Study and subjects	Outcomes	Results
Mauras 2005	Multicentre RPCT 2y trial 58 patients, age 15.8 \pm 1.8y,	Body comp	Body comp, BMD, QoL, Cardiac fn, Carbo metab and Lipid metab

	<p>paed rhGH for GHD, at near FH</p> <p>rhGH stopped for 4wk, re-tested with IIG and reclassified:</p> <p>18 no longer GHD – controls</p> <p>40 persistent GHD – randomised:</p> <p>25 rhGH 20µg/kg/d</p> <p>15 placebo</p>	<p>BMD</p> <p>QoL</p> <p>Cardiac fn</p> <p>Carbo metab</p> <p>Lipid metab</p>	<p>– normal in all groups at baseline and after 2y: possibly due to appropriate treatment in childhood</p> <p>No added advantage from continuing treatment if good metabolic status at FH – treatment can be safely stopped for 2y</p>
Hulthen 2001	<p>40 CO-GHD, age 16-21y</p> <p>rhGH stopped and subdivided as GH-sufficient or GHD</p> <p>Controls: 250 healthy age 17-21y</p>	<p>isometric + isokinetic knee-extensor & flexor strength, handgrip strength, LM, FFM, total body annually for 2 yr</p>	<p>GHD adolescents: LM decreased</p> <p>Increase LM and improved muscle performance seen in healthy adolescents did not occur in GHD</p> <p>GH is important for the maturation of LM and muscle strength in adolescents and young adults.</p>
Attanasio 2002	<p>92 persistent childhood onset (CO) GHD (18-30y), rhGH for 9 (4.3)y until FH, treatment stopped for 1.57 (1.2)y</p> <p>35 adult onset (AO) GHD, hypopituitary, no rhGH, age-matched</p>	<p>DXA LM, FM, BMC</p>	<p>FH SDS: -1.18 (1.16) vs -0.38 (1.12)</p> <p>CO had lower LM, FM, BMC than AO</p> <p>CO-GHD have significant maturational deficit in somatic development despite rhGH in childhood</p>
Shalet 2003	<p>Multinational RCT 2y trial</p> <p>Postpubertal severe GHD, paediatric GH stopped at FH</p> <p>Randomised:</p> <p>58 rhGH 25 µg/kg/d (paediatric dose) vs 59 12.5 µg/kg/d (adult dose) vs 32 no treatment</p>	<p>DXA BMC</p> <p>BMD</p> <p>Bone markers</p>	<p>Total BMC increased with rhGH but not dose dependent:</p> <p>8.1 (7.6)% vs 9.5 (8.4)% vs 5.6 (8.4)%</p> <p>predominantly increased in lumbar spine</p> <p>IGF-I increased and dose dependent:</p> <p>178 (143) vs 114 (119) µg/L</p> <p>GH replacement in adult dose induced progression towards peak bone mass</p>
Attanasio 2004	<p>Multinational RCT same as above</p>	<p>DXA LM, FM</p>	<p>Gain in LM with rhGH but not dose dependent:</p> <p>14.2 (11.7) vs 12.7 (9.4)%</p> <p>Decrease in FM with rhGH but not dose dependent:</p> <p>-6 (26.6) vs -7.1 (22.8)%</p>

			GH-dependent progress to target body composition continues after age at which treatment is usually stopped Females require higher dose than males
Attanasio 2005	RCT 2y 25 rhGH 25 µg/kg/d (paediatric dose) vs 28 12.5 µg/kg/d (adult dose) vs 13 no treatment	Adult GHD-specific Qaire: QLS(M)-H SDS	Age-specific psychological problems (body shape and sexual arousal) worse than healthy subjects; responded positively to rhGH in transition period
Urushihara 2007	RDBPC rhGH fixed dose (21 µg/kg/wk, then 42 then 84 µg/kg/wk) 24-wk, then open individualised rhGH dose using IGF-I levels 37 CO-GHD, age 29y (±7) vs 27 AO-GHD, age 51y (±10) Ht 163.9 (147.4-180.4) vs 160.5 (144-180.7)cm	Japanese SF-36v2 Health Survey at baseline, at completion of RDBPC and end of open phase DXA	CO-GHD had decreases in social functioning and mental health – expected positive effects may not have been identified because of the limited sensitivity of the instrument to changes in QoL in adults with GHD
Carroll 2004	Multicentre, PCT 12m trial 24 severe GHD (re-test GH<3µg/L) adolescents (17±0.3y) at HV<2cm/y Paediatric dose continued for 3m, then 12 continued rhGH 0.35 U/kg/wk for 12m vs 12 pts had placebo (ie stopped rhGH) for 12m	IGF-I DXA LM Lipids Insulin sensitivity	IGF-I decreased in those stopping rhGH LM increased in those on rhGH Insulin sensitivity increased if rhGH stopped Lipid levels – no change in both groups
Drake 2003	same as above NB: small nos. in each group	DXA BMC L-BMD at 0, 6m, 1y	Stopping rhGH at completion of linear growth may limit attainment of peak bone mass
Vahl 2000	RDBPC trial for 1y, then open rhGH for 1y 19 CO-GHD, age 16-26y, on paed rhGH Randomised to rhGH or placebo	IGF-I DXA TBF, LM	Stopping rhGH during transition has potentially unfavourable changes in IGF-I and body composition, which are reversed after restarting
Norrelund 2000	RDBPC trial for 1y, then open rhGH for 1y 18 CO-GHD, age 20±1y, on paed rhGH 18µg/kg/d Open phase rhGH 16µg/kg/d	Insulin sensitivity FM 0,12,24m	Stopping rhGH during transition induces fat accumulation without compromising insulin sensitivity. Direct insulin antagonist effects of continuing rhGH are not fully

			balanced by beneficial effects on body composition – decrease in FM and increase in FFM
Underwood 2003	Multicentre RDBPC 2y trial 64 CO-GHD (GH <5µg/L), age <35y (mean 23.8y), off paed rhGH for minimum 1y (mean 5.6y) Randomised to placebo rhGH 12.5 µg/kg/d rhGH 25 µg/kg/d	BMD Body comp LDL cholester ol QoL ECHO Adverse events	At baseline: spine BMD <-2 SD in 22% overwt or obese 59% total cholesterol >200mg/dl 45% Dose response increase in spine BMD at 24m: 1.3 vs 3.3 vs 5.2% Decrease in LDL cholesterol only in high dose group NS changes in QoL and ECHO

3.0 RECOMBINANT HUMAN GROWTH HORMONE FOR TURNER'S SYNDROME (TS)

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3.1 INTRODUCTION

Turner's syndrome (TS) affects approximately 1 in every 1900 live female births [1] and is caused by the loss or abnormality of the second X chromosome in at least one major cell line in the body.

The two principal features of the condition are short stature and ovarian dysgenesis. Short stature is almost invariable, untreated subjects achieving a final height approximately 21cm shorter than the normal female population [2]. Ovarian failure occurs in the great majority of girls so that oestrogen is required from adolescence and throughout adulthood for the development of secondary sexual characteristics and maintenance of bone and cardiac health. The short stature and ovarian dysgenesis may be accompanied by a large and variable number of additional features, including neck webbing, ptosis, facial naevi, cubitus valgus, peripheral lymphoedema and hyperconvex nails. Renal defects such as horseshoe kidney, left-sided cardiac anomalies, thyroid dysfunction and autoimmune disorders are more common in TS, as are middle ear anomalies, often resulting in significant morbidity during childhood. The distribution of intelligence in TS mirrors the normal distribution of the general population. However, girls with TS can have specific cognitive difficulties, in particular, with number work and visuo-spatial tasks and these, coupled with a tendency towards high activity levels and immature behaviour, can have educational and social implications.

Short stature in TS results from impairment of all three phases of the infancy-childhood-puberty (ICP) model of growth. Mean length at birth is 0.5-1.0 standard deviation scores below the population mean [3,4] and this deficit increases during infancy. Growth rate continues to decline throughout childhood. The pubertal growth spurt is absent in untreated girls, reflecting the deficiency in ovarian oestrogen secretion, and subnormal in girls undergoing spontaneous puberty.

The aetiology of the short stature and poor growth in TS relates to haploinsufficiency of short stature genes on the long arm (q) and particularly on the short arm (p) as a result of the missing or abnormal second X chromosome. The mechanism(s) by which this loss of critical genes results in impaired growth is incompletely understood. Skeletal dysplasia, related to loss of the SHOX genes on Xp is clearly an important component. TS girls frequently show low GH levels on stimulation testing but a link between this apparent GH insufficiency and the response to GH treatment has not been found [5].

3.2 AIMS OF GROWTH HORMONE THERAPY IN TURNER'S SYNDROME

Given that the untreated height in TS is estimated at approximately 20 cm below the maternal height, this translates to a final height (FH) of $163 - 20 = 143$ cm in UK Turner girls.

The primary aim of GH treatment in TS is to correct this growth deficit. Given that TS girls are not classically GH deficient (see above) the rationale of GH treatment is to give a supraphysiological dose aimed at overcoming the skeletal dysplasia inherent to the condition.

