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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	3
BACKGROUND	6
OBJECTIVES	6
METHODS	6
RESULTS	7
Figure 1.	8
Figure 2.	10
Figure 3.	11
DISCUSSION	14
AUTHORS' CONCLUSIONS	15
ACKNOWLEDGEMENTS	15
REFERENCES	16
CHARACTERISTICS OF STUDIES	19
DATA AND ANALYSES	43
Analysis 1.1. Comparison 1 28 IU/m ² /wk versus placebo/no treatment, Outcome 1 HSDS after 1 year of rhGH.	45
Analysis 1.2. Comparison 1 28 IU/m ² /wk versus placebo/no treatment, Outcome 2 HSDS after 1 year according to treatment status.	45
Analysis 1.3. Comparison 1 28 IU/m ² /wk versus placebo/no treatment, Outcome 3 Change in height SDS according to pubertal status.	46
Analysis 1.4. Comparison 1 28 IU/m ² /wk versus placebo/no treatment, Outcome 4 Height velocity (cm/6 mo) after 6 months of rhGH.	46
Analysis 1.5. Comparison 1 28 IU/m ² /wk versus placebo/no treatment, Outcome 5 Height velocity (cm/y) after 1 year of rhGH. .	47
Analysis 1.6. Comparison 1 28 IU/m ² /wk versus placebo/no treatment, Outcome 6 Height velocity (cm/y) according to pubertal status.	47
Analysis 1.7. Comparison 1 28 IU/m ² /wk versus placebo/no treatment, Outcome 7 Change in height velocity SDS.	48
Analysis 1.8. Comparison 1 28 IU/m ² /wk versus placebo/no treatment, Outcome 8 Growth after 2 years of rhGH.	48
Analysis 1.9. Comparison 1 28 IU/m ² /wk versus placebo/no treatment, Outcome 9 Change in bone age.	48
Analysis 2.1. Comparison 2 28 IU/m ² /wk versus 14 IU/m ² /wk, Outcome 1 Final or change in HSDS.	50
Analysis 2.2. Comparison 2 28 IU/m ² /wk versus 14 IU/m ² /wk, Outcome 2 Final/change in height velocity (cm/time period).	50
Analysis 2.3. Comparison 2 28 IU/m ² /wk versus 14 IU/m ² /wk, Outcome 3 Final/change in height velocity SDS.	51
Analysis 3.1. Comparison 3 56 IU/m ² /wk versus 28 IU/m ² /wk, Outcome 1 Change in HSDS.	52
Analysis 3.2. Comparison 3 56 IU/m ² /wk versus 28 IU/m ² /wk, Outcome 2 Change in height velocity (cm/y).	52
ADDITIONAL TABLES	52
APPENDICES	53
WHAT'S NEW	56
HISTORY	56
CONTRIBUTIONS OF AUTHORS	56
DECLARATIONS OF INTEREST	56
SOURCES OF SUPPORT	56
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	57
INDEX TERMS	57

[Intervention Review]

Growth hormone for children with chronic kidney disease

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ABSTRACT

Background

Growth retardation is a common complication of chronic kidney disease (CKD) in children and is of concern to families. Recombinant human growth hormone (rhGH) treatment has been used to help short children with CKD attain a height more in keeping with their age group. However there are concerns about the long-term benefits of rhGH in significantly improving adult height as well as concerns about potential adverse effects (deterioration in native kidney function, increased acute rejection in kidney transplant recipients, benign intracranial hypertension).

Objectives

To evaluate the benefits and harms of rhGH treatment in children with CKD.

Search methods

Randomised controlled trials (RCTs) were identified from the Cochrane Renal Group's Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 12, 2011), MEDLINE (from 1966), EMBASE (from 1980), article reference lists and through contact with local and international experts in the field.

Date of last search: December 29, 2011

Selection criteria

RCTs were included if they were carried out in children aged zero to 18 years, diagnosed with CKD, who were pre-dialysis, on dialysis or post-transplant; if they compared rhGH treatment with placebo/no treatment or two doses of rhGH treatments; and if they included height outcomes.

Data collection and analysis

Two authors independently assessed studies for risk of bias and extracted data from eligible studies. Data was pooled using a random effects model with calculation of mean difference (MD) for continuous outcomes with 95% confidence intervals (CI).