Secondary aims of GH treatment are not established in TS. However, potential benefits include improvement in bone mineral density (BMD), given that osteoporosis is a feature of TS [6] and that GH therapy has a positive effect on BMD [7]. Also, TS girls are at risk from obesity [8] and their physical activity may be less than their peers. GH therapy is known to enhance lean body mass and to decrease fat mass in GH deficient non-Turner patients and a similar effect might be anticipated in GH-treated Turner girls.

3.3 OUTCOME MEASURES OF EFFICACY OF GROWTH HORMONE TREATMENT IN TURNER'S SYNDROME

3.3.1. Effect on final height

Whilst GH is known to augment height velocity in growing girls, the ultimate measure of success in response to growth promoting treatment is final height (FH), defined as height velocity <0.5 cm per year with complete fusion of the epiphyses. While it is not possible to accurately quantify the height "gained" as a result of treatment in any given *individual* (since their final untreated height can never be known) it is possible, by comparing FH in *groups* of treated girls with control girls, parental heights, projected adult height (PAH) (see below) and height predictions, to examine differences between actual and expected FH. The following models can be used to calculate expected FH, with the PAH method being the most favoured.

a) controls:

(i) historical controls: reference data from more than 15 countries are available and are summarised by Rochiccioli et al [2]. Where possible, up-to-date reference data from the same country of origin should be used to allow for any significant geographic or demographic differences.

(ii) controls from a randomised study: the Canadian study (see below) is the only trial to have randomised TS girls to GH treatment or no treatment over an extended period [9].

b) parental heights: the untreated adult height of most girls with TS falls outwith their target range, therefore, a FH *within* this range suggests that treatment has enhanced growth.

c) Projected adult height (PAH): this method estimates adult height by extrapolating from childhood measurements using either the regression equation developed by Lyon et al [10] or reference data [10,11], which

assume that, if untreated, girls with TS will follow the same height centile into adulthood. Height “gain” is expressed as FH minus PAH.

- d) **predicted height:** various models have been developed to predict adult height from bone age calculations, such as Greulich and Pyle, Bailey Pinneau and Tanner and Whitehouse. This model appears no more effective than PAH. Moreover, the validity of using a method devised for normal children in a group of patients with a growth disorder such as TS is questionable.

3.3.2 Effect on Quality of Life

Improvement in height outcome would be expected to result in improved psychosocial wellbeing, given the adverse effects of short stature during childhood (e.g. name-calling and other forms of bullying), and beyond (e.g. the social disadvantages being an unusually short adult).

However to quantify the social and psychological impact of short stature and its amelioration in TS is difficult because of the potential confounding effects of other problems affecting some TS girls in varying degrees. These include social isolation [12], specific learning difficulties [13], and temporary deafness related to middle ear disease [14].

To date there is no agreed method of assessing QoL in TS in relation to GH treatment. However studies, such as the Sheffield quality of life study, are underway and should help to validate meaningful methods of assessment.

3.3.3 Effects of GH on body composition and glucose tolerance

GH has been shown to improve body composition in girls with TS, with a reduction of total fat mass and an increase in total lean body mass but with some reduction in insulin sensitivity [15]. By contrast, in 76 GH-treated girls aged 13.6 years vs 26 untreated girls aged 13.8 years, abdominal fat was significantly lower in the former [16].

3.4 ADMINISTRATION OF GH AND OTHER GROWTH-PROMOTING TREATMENT IN TURNER SYNDROME; THE UK TURNER STUDY 1999-2009

Biosynthetic GH, which has been widely available in the UK since 1985, is given subcutaneously on a daily basis. While it is widely accepted that the dose used should be greater than the 5 mg/m²/week used to treat classical GH deficiency, the dose schedules used vary (see Table below).

Adjunctive use of the anabolic steroid oxandrolone has been advocated but with no consensus as to how effective this measure is in improving final height.

The timing of oestrogen induction of puberty in TS is also controversial. Over 80% of girls require pubertal induction but the effect of delaying induction to as late as 14 years in terms of improving FH (by allowing more time for growth) is unproven.

In 1999 the BSPED embarked on a prospective UK study of growth promoting treatment in Turner's syndrome, funded by the Chief Scientist Office in Scotland 1999-2004 and by BSPED 2004-. Girls have received a standard GH regime of 30 IU/m²/week (equivalent to 10 mg/m²/week) throughout the trial, with randomisation to oxandrolone or placebo at 9 years of age (or at enrolment if aged >9 years), and oestrogen induction in double blind fashion at either 12 or 14 years. Of 104 girls recruited only 14 have withdrawn and the first analysis of the study by Professor Tim Cole, Medical Statistician, is being carried out at the time of writing this report. Submission for publication of this study is scheduled for June 2009.

3.5 EVIDENCE FOR IMPROVED FINAL HEIGHT OUTCOME IN TURNER'S SYNDROME GIRLS TREATED WITH GROWTH HORMONE (TABLE)

The many different GH regimes, along with the inconsistent use of anabolic steroids and timing of pubertal induction, in various studies make direct comparison of outcomes difficult. Reviews of the worldwide literature have reported variable results [17,18], illustrated by the following table published by Guyda in 1999 [18] and updated for the purposes of this report. Although results have varied from centre to centre, **virtually all studies have shown evidence of an increase in treated FH versus expected untreated FH.**

Table - Final height in Turner syndrome girls treated with GH derived from Guyda et al, 1999 [18] and updated to include four studies since 1999

Author (country) [ref]	Yr	N	GH dose (IU/kg/wk)	Age started (yr)	FH (cm)	PH (cm)	FH - PH (cm)
Rochiccioli (France) [19]	'95	117	0.9	12.9	147.7	144.1	+3.6
Massa (Holland) [20]	'95	45	0.8-1.2		152.3	149.7	+2.6
Van den Broeck (5 countries) [21]	'95	78	0.5-1.0	12.9	150.7	147.8	+2.9
Takano (Japan) [22]	'95	12	0.5	10.3	145.1	137.0	+8.1
		16	1.0	9.7	144.0	137.0	+7.0
Heinrichs (Belgium) [23]	'95	31	0.9	12.2	151.3	142.9	+8.4
		15	0.8	14.9	153.8	147.0	+6.8
Taback (Canada) [24]	'96	17	0.9	12.4	148.0	148.2	-0.2
Chu (Scotland) [25]	'97	26	0.5-1.0	12.5	142.6	142.0	+0.6
Nilsson (Sweden) [26]	'96	44	0.7	12.2	152.0	146.0	+6.0
Haeusler (Austria) [27]	'96	20	0.5-0.8	11.8	152.9	143.7	+9.2
Rosenfeld (U.S.) [28]	'98	17 ¹	1.1	9.9	150.4	142.0	+8.4
		43 ²	1.1	9.9	152.1	141.8	+10.3
Plotnick (U.S.) [29]	'98	622	1.0	12.9	148.3	143.8	+6.4
Carel (France) [30]	'98	17	0.9 ³	10.2	148.3	143.1	+5.2
		12	2.1 ⁴	11.0	155.3	144.7	+10.6
Betts (UK) [31]	'99	52	0.8	10.7	150.8 ⁵	146.7 ⁵	+4.1
Sas (Holland) [32]	'99	19	1.2	13.5	155.5	149.2	+6.3
Dacou-Voutetakis (Greece) [33]	'99	35 ⁶	0.7	11.5	146.1	145.0	+1.1
Ranke (43 countries) [34]	'99	979	0.8	13.1 ⁷	148.0 ⁷	144.0 ⁷	+6.7 ⁷

Johnston (England)[35]	'01	58	1.0	9.1	146.8	142.2	+4.6
Quigley (USA)[36]	'02	99	0.8 - 1.1	10.9	148.7		Est
Gault (Scotland) [37]	'03	29	1.1	10.1	151.1	145.4	+5.7
Canadian GH advisory Committee [9]	'05	43 ⁸	0 (control)	10.9	141.0	-	N/A***
		61	0.9	10.3	147.5	-	

¹ Received GH alone with late introduction of oestrogen therapy.

² Received GH plus oxandrolone at a dose of 0.0625 mg/kg/day and late oestrogen therapy.

³ Received standard doses of GH of 0.9 IU/kg/wk; onset at age 11 yr.

⁴ Received adapted doses of GH up to 2.1 IU/kg/wk; onset at mean age of 10 yr for 4 yr, with late introduction of oestrogen therapy.

⁵ Approximate as calculated from SD score (Turner specific) provided by authors.

⁶ Duration of GH therapy was only 2.2 yr.

⁷ KIGS database: median values. Lyon height prediction [15] indicated a gain of 6.7 cm. GH plus oxandrolone at a dose of 0.05 mg/kg/day in 25% of patients and late oestrogen therapy in all.

⁸ 59 patients, 40 treated and 19 control, were followed up for one year or more after protocol completion; mean heights were 149 and 142.2 cm respectively; ***PAH not carried out but difference in height between controls and treated children estimated at + 7.2 cm by ANCOVA at protocol completion

Thus, Guyda found a mean FH achievement of 150cm [18], compared to an untreated mean FH reported elsewhere of 142.9cm [10]. Also, Rosenfeld et al reported a mean FH of 150.4cm, some 8.4cm above the PAH, in a group of 17 girls treated with GH alone and considers 150.0cm as a reasonable target for treatment [28]. Since the publication of Guyda's review, an English randomised trial has reported a mean FH of 146.8cm, with 31% of the 49 girls achieving 150cm [35]. A retrospective study in Glasgow by Gault in 2003 found that 29 girls receiving GH treatment since 1994 reached a mean final height of 151.1 cm [37], significantly better than the low figure of 142.6 cm reported by Chu et al for Scottish girls in 1994 [25]. Gault and co-authors believed that compliance with GH treatment had been enhanced by this single centre's dedicated Turner clinic.

In 2005 the Canadian Growth Hormone Advisory Committee published the results of a randomised controlled study of GH supplementation in TS, which had started in 1989 [9]. Of 154 girls enrolled to either GH or placebo, 61/76 treated and 43/78 controls completed the protocol over a 6-year period. Mean heights at protocol completion are shown in the Table and the estimates of efficacy based on ANCOVA models were of a height difference of 7.6 cm [95% confidence interval 6-8.5 cm], $p < 0.001$, compared with control patients.

Despite data showing that growth in *groups* of girls with TS is improved by GH therapy, the *individual* variation in response to treatment means that some subjects end up short despite GH. Thus Guyda reported minimum FH ranging from 131.5-145cm in five of the studies reviewed in 1999 [18]. Moreover, the Canadian study showed mean (SD) height at protocol completion of 147.5 (6.1) in the treated group, indicating heights in the region of 135 cm for some patients [9].

3.6 FACTORS POTENTIALLY AFFECTING VARIABLE RESPONSE TO GH TREATMENT IN TS

The following factors have been identified as potential predictors of response to GH treatment:

- age at start of treatment – retrospective reviews in the US and the UK have found the best results are associated with a younger age at the start of treatment [29,31].
- duration of treatment – a positive correlation between FH and duration of treatment has been identified [19,29,34].
- dose of GH – a significantly greater growth rate has been reported with higher doses [22,31]. Promising results have been shown with doses \rightarrow 58 IU/m²/week (\cong 2.1 IU/kg/wk) [30,32] although the long-term safety of such very high doses requires further investigation.
- frequency of injections – the best responses have been found with more injections per week [20,34].
- height at start of treatment – studies have found that the tallest girls at the beginning of treatment achieve the greatest FHs [19-21]. However, a negative correlation between initial height and FH minus PAH [19-23] suggests that the shortest girls benefit most from treatment.
- mid-parental height – those with tall parents appear to reach the most favourable FHs, demonstrating the genetic influence [19,29,34].
- bone age (BA) – a negative correlation has been found between BA and FH-PAH [20,21,26,27] suggesting that as the skeletal system matures, the benefits of GH therapy are reduced.
- compliance – family motivation and commitment are as important in influencing response to treatment. None of the above factors is relevant if treatment is not administered in the first place.
- adjunctive treatment with oxandrolone - used in combination with GH, this anabolic steroid has been shown to increase growth velocity [26,28,31,38]. However its impact on FH remains a matter of debate and should be clarified by the UK Turner study (see above) in which either oxandrolone or placebo has been given from 9 years of age until FH attainment.
- timing of oestrogen induction. This remains a very contentious matter. Advocates of late induction claim that early addition of estrogen decelerates height velocity & reduces the gain in height [26], that estrogen replacement begun as early as 14 years can compromise height potential [28], and that TS girls induced at 15 rather than 12 years became significantly taller as adults [39] and that the greatest ‘gains’ in adult height were in those beginning E2 after 15 years of age [40]. By contrast other authors have claimed that systemic oestrogen can be initiated earlier without compromising growth [41], that by using high GH doses earlier oestrogen induction can be initiated without compromising FH [32] and that there is no link between the age of induced puberty and adult height [42]. One study has suggested that the number of “oestrogen-free” years of GH treatment was a significant factor in FH outcome [40]. The UK Turner study in which patients have been randomised in double-blind fashion to receive oestrogen at 12 or 14 years and are being followed to FH, should help to resolve this controversy.

3.7 CURRENT UK PRACTICE

This has to some extent been influenced by the UK Turner study which employs a GH dose of 10mg/m²/week (\cong 1.0 IU/kg/week) in daily injections, beginning when height falls below -2 SD or when the family identifies short stature as a problem and preferably by 8 years of age.

The most recent published audit of UK practice showed that the mean age of starting treatment had fallen significantly from 10.4 to 8.5 years, the starting dose has risen significantly from 0.55 to 0.95 IU/kg/week (\cong 15.4 to 26.6 IU/m²/wk) and the frequency of injections had increased from 3 to 6/7 per week [31].

3.8 CONCLUSIONS & RECOMMENDATIONS

There is now unequivocal evidence that GH therapy is effective in the treatment of short stature in TS. Groups of girls do well, with an increase in growth and improvement in final height. However, a small number of individuals continue to fare poorly in terms of FH outcome and research is needed to ascertain the cause of this so that strategies can be developed to help these poor responders.

The impact of improved FH on Quality of Life in TS is difficult to measure partly because of confounding factors, and also because large scale studies using validated methods have yet to be carried out. A theoretical strategy would be to examine QoL in treated versus untreated patients. This strategy would complement the recommendations of a recent Cochrane review which examined the efficacy of GH on growth and concluded that *'additional trials of the effects of hGH carried out with control groups until final height is achieved would allow better informed decisions about whether the benefits of hGH treatment outweigh the requirement of treatment over several years at considerable cost'* [43]

We believe that, in the light of the Canadian study of 2005, it would be hard to obtain ethical consent to examine FH outcome and to carry out QoL assessment in untreated TS girls. Moreover, even if this were achievable it would be hard to persuade families to enrol in such a study. It is of note that the drop-out in the control arm of the Canadian study was much higher than the treatment arm – 35 vs 15 subjects respectively – during the early phase of the study in 1989. Moreover, it would be difficult to countenance allowing TS girls to drift further and further away from their peer groups during the childhood and adolescent years when the effects of GH in helping to normalise short and medium term growth are so well established.

Questions remain as to the optimal dose of GH, the best age at which to begin treatment, the optimal age at which to induce puberty, and the role of oxandrolone in improving GH outcome. Randomised prospective trials, adequately powered and appropriately funded, are required to find answers to these questions. The results of the UK Turner study which examines the effects of timing of estrogen induction and of oxandrolone on FH should be published by the end of 2009.

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4.0 RECOMBINANT HUMAN GROWTH HORMONE FOR GROWTH FAILURE IN CHILDHOOD CHRONIC RENAL FAILURE (CRI)

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4.1 INTRODUCTION

The 2002 NICE Guidance made the following recommendations regarding recombinant human growth hormone (somatropin)(rhGH) treatment children with Chronic Renal Insufficiency (CRI):

- Growth hormone (GH) treatment is currently recommended for growth failure in prepubertal children with CRI provided:
 - nutritional status has been optimised
 - metabolic abnormalities have been optimised
 - steroid therapy has been reduced to minimum.
- GH treatment should be stopped after a renal transplantation, and only re-established after one year if it has been ascertained that catch-up growth has not occurred.
- Treatment to be initiated and monitored by a paediatrician with special expertise in the management of children with GH disorders.

This report provides an update from published literature since 2000, and some additional pre-2000 references not included in previous review [Appendix A]. Of note, during the update period several final height studies have been reported and the Cochrane Review of Growth Hormone for children with chronic kidney disease has been updated (Vimalachandra et al 2006).

A recurring theme in many studies is that poor growth responses were seen with older age, long duration of dialysis, severe short stature at time of commencement of rhGH. This stresses the need for early optimisation of concomitant factors (eg nutrition, metabolic bone disease, steroid minimisation). Early institution of rhGH where appropriate can be expected to lead to improved growth responses and final height outcome (Mehls et al 2008; Nissel et al 2008).

4.2 FINAL HEIGHT (cm or SDS)

Since the initial NICE review there have been further publications reporting on final height outcome in children with CRI treated with rhGH.

The North American Pediatric Renal Transplant Cooperative Study reflects US clinical practice in care of children and adolescents with CRI. Notably, only 4.5% of the total population received rhGH, with percentages of subgroups as follows: conservative management (2.7%), dialysis (5.8%) and transplant (4.9%) (Fine et al 2000). Final Height had improved from baseline in all GH treated groups (0.7, 0.35, 0.49 SDS respectively), whereas the non-GH treated groups had remained virtually static. However, the small numbers of treated patients include predominantly those with severest short stature, which is shown to lessen the growth response, thus final height figures may be overly pessimistic.

Australian final height data in CRI children treated with rhGH was previously reported in abstract form, and is now peer-reviewed (Crompton 2004). For the 38 children who had reached final height, pre-GH Height SDS was -2.65 and final height SDS was -2.3 (161.8 cm for males and 149.5 cm for females).

All the RCT studies are short term and thus do not given information on final height. The best proxy is to compare GH treated versus non-GH treated groups. Estimates of improvement in final height range from 0.5 to 1.7 SDS (Mehls, Wuhl, Tonshoff, Schaefer, Nissel, & Haffner 2008; Nissel, Lindberg, Mehls, & Haffner 2008), all of which compare favourably against the progressive height deficit in the non-GH treated CRI population, reaching mean final height of -2.06 SDS for males and -1.4 SDS for females as described below.