Main results

Sixteen studies (enrolling 809 children) were identified. Risk of bias assessment indicated that study quality was poor or poorly reported with only four and five studies respectively reporting adequate allocation concealment or blinding of study participants and investigators. Treatment with rhGH (28 IU/m²/wk) compared with placebo or no specific therapy resulted in a significant increase in height standard deviation score (HSDS) at one year (8 studies, 391 children: MD 0.82, 95% CI 0.56 to 1.07), and a significant increase in height velocity at six

months (2 studies, 27 children: MD 2.85 cm/6 mo, 95% CI 2.22 to 3.48) and one year (7 studies, 287 children: MD 3.88 cm/y, 95% CI 3.32 to 4.44). Height velocity, though reduced, remained significantly greater than untreated children during the second year of therapy (1 study, 82 children: MD 2.30 cm/y, 95% CI 1.39 to 3.21). Compared to the 14 IU/m²/wk group, there was a 1.18 cm/y increase in height velocity in the 28 IU/m²/wk group (3 studies, 150 children: 1.18 cm/y, 95% CI 0.52 to 1.84). The frequency of reported side effects of rhGH was generally similar to that of the control group.

Authors' conclusions

One year of 28 IU/m²/wk rhGH in children with CKD resulted in a 3.88 cm increase in height velocity above that of untreated patients. Studies were too short to determine if continuing treatment resulted in an increase in final adult height.

PLAIN LANGUAGE SUMMARY

There is some evidence that human growth hormone may help reduce growth problems in children with chronic kidney disease

The kidneys filter blood. Children with chronic kidney disease (CKD) may progress to end-stage kidney failure and need their blood filtered by machine (dialysis) or they need a kidney transplant. CKD can stunt growth in children. Growth hormone (rhGH) has been used to help children grow to a more average height for their age but rhGH may have adverse effects including added risk of transplant rejection and high pressure in the brain. This review of 16 studies enrolling 809 children found that rhGH increased height in children with CKD by about 4 cm after 1 year and by a further 2 cm after 2 years of treatment compared with no treatment. The frequency of reported side effects of rhGH was generally similar to that of the control group.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. rhGH 28 IU/m²/wk versus placebo/no treatment for children with chronic kidney disease

rhGH 28 IU/m²/wk versus placebo/no treatment for children with chronic kidney disease

Patient or population: children with chronic kidney disease

Settings: Tertiary Children's Hospitals

Intervention: rhGH 28 IU/m²/wk

Comparison: Placebo/no specific treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo/no specific treatment	rhGH 28 IU/m ² /wk				
HSDS after 1 year of rhGH Follow-up: 6-12 months		The mean HSDS after 1 year of rhGH in the intervention groups was 0.91 higher (0.58 to 1.23 higher)		331 (8 studies)	⊕⊕⊕⊖ moderate ¹	
Height velocity (cm/6 mo) after 6 months of rhGH from baseline to 6 months Follow-up: 0-6 months		The mean height velocity (cm/6 mo) after 6 months of rhGH from baseline to 6 months in the intervention groups was 2.85 higher (2.22 to 3.48 higher)		27 (2 studies)	⊕⊕⊖⊖ low ¹	
Height velocity (cm/y) after 1 year of rhGH Follow-up: 0-12 months		The mean height velocity (cm/y) after 1 year of rhGH in the intervention groups was 3.88 higher (3.32 to 4.44 higher)		287 (7 studies)	⊕⊕⊕⊖ moderate ¹	
Change in height velocity SDS from baseline to 6 months Follow-up: 0-6 months		The mean change in height velocity SDS from baseline to 6 months in the intervention groups was 7.8 higher (6.09 to 9.51 higher)		27 (2 studies)	⊕⊕⊖⊖ low ¹	

Change in height velocity SDS from baseline to 1 year
Follow-up: 0-12 months

The mean change in height velocity SDS from baseline to 1 year in the intervention groups was
6.14 higher
(3.42 to 8.86 higher)

22
(2 studies)

⊕⊕⊕⊕
low¹

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ All studies small and generally of low methodological quality

Summary of findings 2. rhGH 28 IU/m²/wk versus 14 IU/m²/wk for children with chronic kidney disease

rhGH 28 IU/m²/wk versus 14 IU/m²/wk for children with chronic kidney disease

Patient or population: children with chronic kidney disease

Settings: Tertiary Children's Hospitals

Intervention: rhGH 28 IU/m²/wk

Comparison: rhGH 14 IU/m²/wk

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	rhGH 14 IU/m ² /wk	rhGH 28 IU/m ² /wk				
Final or change in HSDS from baseline to 1 year Follow-up: 0-12 months		The mean final or change in HSDS from baseline to 1 year in the intervention groups was 0.2 higher (0.09 lower to 0.48 higher)		145 (3 studies)	⊕⊕⊕⊕ moderate ¹	
Change in height velocity (cm/time period) from baseline to 1 year Follow-up: mean 0-12 months		The mean change in height velocity (cm/time period) from baseline to 1 year in the intervention groups was 1.18 higher		150 (3 studies)	⊕⊕⊕⊕ moderate ¹	

	(0.52 to 1.84 higher)		
Change in height velocity SDS from baseline to 1 year Follow-up: 0-12 months	The mean change in height velocity SDS from baseline to 1 year in the intervention groups was 1.48 higher (0.03 to 2.93 higher)	106 (2 studies)	⊕⊕○○ low ¹

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Small studies of poor methodological quality

BACKGROUND

Chronic kidney disease (CKD) is an uncommon but important condition. As defined by the need for dialysis or kidney transplant (stage 5 CKD; [K/DOQI 2002](#)), 32/1,000,000 children under the age of 15 have CKD ([Disney 1999](#)). Many more children have less advanced CKD (stage 3 CKD with glomerular filtration rate (GFR) 30 to 59 mL/min/1.73 m² and stage 4 CKD with GFR 15 to 29 mL/min/1.73 m²). The frequency of this problem is unclear. Growth retardation, one of the complications of CKD, is of concern to families in over 90% of children with stage 5 CKD ([Reynolds 1995](#)). Approximately 60% of boys and 41% of girls who started renal replacement therapy before the age of 15 years attain a final adult height more than two standard deviations (12 cm) below the mean for healthy adults ([Rizzoni 1985](#)). Impairment of growth can begin when the GFR falls to 50% of normal, and becomes an increasing problem once the GFR falls below 25% ([Tönshoff 1995](#)).

Over the past 20 years, recombinant human growth hormone (rhGH) treatment has been used to help short children with CKD attain an adult height more in keeping with their age group ([Berard 2008](#); [Fine 1995a](#); [Haffner 2000](#)). However, there have been concerns that rhGH may have an adverse effect on the preservation of native kidney function, predispose to acute rejection in kidney transplant recipients, and cause benign intracranial hypertension (BIH) and slipped capital femoral epiphysis ([Clayton 2000](#)).

Although several studies of rhGH treatment in children with CKD have been undertaken, uncertainty exists on the magnitude of benefits and side effects of the treatment ([Fine 1995a](#)). A systematic review of rhGH treatment was undertaken to evaluate growth outcomes to establish the effect of treatment over time. We sought to establish if the growth outcomes remained linear over time or if there was a waning effect of the treatment. Secondly, we examined the effect of varying doses of the treatment. Thirdly, we attempted to explore the effect of the following factors on treatment: age, sex, pubertal status and the stage of CKD (pre-dialysis, on dialysis, post-transplant). Finally, the study evaluated potential side effects of rhGH treatment.

OBJECTIVES

This review aims to evaluate the benefits and harms of rhGH treatment in children aged zero to 18 years, diagnosed with CKD who are treated conservatively (CKD stages 3, 4), treated with dialysis (CKD 5D) or treated with a kidney transplant (CKD 5).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) that compared rhGH treatment with placebo/no treatment or that compared two doses of rhGH.

Types of participants

Children between the ages of zero to 18 years, diagnosed with CKD who are pre-dialysis (preD), on dialysis (Dial) or post-transplant (TP).

Types of interventions

rhGH treatment compared with placebo/no treatment or comparison of two doses of rhGH treatment.