Final height (FH) in the non-GH treated French population with childhood onset CRI was shown to be lower than in a normal population (Andre et al 2003), and provides a useful comparator for final height outcome studies in the GH treated groups. For these 60 patients (aged 21-36 years old), final heights were: 161.6±8 cm for males [-2.06±1.3 SDS] and 154.3±8.1 cm for females (-1.4±1.4 SDS). This was subdivided into Group A (those who were on conservative treatment at 16 years of age, n=22) and Group B (end-stage renal failure [ESRF] n=38, comprising half on hemodialysis (HD) and half with a functional renal transplant (RTx)). FH in conservative group A (-1.15±1.4 SDS) was significantly higher than in the dialysis/transplant group (-2.1±1.3 SDS). Overall, 45% of all patients (56% of males and 23% of females) had a final height below -2 SDS (41% in group A and 47% in group B). Interestingly, these figures from 2003 are not dissimilar to the final height data reported almost two decades previously, when Rizzoni found that 60% of boys had a final height below -2 SDS, although the figure for girls of 41% with final height below -2 SDS has improved (Rizzoni et al 1985). This lack of change may potentially be explained by the improvement in renal impairment treatments, being offset by an improved survival rate for more severe renal pathologies.

The Andre et al study also demonstrated that a continuation of growth after 18 years of age was observed in 23 males (71.8%): +5.2 cm (+0.87 SDS) and to a lesser extent in 14 females (50%): +1.75 cm (+0.3 SDS), and generally involved those with pubertal delay (Andre, Bourquard, Guillemin, Krier, & Briancon 2003). This highlights that studies reporting final height based on measurements at 18 years in the CRI population may underestimate the true adult height and longer-term follow-up studies may be needed to determine the true effect of GH.

4.3 HEIGHT STANDARD DEVIATION SCORES

Improvements in height standard deviation scores during childhood have been outlined in the NICE 2002 review, but there are several additional post-2000 studies that are worth highlighting.

1. Longer term data (up to 8 years) is provided by Hokken-Koelega, with some further outcome data from the randomised trials commenced

between 1988 and 1991 (Hokken-Koelega et al 2000). Results are encouraging with mean height reaching the lower end of growth chart (Height SDS -2) after 3 years of GH therapy and reaching target height by 6 years of GH therapy. In addition, factors associated with better Height SDS by 4 years of therapy were younger age at GH commencement, less severe short stature and shorter duration of dialysis.

2. Van Dyk 2001 reported 21 prepubertal children commencing GH at a median age of 5 years (range 1.8–8.7 years), with a minimum duration of treatment of 12 months with 12 longer than 2 years (Van & Proesmans 2001). During this short time frame there was a significant improvement in Height SDS score from -2.29 to -1.31 after 1 year and to -1.07 after 2 years.
3. Fine et al completed a further RCT on GH therapy in short stature in CRI, this latest study examining 68 children and adolescents with renal transplant and short stature (Height SDS -2.95) (Fine et al 2002). This study showed an increase in Height SDS of $+0.49 \pm 0.10$ after 12 months of GH therapy, compared to -0.10 ± 0.08 in control group ($P < 0.001$).
4. The effect of GH therapy was reported in specific renal pathologies and shown to increase height SDS in these groups. Firstly, autosomal recessive polycystic kidney disease was reported in 5 children aged 4.5–11.9 years who received rhGH therapy for 0.3–5.4 years. All responded to rhGH (Z-score before -2.8 vs. -1.26 after treatment, $P=0.03$) (Lilova et al 2003).
5. Kari subdivided their group of 32 children with CRI receiving GH therapy into those managed conservatively (i.e. renal replacement therapy) ($n=21$) and those on dialysis ($n=11$), either haemodialysis or peritoneal dialysis (Kari & Rees 2005). The conservatively managed group (Group A) had a mean glomerular filtration rate (GFR) of $24 \pm 12 \text{ mL min}^{-1}/1.73 \text{ m}^2$ at the start of rhGH and showed significant improvement in Height SDS, from -2.5 ± 1.4 at baseline up to -1.6 ± 0.6 after 3 years of GH therapy ($P=0.001$). No further change in Ht SDS was noted in subsequent years of GH therapy. However, patient numbers had more than halved by later time points. Moreover, most catch-up growth is known to occur in the first 3 years of GH therapy generally, and this would be consistent with other GH indications as well. The GFR of the dialysed group (Group B) is not mentioned, although it is noted the dialysed group were older, which is known to correlate negatively with growth response to GH (Mahan & Warady 2006). Group B also had delta Ht SDS 0.4 over first year of GH therapy. Although further improvement was not documented by 2 years and later, the dataset of these later time points is too small, as patient numbers had more than halved. The authors explained that their group had a low prevalence of GH use in CRI of 4.4%, attributed to their 'aggressive use of enteral feeding' (Kari et al 2000). This suggests that non-responders to enteral feeding will probably have been over-represented in the GH therapy group, i.e. greater proportion with more severe renal disease in the GH-treated group. This may in turn explain the lesser delta Height SDS in this study compared to others.

4.4 OTHER AUXOLOGY: HEAD CIRCUMFERENCE SDS

Although the Van Dyk study provides only short term data for linear growth (Van & Proesmans 2001), an interesting and important finding was that mean head circumference SDS improved significantly from -2.04 to -1.45 after 1 year, with this degree of improvement evident after 6 months of GH therapy in those younger than 5 years (this difference between the groups assumedly reflecting the greater rate of head growth in the first 5 years of life). It had been recognised since the 1980s that head circumference and brain maturation are adversely affected in children with CRI in infancy (McGraw & Haka-Ikse 1985; Bock et al 1989). The evidence of a beneficial effect of GH upon the auxological parameter of head circumference is thus encouraging.

4.5 HEIGHT VELOCITY AND HEIGHT VELOCITY STANDARD DEVIATION SCORES

Several studies since 2000 report on Height Velocity in children with CRI treated with GH.

The Cochrane Review examined Randomised Controlled Trials (RCTs) (up to June 2005) comparing rhGH treatment with placebo/no treatment or comparing two doses of rhGH treatments on children with CRI (Vimalachandra, Hodson, Willis, Craig, Cowell, & Knight 2006). Fifteen RCTs (629 children) were identified.

- Treatment with rhGH (28 IU/m²/wk) resulted in a significant increase in height SDS at 1 year (delta SDS 0.78, 95% CI 0.52 to 1.04), and a significant increase in height velocity at 6 months (2.85 cm/6 mo, 95%CI 2.22 to 3.48) and one year (3.80 cm/y, 95%CI 3.20 to 4.39).
- Compared to the 14 IU/m²/wk group, there was a 1.34 cm/y (0.55 to 2.13) increase in height velocity in the 28 IU/m²/wk group.
- One year of 28 IU/m²/wk rhGH in children with CRI resulted in a 3.80 cm/y increase in height velocity above that of untreated patients.

4.6 BODY COMPOSITION, GLUCOSE AND LIPID METABOLISM

Effect of rhGH on body composition in children with CRI:

- Johnson studied 7 children at baseline and after 6 months of GH therapy and found significant improvements in 4 parameters: reduction in fat mass and fat percentage and increase in fat free mass and total body bone mineral mass (Johnson et al 2000).

Glucose Metabolism:

- The German Study Group for Growth Hormone Treatment in Chronic Renal Failure examined metabolic effects of rhGH in 53 prepubertal children with CRI and reported on yearly oral glucose tolerance tests (OGTT) during rhGH therapy for up to 5 y, compared against controls: 12 age-matched children treated with rhGH for idiopathic short stature (Haffner et al 1998). Notably the group also included patients remaining on rhGH once transplanted, which differs from UK practice. The most marked degree of hyperinsulinaemia was found in the transplanted patients (1402 ± 179 pM) and correlated positively with their methylprednisolone dosage, whereas CRI patients on conservative renal treatment had insulin levels

(829 ± 94 pM) not significantly different than the idiopathic short stature controls (719 ± 89 pM). Importantly no patients developed impaired glucose tolerance, impaired fasting glucose or diabetes.

- 2 RCTs examined and detected no significant differences in glucose tolerance between treated and non-GH treated groups (Fine et al 1994; Guest et al 1998).
- Another RCT found degree of hyperinsulinaemia in the GH treated group after 6 months, but no effect on glucose tolerance (Hokken-Koelega et al 1996).

Lipid Profiles:

- Lipid profiles were examined on 11 patients with CRI participating in the double blind placebo-controlled RCT of GH therapy (Hokken-Koelega, Stijnen, de Jong, Donckerwolcke, Groothoff, Wolff, Blum, de Muinck Keizer-Schrama SM, & Drop 1996). Although they found that mean serum levels of total cholesterol, low density lipoprotein, apolipoprotein-A1 and -B were elevated at baseline compared with children without CRI, none of the levels altered during GH therapy. This study did not examine lipoprotein A.
- One study has looked at effect of GH therapy on lipid profile only in renal transplant patients (Ghio et al 2002). Reassuringly most parameters were unchanged (cholesterol, triglycerides or apolipoproteins), although lipoprotein A [Lp(a)] which is a marker cardiovascular morbidity rose during GH therapy. It is not yet established if these levels return to pre-treatment levels upon GH cessation, so further studies are needed.