Types of outcome measures

The growth outcomes were collected in the form of standard deviation score (SDS). As such, an individual's height SDS (HSDS) was calculated as follows:

- (actual height - mean height for age)/standard deviation at that age

Normal children have a height that ranges between -2 and +2 SDS. If a change in HSDS is negative, it implies growth failure and if positive, catch-up growth.

Primary outcomes

The primary outcome measures were the end of treatment HSDS or change in HSDS from treatment onset to completion and the end of treatment height velocity or change in height velocity.

Secondary outcomes

Secondary outcomes sought included final or change in HSDS and height velocity during puberty, final or change in height velocity SDS, final height, change in bone age, quality of life, and adverse effects of rhGH treatment (kidney function, rejection episodes, benign intracranial pressure and any other possible side effects reported).

Search methods for identification of studies

Initial search

A systematic and comprehensive literature search was carried out to identify eligible RCTs. Two authors independently searched the following electronic databases without language restriction, using the optimally sensitive search strategies developed for identification of RCTs ([Dickersin 1995](#); [Lefebvre 1996](#)). (see [Appendix 1 - Electronic search strategies](#)).

1. The Cochrane Controlled Trials Register (Issue 1, 2000)
2. MEDLINE (1966-April 2000)
3. EMBASE (1980-April 2000)
4. Additional studies were located through article reference lists and through contact with local and international experts in the field.

Review updates

- First update: The Cochrane Renal Group's specialised register (July 2005) and The Cochrane Central Register of Controlled Trials (CENTRAL, in *The Cochrane Library* Issue 3, 2005) were searched.
- Second update: The Cochrane Renal Group's specialised register was searched up to December 29, 2011 for the second update. CENTRAL and the Renal Group's specialised register contain the handsearched results of conference proceedings from general and speciality meetings. This is an ongoing activity across the Cochrane Collaboration and is both retrospective and prospective. Please refer to The Cochrane Renal Review Group's Module in *The Cochrane Library* for the complete list of

nephrology conference proceedings searched ([Cochrane Renal Group](#)).

Data collection and analysis

Selection of studies

At least two people independently screened titles and abstracts of studies identified through the searches and selected studies that met the inclusion criteria. This process favoured over-selection to avoid losing relevant studies. In the event of uncertainty or no abstract available, the full article was obtained. Any disagreement on study selection was resolved through discussion and consultation with a third author.

Data extraction and management

Data extraction and assessment of the risk of bias were carried out independently by at least two people using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Information was collected on participant characteristics (number, age, sex, pubertal stage, stage of CKD, comorbidities), intervention (type of growth hormone, dose, duration, co-interventions) and primary and secondary outcome measures. Authors were contacted to obtain any missing data, as well as raw data when necessary. Any discrepancies in data extraction were discussed with another author. In the case where the results of a study were published more than once, or the results discussed in a number of publications, the most complete data were obtained using all sources and included in the analysis only once.

Assessment of risk of bias in included studies

The following items were assessed using the risk of bias assessment tool ([Higgins 2011](#)) (see [Appendix 2](#)).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
 - * Participants and personnel
 - * Outcome assessors
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

Difference in means was calculated for continuous outcomes of individual studies to estimate the size of the intervention effects. Overall treatment effects (mean difference (MD)) were computed using a random effects model which takes into account between study variability as well as within study variability.

Unit of analysis issues

In the case of cross-over studies, data from the first half of the study was extracted where these were reported separately and used in the analysis.

Dealing with missing data

We contacted the trialists to request missing patient data due to loss to follow-up and exclusion from study analyses in an effort to carry out intention-to-treat analyses. Where the missing dichotomous or continuous data were few and unlikely to affect the overall results, we analysed the available data.

Assessment of heterogeneity

Heterogeneity was analysed using Cochran's Q statistic ([Pettiti 1994](#)) with an alpha of 0.05 used for statistical significance and quantified with the I^2 statistic. I^2 values of 30% to 60%, 50% to 90% and 75% to 100% correspond to low, substantial and considerable levels of heterogeneity ([Higgins 2011](#)).

Assessment of reporting biases

The search strategy included searching major databases and conference proceedings without language restriction in an attempt to reduce publication bias related to failure of authors to publish negative results or inability to publish negative results in journals indexed in major databases. Where multiple publications of the same study were identified, data were included from the most recent publication and preferably the definitive publication. However all publications were reviewed to identify outcomes not reported in the index publication in an attempt to reduce outcome reporting bias. There were insufficient studies to assess for publication bias using funnel plots.

Data synthesis

Data were pooled using the random-effects model for continuous data.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was planned to explore the effects of age, sex, pubertal status, and stage of CKD on rhGH treatment. There were sufficient data to investigate pubertal status and stage of CKD.

Sensitivity analysis

Sensitivity analyses were performed to test decisions where inclusion of a study, with a higher MD in HSDS, might have altered the results of the meta-analysis.

RESULTS

Description of studies

Results of the search

The flow chart of study inclusion for this review is shown in [Figure 1](#).

Figure 1. Flow chart comparing study selection, interventions investigated, numbers of children and outcomes reported between initial review and latest update

The original search identified 337 titles and abstracts, of which 297 were excluded. The excluded studies were either clearly not clinical studies or rhGH treatment was only used in children with idiopathic short stature. Full assessment of the remaining 40 papers identified 12 articles that addressed the use of rhGH treatment in children with CKD and provided data on clinically important outcomes of which two papers reported data on a subset of patients within other studies (Broyer 1996 (TP); Fine 1994 (preD)). Thus 10 studies enrolling 620 children were evaluated (Broyer 1996 (TP); Fine 1994 (preD); Hokken-K 1991 (preD/Dial); Hokken-K 1994 (preD/Dial); Hokken-K 1994 (TP); Hokken-K 1996 (TP); Ito 1997 (TP); Kitagawa 1997 (Dial); Kitagawa 1997 (preD); Maxwell 1998a (TP); Maxwell 1998b (TP); Powell 1997 (preD)). From Ito 1997 (TP), only data on transplant patients were included since data on the same dialysis (Kitagawa 1997 (Dial)) and predialysis patients (Kitagawa 1997 (preD)) were taken from the Kitagawa trial.

A further search in July 2005 of The Cochrane Central Register of Controlled Trials (CENTRAL, in *The Cochrane Library*, Issue 3 2005), the Cochrane Renal Group's specialised trials register, MEDLINE and EMBASE identified 23 further potentially relevant articles. Of these 23 articles, five were considered to be newly identified studies (Fine 2002 (TP); Ghio 2002 (TP); Hertel 2002 (preD/Dial); Kuizon 1998 (Dial); Sanchez 2002 (TP)) and four were abstracts of previously included studies (Broyer 1996 (TP); Ito 1997 (TP); Powell 1997 (preD)). In addition one abstract provided extra information on kidney function for Powell 1997 (preD) and one article described a study of body proportions measured during two previously included studies (Hokken-K 1991 (preD/Dial); Hokken-K 1994 (preD/Dial)). Thus an additional five studies involving 150 children were included.

In December 2011 the Cochrane Renal Group's specialised trials register was searched and identified 13 articles of which two, after full text assessment, were new RCTs (Callis 1996 (preD); Santos 2010 (preD/Dial)) and nine were publications related to previously included studies. On re-assessing risk of bias of the existing included studies, Ghio 2002 (TP) was excluded as the study was considered not to be randomised. Therefore the review now contains 16 studies enrolling 809 children.

Included studies

Fourteen of the 16 studies used a parallel design while the other two were cross-over studies. The studies varied in duration (six months to 2.5 years) and included children from the USA, Europe and Japan. At enrolment, most children were prepubertal or early pubertal, with one study including late pubertal children (Hokken-K 1994 (TP)). Three studies included only pre-dialysis patients