4.7 QUALITY OF LIFE

There are currently no studies examining the effect of GH therapy on parameters of Quality of Life (QOL) in children and adolescents with CRI. However, amongst studies looking at QOL in the CRI population, there is indication that height deficiency in CRI represents additional negative impact on quality of life markers in this patient group already burdened with many consequences of CRI.

- UK based qualitative research assessed the concerns for future health in 30 children with CRI and their parents. Even though 50% of patients had additional extra-renal complications, height was a major concern for 30% of parents and 28% of children. Reynolds highlights that growth impairment was rated as one of the significant concerns for the future by both patients and families and should not be minimised against other morbidities in CRI (Reynolds et al 1995).

4.8 SIDE EFFECTS

The BSPED 2001 submission mentioned concern that there had been cases of avascular necrosis (AVN) of the femoral head and slipped femoral epiphysis reported in children with CRI on GH treatment (unreferenced in 2001 document). However, Boechat 2001 provide reassurance that AVN occurs as a complication in CRI at the same prevalence (7%) in both the GH treated groups (n=139) and the control group (n=66) (Boechat et al 2001).

The Cochrane updated review also found that the frequency of reported side-effects was similar between the GH treated and non-GH treated groups, e.g. kidney function, acute rejection in kidney transplant recipients, benign intracranial hypertension and slipped capital femoral epiphysis (Vimalachandra, Hodson, Willis, Craig, Cowell, & Knight 2006).

Body proportions: Hokken-Koelega and colleagues had previously published a double-blind placebo controlled cross-over trial (n=15) (Hokken-Koelega et al 1991) and double-blind dose-response trial (n=22) (Hokken-Koelega et al 1994), both showing significant increase in Height SDS and was considered in the NICE 2001 submission. Further analysis of those 37 patients is now reported, examining body proportions before and during GH therapy (de Graaff et al 2003). Various body segments, such as sitting height, arm span, tibia, hand and foot length, biacromial and biiliacal diameter were measured and all showed the same degree of reduction height SDS ie proportionate growth impairment. During GH therapy there was a similar increase in all measured body segments, indicating GH therapy did not induce disproportionate catch-up growth.

There was no difference in acute rejection episode rate between GH treated and control arm in an RCT in 68 transplanted children with CRI (Fine, Stablein, Cohen, Tejani, & Kohaut 2002).

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Appendix: Summary of key publications since 2000

FINAL HEIGHT (cm or SDS)

	Study and subjects	Final height definition	Results of final height
Fine 2000	North American Pediatric Renal Transplant Cooperative Study GH treated group Non-GH treated group Conservative (9 had GH, 335 no GH) Dialysis (22 had GH, 377 no GH) Transplant (72 had GH, 1480 no GH)	Height measured at ≥ 18 years	Delta Ht SDS (baseline to final height) GH treated cf non GH treated for each: Conservative +0.70 cf -0.02 (p=0.036) Dialysis + 0.35 cf 0.06 (p=0.09) Transplant + 0.49 cf 0.04 (p=0.001)
Crompton 2004	Retrospective from OZGROW (Australia-wide database) for all patients treated with rhGH CRI patients n=183 Duration of GH therapy 1.2 - 10.5 years (mean 5.3 years). Subset (n=39) reached final height (This study had been presented in abstract form when included in earlier NICE review. Now published in peer-reviewed literature)	Height SDS Final Height	Ht SDS at start and end of rhGH treatment: Conservative management: -2.6 to -2.1 Dialysis: -2.7 to -2.3 Transplant: -3.1 to -2.8 (P = 0.0001) Whole group -2.9 to -2.4 Final Height in subset of 39 mean Ht SDS: before rhGH therapy -2.65 at final height it was -2.3 Mean final height: males 161.8 cm and females 149.5 cm.
Nissel 2008	Retrospective Pfizer International Growth Database (KIGS) N=240 with CKD. At baseline: 39% prepubertal and 61% pubertal; 45% were on conservative treatment for CKD, 28% dialysis, 27% post	'Near Final Height' i.e. Height velocity <1cm/yr	Mean Ht SDS at GH start: -3.6 Delta Ht SDS from baseline to nr final height: 1.2 SDS in males, 1.6 SDS in girls Best FH in those with normal pubertal onset (Ht SDS -2.0) or early puberty onset (Ht SDS -2.2) compared to FH SDS with

	renal transplantation		late puberty (FH SDS -2.9) or severe pubertal delay (FH SDS -3.6) Overall 40% reached FH in normal range.
Andre 2003	Retrospective. <u>No</u> GH treatment i.e. 'Natural History' group 60 patients (21-36 years old; 28 females and 32 males), At 16 years of age, 22 were on conservative treatment (CT, group A) and 38 were in end-stage renal failure (ESRF, Group B), half of whom were on haemodialysis and half had a functional renal transplant.	HV<0.5cm/y Height at 16 years and 18 years and final height	Whole group FH: 161.6±8 cm for males [-2.06±1.3 SDS] and 154.3±8.1 cm for females (-1.4±1.4 SDS). (45% below -2 SDS) Group A: -1.15±1.4 SDS (41% below -2 SDS) Group B: -2.1±1.3 SDS (47% below -2 SDS) FH was reached at 20.2±1.8 years in males and 18.8±2 years in females.

DOSE DURING CHILDHOOD AND ADOLESCENCE

	Study and subjects	Outcomes	Results
Vimalachandra 2006 (Cochrane Review)	RCTs up to June 2005: Fifteen RCTs (629 children) rhGH 28 IU/m ² /wk versus 14 IU/m ² /wk	Height Velocity increase over 1 year	Height Velocity increased by 0.55 cm/yr in low dose group, compared to 2.13 cm/year increase in the high dose group, i.e. 1.34 cm/y extra increase in the high dose group.
Hertel 2002	RCT, rhGH 28 IU/m ² /wk vs 14 IU/m ² /wk aged 3.4-15.1 years 23 completed 1 st year, 16 completed 2 nd year	Height Velocity SDS	Increased by 1.3 in low dose group compared to 2.1 in high dose group (p < 0.05)

HEIGHT SDS, HEIGHT VELOCITY AND HEIGHT VELOCITY SDS

	Study and subjects	Outcomes	Results
Kari 2005	Retrospective 32 children with CRI on GH for > 1yr (mean duration 3.7 ±	Height SDS at 0,1,2 years of rhGH	Results of Ht SDS for all 32 children: -2.5±1.2 at GH start -2.3±0.7 at 1 year (P=0.3),

	<p>2.5y). Group A (n=21): managed conservatively (i.e renal replacement therapy) Group B (n=11): Dialysis</p>		<p>-2.1±0.7 at 2 years (P=0.01), -1.7±0.7 at 3 years (P=0.02).</p> <p>Group A: Ht SDS improved from: -2.5±1.4 at GH start -2.1±0.7 at 1 year (P=0.3), -2.0±0.7 at 2 years (P=0.01), -1.6±0.6 at 3 years (P=0.001).</p> <p>Group B: Ht SDS improved from: -2.7±0.5 at GH start -2.3±0.5 at 1 year (P=0.02)</p> <p>29 / 32 children were transplanted and thus ceased GH, mean±SD age 12.1±4.0 years. At transplant, Mean Ht SDS was -1.8±0.8 and there was no change over the following 5 years.</p>
Vimalachandra 2006	<p>RCTs up to June 2005: Fifteen RCTs (629 children) rhGH 28 IU/m²/wk versus placebo One year duration</p>	<p>Height Velocity Height SDS</p>	<p>3.8 cm/yr increase in height velocity 0.78 increase in height SDS</p>
Van Dyck 2001	<p>Open Label 21 prepubertal patients with CRI children < 5years (n=10) children > 5years (n=11) Median GFR 17 ml/min/1.73m² at GH commencement. GH started at a median age of 5 years (range 1.8–8.7 years). Duration of GH treatment: minimum 12 months, 19/21 had > 18 months, 12/21 had > 24 months</p>	<p>Mean height SDS Mean BMI SDS Mean Head Circumference SDS</p>	<p>Mean height SDS increased significantly from -2.29 to -1.31 after 1 year and to -1.07 after 2 years Mean BMI SDS within normal range throughout Mean head circumference SDS improved significantly from -2.04 to -1.45 after 1 year and remained stable thereafter. In children < 5years the increase in head circumference SDS was already significant after 6 months of therapy, in those > 5 years, significance was</p>

			reached only after 1 year
Fine 2002	<p>RCT</p> <p>68 with transplant and short stature (Ht SDS - 2.95)</p> <p>1 year randomisation, then all on GH</p> <p>On GH (n=30) Controls (n=22)</p>	<p>Delta Ht SDS</p> <p>Acute Rejection Episodes</p>	<p>Delta ht SDS: +0.49 ± 0.10 in treatment group -0.10 ± 0.08 in control group (P < 0.001).</p> <p>Safety: Acute rejection episodes: year 1: 0 in treatment group and 3 in control group. After year 1, all on rhGH: 3 in treatment group, 2 in control group. No difference in adverse events between the two groups.</p>
Hokken-Koelega 2000	<p>Randomised</p> <p>45 prepubertal children 28 boys, 17 girls, age mean ± SD 7.8±3.4 years</p> <p>CRI and short stature started GH therapy between 1988 and 1991</p> <p>Dose 28 IU/m²/week</p>	Height SDS	<p>Baseline -2.95 ± 1.00</p> <p>After 3 years GH therapy, mean Height SDS -2SDS.</p> <p>Reached Target height by 6 years GH therapy. (P<0.001).</p>