(Callis 1996 (preD); Fine 1994 (preD); Powell 1997 (preD)); one study included only dialysis patients (Kuizon 1998 (Dial)); five studies included pre-dialysis and dialysis patients (Hertel 2002 (preD/Dial); Hokken-K 1991 (preD/Dial); Hokken-K 1994 (preD/Dial); Kitagawa 1997 (Dial); Kitagawa 1997 (preD); Santos 2010 (preD/Dial)) but the two groups could only be separated in one study (Kitagawa 1997 (Dial); Kitagawa 1997 (preD)) and this study was treated as two studies of dialysis and predialysis patients respectively. The remaining eight studies enrolled children with kidney transplants (Broyer 1996 (TP); Fine 2002 (TP); Hokken-K 1994 (TP); Hokken-K 1996 (TP); Ito 1997 (TP); Maxwell 1998a (TP); Maxwell 1998b (TP); Sanchez 2002 (TP)). Maxwell 1998a (TP) and Maxwell 1998b (TP) was treated as two studies as data on pubertal and prepubertal children were reported separately. Three studies compared rhGH (28 IU/m²/wk) with placebo (Fine 1994 (preD); Hokken-K 1991 (preD/Dial); Hokken-K 1996 (TP)) and seven studies compared rhGH (28 IU/m²/wk) with no treatment (Broyer 1996 (TP); Fine 2002 (TP); Kuizon 1998 (Dial); Maxwell 1998a (TP); Maxwell 1998b (TP); Powell 1997 (preD); Sanchez 2002 (TP); Santos 2010 (preD/Dial)). The remaining six studies compared two different doses of rhGH: five studies compared 28 IU/m²/wk with 14 IU/m²/wk (Callis 1996 (preD); Hertel 2002 (preD/Dial); Hokken-K 1994 (preD/Dial); Ito 1997 (TP); Kitagawa 1997 (Dial); Kitagawa 1997 (preD)) and one study compared 56 IU/m²/wk with 28 IU/m²/wk (Hokken-K 1994 (TP)). The type of rhGH administered in the studies included Norditropin®, Nutropin®, Genotropin® and Genotonorm®.

The primary publication of the Broyer 1996 (TP) study included 203 children of whom efficacy (change in HSDS and height velocity) was evaluated in 125 children (66 treated and 59 untreated) and safety (GFR, acute rejection, other adverse effects) was evaluated in 180 children. The data on growth was reported separately for prepubertal children, children entering puberty and pubertal children and not for the entire group. Therefore for the analyses of growth overall (Analysis 1.1; Analysis 1.2; Analysis 1.5; Analysis 1.9), data from the 1998 publication by Guest et al, of 85 French children (41 treated, 44 untreated) are included while the data from Broyer 1996 (TP) are separately reported in Analysis 1.3 and Analysis 1.6.

Excluded studies

Three studies (Ghio 2002 (TP); Jedrzejowski 2002; Laine 1995) were excluded as they were not RCTs.

Risk of bias in included studies

Risk of bias is reported for each study in [Characteristics of included studies](#) and is summarised in [Figure 2](#) and [Figure 3](#).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Broyer 1996 (TP)	?	+	-	?	?	?	-
Callis 1996 (preD)	?	?	-	?	?	?	-
Fine 1994 (preD)	?	?	+	?	-	+	-
Fine 2002 (TP)	?	+	-	?	-	+	-
Hertel 2002 (preD/Dial)	?	?	-	?	+	+	-
Hokken-K 1991 (preD/Dial)	?	?	+	?	+	+	-
Hokken-K 1994 (preD/Dial)	?	?	+	?	+	+	-
Hokken-K 1994 (TP)	?	?	+	?	+	+	-
Hokken-K 1996 (TP)	?	?	+	?	+	+	-
Ito 1997 (TP)	?	?	-	?	-	?	?
Kitagawa 1997 (Dial)	?	?	-	?	-	?	?
Kitagawa 1997 (preD)	?	?	-	?	-	?	?
Kuizon 1998 (Dial)	?	?	-	?	?	?	?
Maxwell 1998a (TP)	?	?	-	?	+	+	-
Maxwell 1998b (TP)	?	?	-	?	+	+	-
Powell 1997 (preD)	?	?	-	?	-	?	-
Sanchez 2002 (TP)	?	+	-	?	+	+	-
Santos 2010 (preD/Dial)	?	+	-	?	+	+	-

Allocation

No study provided information on sequence generation. Adequate allocation concealment was reported in four studies (Broyer 1996 (TP); Fine 2002 (TP); Sanchez 2002 (TP); Santos 2010 (preD/Dial)).