BODY COMPOSITION, GLUCOSE METABOLISM, LIPIDS

	Study and subjects	Outcomes	Results
Johnson 2000	<p>Observational</p> <p>N=7 children with Chronic Renal Failure on rhGH 0.35 mg/kg/week</p> <p>Measurements at baseline and after 6 months of rhGH</p>	<p>Fat Mass (FM)</p> <p>% fat</p> <p>Fat free Mass (FFM)</p> <p>Bone Mineral Density (BMD)</p> <p>Total Bone Mineral Mass (TBMM)</p>	<p>significant reductions (improvement) in:</p> <ul style="list-style-type: none"> • FM (4.4±1.4 kg vs. 3.6±1.2 kg, P=0.002) • percentage fat (18.6±3.9% vs. 14.5±3.4%, P=0.04), <p>Significant increases in (improvement) in:</p> <ul style="list-style-type: none"> • FFM (17.9±3.0kg vs. 20.7±3.6kg, P=0.04) • TBBM (776±171g vs. 844±177g, P=0.001).
Haffner 1998	<p>53 prepubertal children with CRI on rhGH monitored for up to 5 years</p> <p>annual oral glucose</p>	<p>fasting glucose, insulin, HbA1C,</p>	<p>No change in fasting or stimulated glucose concentrations during GH therapy</p>

	tolerance tests (oGTT) Group included those on conservative management, dialysis and also transplant patients (latter on methylprednisolone) Controls: 12 age-matched children treated with rhGH for idiopathic short stature.	triglycerides, cholesterol. Glucose, and insulin responses during OGTT	Insulin levels higher in subsets of CRI on dialysis or transplanted compared to conservatively treated CRI patients and controls during GH therapy <ul style="list-style-type: none"> transplant (1402 ± 179 pM) dialysis (1025 ± 114 pM) conservatively treated (829 ± 94 pM) controls (719 ± 89 pM) ($p < 0.01$)
Ghio 2002	Case controlled GH in transplant patients 9 children treated with GH for 1 year Controls: 12 matched non-GH treated Studied at 0, 6 and 12 months	lipoprotein (a [Lp(a)] cholesterol triglycerides apolipoprotein A (APO A) apolipoprotein B (APO B), APO B/APO A ratio	RhGH therapy had no effect on cholesterol, triglycerides or apolipoproteins Lp(a) did increase in rhGH treated group: <ul style="list-style-type: none"> baseline 6.7 ± 5.7 mg/dL 6 month 11.8 ± 10.7 (p=0.018) 12 months 13.6 ± 15.1 (p=0.04)
Hokken-Koelega 1996	RCT placebo controlled, double blind N=11 GH dose 28 IU/m ² /week	Lipids: total cholesterol, low density lipoprotein, apolipoprotein-A1 and -B. Glucose met: OGTT	Lipids: <ul style="list-style-type: none"> Elevated in these CRI patients compared to normal population. Did not change significantly during GH therapy. Glucose Metabolism: <ul style="list-style-type: none"> No change in glucose levels Significant increase in insulin levels

SIDE EFFECTS

	Study and subjects	Outcomes	Results
Boechat 2001	205 children with CRI mean age 6 y GH treated group n=139 Control group n=66 Serial Xrays of femoral head 6-month intervals during the study (range, 1–7 years; mean, 3 years \pm 2).	Presence of avascular necrosis (AVN) of the femoral head	AVN present in 14 of 205 (7%) Incidence equal in GH treated group compared to control group

Kari 2005			No patients developed Benign Intracranial Hypertension
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QUALITY OF LIFE

	Study and subjects	Outcomes	Results
Reynolds 1995	Qualitative research: 30 children with CRI and parents from 4 UK centres 24 males and 6 females age range 2-18 years	assess psychological functioning evaluate concerns about growth	50% of patients had additional extra-renal complications height was a major concern for 30% of parents and 28% of children

5.0 THE USE OF RECOMBINANT HUMAN GROWTH HORMONE IN CHILDREN WITH PRADER-WILLI SYNDROME (PWS)

Prepared by Professor Gary Butler, University College London and Great Ormond Street Hospitals.

Since the indication for GH treatment for children with PWS and the recommendation in the 2002 NICE appraisal that the aim of treatment was to improve body composition as well as promoting growth, Paediatric Endocrinologists have gradually gained more experience with the use of GH in this condition, with greater realization about the necessary parameters to ensure safety of treatment and the observation of the wider benefits of treatment other than growth promotion. For a wider contemporary review of the condition and detailed evaluation of the benefits of treatment see Goldstone et al (2008).

5.1 WHAT IS ALREADY KNOWN ABOUT PWS AND GROWTH- A RECAP

Size at Birth

Slow intrauterine growth is common, median BW SDS of -1.37, 20% being below -2.0 SDS, the definition of small for gestational age. Median birth length is -0.46 SD.

Growth during childhood and adolescence

A slower postnatal growth trajectory is usual and typical. This may initially be related to hypotonia, feeding difficulties and reduced nutritional intake, but even if this is corrected and even when the hyperphagic phase takes over from the second year onwards, growth in height follows a predictable pattern. This may in part be due to reduced spontaneous GH secretion. PWS specific growth charts are available (Butler et al 1991). Partly due to the slow childhood growth and compounded by a truncated adolescent growth spurt, adult height in PWS individuals remains below the predicted normal range, 159-162 cm in males and 149-150 cm in girls (Wollmann et al 1998, Hauffa et al 2000).

GH secretion

Spontaneous GH secretion is reduced in PWS children. Peak GH levels falls below 10 ug/l in 70% (the traditional cut-off to define GH deficiency). However testing of GH status is not a requirement prior to initiating GH treatment.

5.2 EVIDENCE FOR THE EFFECTIVENESS OF GH

GH treatment

At the time of the last appraisal only short-term good quality data were available. This section describes the current evidence of the effect of GH in PWS patients accumulated since 2002.

Initial growth response

Two RCTs have demonstrated significant increases in height and height velocity over the first two years on GH treatment using a standard dosing

schedule of 1.0 mg/m²/d. This has been matched by improvements in body composition, namely a reduction in body fat and a significant increase in lean body mass (Carrel et al 2002, Allen and Carrel 2004). Subsequent years treatment have maintained the advantages on growth, body composition and bone mineral density as long as the dose is kept at this level (Carrel et al 2002). A concomitant increase in foot length was not seen (Eiholzer et al 2009).

Adult Height

A number of cohort studies have reported adult heights in PWS patients treated with GH.

Angulo et al (2007) reported a highly significant increase of Ht SDS from pre-treatment -1.9 SD to -0.3 SD in an observational study of 21 patients after 7.9 +/-1.7 years GH treatment. A parallel untreated group showed an overall fall in adult height SDS to -3.1 SD, giving a net gain of 3.4 SD (approx 25 cm) with GH treatment.

Lindgren and Lindberg (2008) reported in an observational study of 22 patients that adult height at a median age of 18.1 years was -0.5 SDS in females and -0.9 SDS in males following a median of 10.2 years GH treatment at 0.03 mg/kg/day.

The large pharmaceutical database KIGS has reported a median adult height of -1.0 SDS in 33 patients after a mean of 7.9 yr GH treatment.

Body composition

Lindgren and Lindberg (2008) also reported improvements in body composition. However Fillion et al (2009) have challenged the association of improvements in body composition with GH treatment citing other factors such as parental motivation and dietary input.

5.3 CONCERNS ABOUT GH TREATMENT

Scoliosis

The prevalence of scoliosis in children with PWS is high (37.5 % reports ranging from 15 to 86%) (de Lind van Wijngarden et al 2008). However de Lind van Wijngarden et al (2009) have subsequently demonstrated no adverse effect of GH treatment on the onset of scoliosis or curve progression in a RCT of 91 patients with PWS.

Metabolic parameters

Only six out of 675 PWS children treated with GH in the KIGS database developed diabetes (five type-2 and one type-1) (Craig et al 2006). Indeed adiponectin levels (which are inversely related to obesity and insulin resistance) increased in a RCT of GH treatment in 20 prepubertal children with PWS (Festen et al 2007).

Link with increased mortality

The KIGS database has listed five cases of sudden death out of 675 GH treated patients (Craig et al 2006). Three were morbidly obese and the causes of death were respiratory.

Tauber et al (2008) confirmed the cause of death was due to respiratory causes in 61% out of 64 children with PWS who died suddenly. Of these children 28 had received GH therapy with no difference between treated or untreated patients. Most deaths in the treated group occurred in the first nine months after commencing GH treatment, so additional caution at initiation is emphasised.

Verillo et al (2008) showed a worsening of sleep efficiency associated with GH treatment in PWS children. Although respiratory complications are not a contraindication to GH treatment, and there is no directly observed aggravation of sleep-related breathing disorders by GH (Festen et al 2006), a careful evaluation of at risk patients, especially those with extreme obesity is proposed (Stafler and Wallis 2008).

5.4 ADDITIONAL BENEFITS OF GH ON PSYCHOMOTOR DEVELOPMENT

Anecdotally, muscular hypotonia is reported to improve on GH therapy. However Eiholzer et al (2008) were unable to distinguish a GH specific improvement in very young (mean age 1.0 years) children with PWS in a three-limb trial of GH in comparison with Coenzyme Q(10). Currently no data on quality of life changes are available.

5.5 CONCLUSION

- GH clearly demonstrates a significant improvement in long-term height gain, with normalisation of adult height in the majority of patients.
- Short-term improvements in body composition are seen but more data are required on long term outcomes and elucidating the direct effects of GH treatment itself.
- The benefits on muscular tone and strength, quality of life and psychomotor development need further research.
- The only significant adverse effect is acute respiratory obstruction, mainly in very obese patients after the initiation of GH treatment, but the risk of sudden death may be reduced by careful pre-evaluation and selection of patients for GH treatment.

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6.0 RECOMBINANT HUMAN GROWTH HORMONE IN CHILDREN BORN SMALL FOR GESTATIONAL AGE (SGA)

Prepared by Dr Jeremy Kirk, Birmingham Children's Hospital.

6.1 DEFINITION

The diagnosis of small for gestational age (SGA) is an auxological one, based on size at birth. Although a number of different cutoffs have been historically used, current classification of SGA is defined as a birth length and/or birthweight below -2 standard deviations (SDS) for gestational age and sex, which is equivalent to the 2nd centile.

Children born SGA are a very heterogeneous group, and include normal children along with pathological maternal, placental or fetal causes impacting on genetic and environmental influences.

6.2 NATURAL HISTORY

The majority of children born SGA show spontaneous catch-up growth in the first 6 months after birth, with 80-90% having heights in the normal range by 2 years of age. Catch-up growth may, however, take up to 4 years in children born both SGA and also premature. At 18 years of age ~8% of patients born SGA remain short. The best predictors of catch up growth appear to be longer birth length and taller mid parental height.

Children born SGA, especially those showing post-natal catch-up growth (adiposity rebound) are also at increased risk of the metabolic syndrome, which includes insulin resistance, type 2 diabetes, hyperlipidaemia & hypertension with cardiovascular disease.

6.3 GH THERAPY IN SGA

Although early studies of growth hormone (GH) indicated that short-term growth was not improved (Tanner et al., 1971), there is now a large literature showing the benefit of GH, both in the short and long term in children born SGA, including to final height.

A product licence for GH in SGA was granted by the European Agency for the Evaluation of Medicinal Products (EMA) in 2003, and after the publication of the initial NICE guidance on GH in children in May 2002. There are differences between the SGA licences granted in the USA, and the EMA in Europe, which are shown below:

	FDA (USA)	EMA (Europe)
From age (years)	2.0	4.0
Height at start of GH (SDS)	Not stated	-2.5
Height velocity pre-treatment	"No catch up"	<0 SDS for age and sex

Reference to mid-parental height (MPH)	Not stated	Height SDS >1SD below MPH
Starting dose of GH	70µg/kg/day	35µg/kg/day

The doses of GH in children born SGA are higher than that used in GH deficiency, and reflect an element of resistance, either at the level of GH or IGF-1 action. In addition, qualitative and quantitative abnormalities in GH secretion have been demonstrated in some patients born SGA, although this does not appear to predict the response to therapy.

6.4 SHORT TERM GH THERAPY

There are now a number of published short term studies, using varying doses of GH (usually low (35µg/kg/day) or high dose (70µg/kg/day)). GH produces significant growth acceleration, most marked in the first year of therapy, with up to a doubling of height velocity, with the increased height velocity sustained during subsequent years of therapy compared to untreated controls and placebo treated patients. Although the higher dose produces more rapid normalization of height this can be at the expense of raised IGF-1 levels.

6.5 INTERMITTENT GH THERAPY

GH therapy has also been used intermittently, with initial continuous treatment for 2-3 years (dose 33-100µg/kg/day), followed by a withdrawal phase of 1-2 years, and then either no further treatment, or low or high dose (33 or 66 µg/kg/day) GH treatment. Discontinuous high dose therapy (100µg/kg/day for 2 years) produced an equivalent height increment to continuous low dose (33-µg/kg/day for 6 years), with reduced exposure of patients to GH, although numbers were small and further studies with longer term follow-up are required. However, the consensus statement on the management of the SGA child did not recommend withdrawal of GH therapy after 2-3 years as it lead to 'catch down' growth (Clayton et al 2007).

6.6 FINAL HEIGHT

There is now increasing published data on SGA patients treated with GH until final height, with varying ages at start of therapy, dose regimens and also lengths of GH treatment. The increase in mean adult height SDS ranges from 0.1 to 2.1 (~0.7-14cm). There is evidence that the earlier treated patients have the greatest height increment, although high dose GH does not appear to produce a consistently greater increment in height than low dose e.g. a difference of 0.4SD (~2.5cm) in final height in one study (de Zegher & Hokken-Koelega, 2005).

6.7 OTHER EFFECTS

Insulin sensitivity, which is already reduced in children born SGA, is further worsened by GH therapy (Cutfield et al., 2003, van Pareren et al, 2003, Willemsen et al., 2008). In the two latter studies, insulin sensitivity recovered

after discontinuation of GH therapy, but not in the former. To date GH has not been shown to cause diabetes in children born SGA (Cutfield et al., 2006). SGA children treated with GH also show an increase in muscle and a decrease in adipose tissue. IQ scores and behaviour have been shown to improve during GH therapy in some studies, but not others.

6.8 SUMMARY

Children born small for gestational age (SGA) are a heterogeneous group, in whom the majority demonstrate postnatal catch up growth and achieve heights in the normal range within the first years of life (longer in those born prematurely). In those children born SGA who fail to catch up and remain short, GH from 4 years of age produces an increase in short term growth, with improved long term growth often producing a final height within the normal range, and increments of up to 14cm. SGA currently has a licence for GH therapy in the UK, granted in 2003 after the last NICE review of GH therapy in children.

These children are at risk of long-term metabolic complications (cardiovascular, reproductive, metabolic (carbohydrate, lipids): so called “metabolic syndrome”), and it is unclear whether GH therapy exacerbates these problems, and moreover whether they persist after discontinuation after GH therapy.

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Appendix: Summary of key publications since 2000: SGA

UNTREATED FINAL HEIGHT

	Study and subjects	Outcomes	Results
Karlberg and Albertsson-Wikland, 1995	Swedish healthy full-term singleton birth cohort (n = 3650) followed from birth to final height	Final height	>86% of healthy full-term singleton SGA infants achieved catch-up in height during the first 6-12 months. of life. At 18y of age 7.9% of children born SGA remained short.

SHORT TERM GROWTH ON GH

	Study and subjects	Outcomes	Results
Boguszewski et al., 1998	48 children randomly allocated to three groups: control group (n=12) received no treatment for 2 y, one group treated with GH at 0.1IU/kg/d (n=16), and one group treated with GH at 0.2 IU/kg/d (n=20).	Increase in height SDS after 3 years of GH therapy	There was no height increase after 3 years in the untreated group, but a mean(SD) HtSDS increase of 0.18(0.18) on 0.1IU/kg/d, & 0.41(0.16) on 0.2IU/kg/d.
Sas et al., 1999	79 SGA children with short stature randomly and blindly assigned to 1 of 2 GH doses (3 vs. 6 IU/m ² /day).	Increase in height SDS after 5 years of GH therapy	Although the 5-yr increase in mean(SD) height SDS was higher in high dose:(2.6(0.9)) than in low dose group (2.2(0.6)), this was not statistically significant (<i>P</i> = 0.057).

FINAL HEIGHT ON GH

	Study and subjects	Outcomes	Results
Van Pareren et al., 2003	54 short children born SGA in a randomized, double-blind, dose-response trial, assigned to ~33 (Group A) or ~67µg/kg/d (Group B) of GH therapy.	Final height	Mean(SD) Adult height SDS was -1.1(0.7) for Group A and -0.9(0.8) for Group B, with a mean(SD) gain in height SDS of 1.8 (0.7) for Group A & 2.1 (0.8) for Group B.
Carel et al., 2003	Short children born SGA (mean age 10.5y. for girls & 12.5y. for boys)	Final height	Mean(SD) height gain in adult height was 0.5(0.8) and 1.1(0.9)

	assigned to receive either ~67µg/kg/d (N=102) or no treatment (N=47) until Adult Height.		SDS in the control and treated groups, respectively (P= 0.002). Multivariate analyses showed independent effects of treatment (0.6 SDS) and treatment duration (0.4 SDS/yr).
Dahlgren et al., 2005	77 prepubertal children born SGA treated with GH at 33 µg/kg/day, beginning before the onset of puberty.	Final height	The difference between adult and pretreatment projected height was 1.3 SD (9 cm) for the entire group. Among those treated for >2 y before puberty, mean gain in final height was 1.7 SD, compared to 0.9 SD in those starting GH therapy <2 y before puberty.

INSULIN SENSITIVITY ON AND OFF GH THERAPY

	Study and subjects	Outcomes	Results
Van Pareren et al., 2003	Effects of stopping long-term GH therapy in 47 adolescents born SGA assessed using oral glucose tolerance tests for two GH dosage groups (3 vs. 6 IU/m ² /d).	Response to oral glucose tolerance tests (glucose levels and area under the curve (AUC)) plus insulin (fasting and AUC).	Fasting glucose levels & 120-min AUC for glucose 6 mo. after stopping GH showed no difference from pretreatment levels for both GH dosage groups. After stopping GH, fasting insulin levels returned to pretreatment levels (8.4 mU/l), but 120-min AUC for insulin decreased, compared with 6-yr levels (P < 0.01), regardless of GH dosage group.
Cutfield et al., 2003	Twelve short non-GH-deficient children born SGA (7 boys/5 girls) investigated before (N=11) & during (12) GH therapy (21±6 mo.) at 20 IU/m ² /week, studied at mean(SD) 9.3±1.0 years of age.	Insulin sensitivity index measured before & during GH therapy	During GH, insulin sensitivity fell by mean(SD) of 44(10)% (P = .018), with compensatory rise in the acute insulin response:123(59)% (P < .009). Insulin sensitivity was unchanged after stopping GH: 31.6 (20.5-42.3) before treatment, 11.5 (5.7-24.4) with treatment, and 10.7(6.2-16.9) 10 ⁻⁴ .

			min ⁻¹ μU/mL after treatment.
Willemsen et al., 2008	48 SGA adolescents studied at adult height, whilst on GH, and also 6 mo. after stopping, compared with 38 AGA controls at both time points.	Insulin sensitivity (Si), glucose effectiveness (Sg), beta cell function, acute insulin response	After stopping GH, Si (P=0.006), Sg (P=0.009) and disposition index (P=0.024) increased, whereas insulin secretion (acute insulin response; NS, decreased). Compared with AGA controls, Si was lower during GH and became similar after GH stop, acute insulin response was higher at both time points, and glucose effectiveness and disposition index became higher.

7.0 RECOMBINANT GROWTH HORMONE THERAPY IN SHOX DEFICIENCY

Prepared by Dr Justin Warner, University Hospital of Wales, Cardiff.

7.1 INTRODUCTION

The short stature homeobox-containing gene, SHOX, is located on the distal ends of the X and Y chromosome and encodes a homeodomain transcription factor which is responsible during early fetal life for a significant proportion of long bone growth. Since genes in this pseudoautosomal region do not undergo X inactivation, healthy individuals express two copies of SHOX, one on each sex chromosome in both 46XX and 46XY individuals. Mutations or deletions of this gene, including those with Turner syndrome (TS), who are haploinsufficient for SHOX, have variable degrees of growth impairment with or without a spectrum of skeletal anomalies consistent with dyschondrosteosis. In addition to its role underlying the growth deficit seen in TS, SHOX haploinsufficiency or gene deficiency (SHOX-D) is also the primary cause of short stature in most patients with Leri-Weill syndrome (LWS). SHOX-D has also been demonstrated in patients with idiopathic short stature and unremarkable phenotype (Huber et al 2006, Rappold et al 2002, Binder et al 2003). On the basis of a number of screening studies, SHOX-D appears to be a relatively frequent cause of short stature, with approximately 70% of patients with LWS and 2-15% of children with idiopathic short stature having deletions or mutations in SHOX.

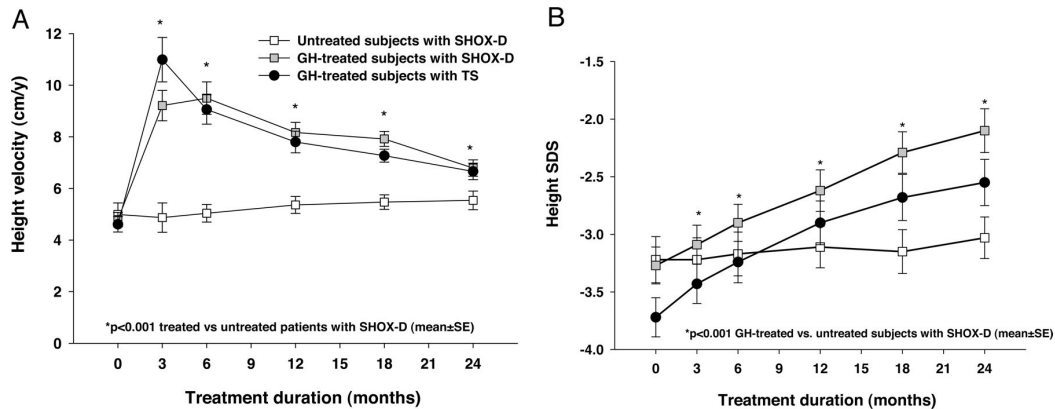
Growth hormone (GH) therapy is well established in girls with TS and is further described in this report. Until recently experience with GH treatment in patients with SHOX-D was limited and confined to case reports and small uncontrolled studies (Binder et al 2004, Ogata et al 2001, Shanske et al 1999, Munns et al 2003). Described below is the only published randomised control study of GH therapy in SHOX-D and the grounds for the licence for its usage being granted (Blum et al 2007).

7.2 TREATMENT OF PATIENTS WITH SHOX-D WITH GH

Results from a 2 year, multicentre, three arm, randomised controlled, open-label clinical study is now available (Blum et al 2007). 52 prepubertal subjects with confirmed SHOX-D were randomised either to GH therapy (n=27) or an untreated control group (n=25). Since the pathogenesis of growth failure in TS is similar to SHOX-D a third group of patients with TS were enrolled and treated with GH. All GH treated patients received 50mcg/kg/day of subcutaneous GH.

7.3 HEIGHT VELOCITY AND GAIN IN HEIGHT SDS

Height velocity and height SDS improved markedly in response to GH in the treated SHOX-D and TS group but changed minimally in the untreated SHOX-D group



Blum, W. F. et al. *J Clin Endocrinol Metab* 2007;92:219-228

At the end of 2 years therapy with GH 41% of GH treated subjects with SHOX-D and 31% of patients with TS had achieved a height in the normal range for age and gender (> -2.0 SDS) whereas this was the case for only one subject in the untreated subjects with SHOX-D (who started with a height SDS of > -2.0 SDS and remained there) (see Figure).

IGF-1 levels rose significantly, as expected, in the GH treated patients, into the upper half of the normal range on average but with some patients exceeding $+2.0$ SDS. No serious adverse events were noted and no significant difference in advancement in bone age between the groups was observed.

7.4 CONCLUSION

GH significantly improves height velocity and height SDS in SHOX-D patients over 2 years. Final height data is not yet available in this study group. There is no published data on quality of life in this patient group in response to GH therapy but assumptions could probably be made that it is similar to GH treated girls with TS.

7.5 REFERENCES

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8.0 FINAL CONCLUSIONS

- The data presented in this document represents up to date research in the field of paediatric growth disorders. Randomised controlled trials are presented where available; otherwise high quality peer reviewed published research is presented.
- The BSPED strongly support the ongoing use of recombinant human growth hormone in children with growth disorders associated with GH deficiency, chronic renal insufficiency, Turner syndrome, Prader-Willi syndrome, small for gestational age and SHOX deficiency which are currently being reviewed by NICE.
- The BSPED recognise there remains a small proportion of GH prescribing 'off licence'. Although this was not part of the NICE review and has not been considered in this document, nevertheless there are patient groups where GH therapy has resulted in a short-term improvement in height velocity, although as expected, not as great as that seen in patients with GH deficiency. In these children the following guidelines might be appropriate:
 - Treatment should only be undertaken in specialist centres that regularly participate in national audit of their clinical activities or research, and thus would allow examination of treatment outcomes in this category of patients throughout the UK.
 - Any potential benefits and adverse medical events of therapy are discussed fully with the parents and child prior to treatment.
 - The response to treatment is carefully monitored, and the need for ongoing treatment re-evaluated annually.
- In accordance with NICE recommendations in 2002 the BSPED have set up an ongoing register of GH prescribing in the UK. The results presented in this document confirm that there has been little change in prescribing practice over the last 5 years.
- There remains a dearth of data relating to Quality of Life (QoL) in children receiving GH. There are many confounding factors in childhood that make assessing QoL very complicated. However, several members of the BSPED are participating in an ongoing research project in the UK to help establish some data in this area but results will not be available until later in 2009.
- We would recommend that GH prescribing be limited to those paediatricians who are recognised paediatric endocrinologists (in either a teaching or a district hospital) or general paediatricians who have received approved training in paediatric endocrinology and who maintain links with a tertiary centre and are member of the BSPED.
- Post marketing surveillance programmes are vital for the ongoing monitoring of efficacy and safety and are to be advocated for all growth hormone preparations.