Blinding

There was considered to be a low risk of performance bias in five studies (Fine 1994 (preD); Hokken-K 1991 (preD/Dial); Hokken-K 1994 (preD/Dial); Hokken-K 1994 (TP); Hokken-K 1996 (TP)). There

was considered to be a high risk of performance bias in 11 studies (Broyer 1996 (TP); Callis 1996 (preD); Fine 2002 (TP); Hertel 2002 (preD/Dial); Ito 1997 (TP); Kitagawa 1997 (Dial); Kitagawa 1997 (preD); Kuizon 1998 (Dial); Maxwell 1998a (TP); Maxwell 1998b (TP); Powell 1997 (preD); Sanchez 2002 (TP); Santos 2010 (preD/Dial)) because studies were not blinded and the outcome could potentially be biased by knowledge of treatment groups.

In four double-blind studies, the same investigator measured each child throughout the study (Hokken-K 1991 (preD/Dial); Hokken-K 1994 (preD/Dial); Hokken-K 1994 (TP); Hokken-K 1996 (TP)). However it was unclear whether this investigator was blinded to the treatment groups. Thus no study reported on whether outcome assessors were blinded.

Incomplete outcome data

Eight studies were considered to be at low risk of bias (Hertel 2002 (preD/Dial); Hokken-K 1991 (preD/Dial); Hokken-K 1994 (preD/Dial); Hokken-K 1994 (TP); Hokken-K 1996 (TP); Maxwell 1998a (TP); Maxwell 1998b (TP); Sanchez 2002 (TP); Santos 2010 (preD/Dial)) while five were considered to be at high risk (Fine 1994 (preD); Fine 2002 (TP); Ito 1997 (TP); Kitagawa 1997 (Dial); Kitagawa 1997 (preD); Powell 1997 (preD)). In the remaining three studies it was unclear whether the number of children excluded from analysis or lost to follow-up would influence the study results (Broyer 1996 (TP); Callis 1996 (preD); Kuizon 1998 (Dial)).

Selective reporting

Whether there was selective reporting of outcomes was unclear in six studies (Broyer 1996 (TP); Callis 1996 (preD); Ito 1997 (TP); Kitagawa 1997 (Dial); Kitagawa 1997 (preD); Kuizon 1998 (Dial); Powell 1997 (preD)). In the remaining 11 studies it was considered that all outcomes had been reported.

Other potential sources of bias

Two studies did not report on sponsorship (Ito 1997 (TP); Kitagawa 1997 (Dial); Kitagawa 1997 (preD)). The other 14 studies were funded by pharmaceutical companies.

Effects of interventions

See: [Summary of findings for the main comparison rhGH 28 IU/m²/wk versus placebo/no treatment for children with chronic kidney disease](#); [Summary of findings 2 rhGH 28 IU/m²/wk versus 14 IU/m²/wk for children with chronic kidney disease](#)

Sixteen studies enrolling 809 children were evaluated. There were no substantial differences between summary estimates calculated using random and fixed effects models and only results of the random effects models are reported here.

Change in height standard deviation score

rhGH versus placebo/no treatment

The effect of rhGH compared to placebo/no specific treatment on HSDS was reported in eight studies (Broyer 1996 (TP); Fine 1994 (preD); Fine 2002 (TP); Kuizon 1998 (Dial); Maxwell 1998a (TP); Maxwell 1998b (TP); Powell 1997 (preD); Sanchez 2002 (TP); Santos 2010 (preD/Dial)). Children treated with rhGH for one year showed an increase in HSDS of 0.82 compared with placebo/no specific treatment (Analysis 1.1 (8 studies, 331 children): MD 0.82, 95% CI

0.56 to 1.07). In a child of age 10, an MD of 0.82 approximates to about 5 cm of growth in one year.

Although there was some heterogeneity ($I^2 = 44\%$) in the degree of benefit of rhGH compared with placebo/no specific treatment, all studies reported an improvement in HSDS with therapy. In subgroup analysis (Analysis 1.2) heterogeneity in the efficacy of rhGH on HSDS was not explained by differences between studies involving transplant patients and those with CKD or end-stage kidney disease (ESKD). Heterogeneity was reduced in sensitivity analyses by removal of the studies by Sanchez 2002 (TP) and Santos 2010 (preD/Dial), which showed larger differences in HSDS between rhGH treated and non-treated children. There was no obvious variation demonstrated in the change of HSDS with pubertal status in one study (Analysis 1.3).

In one study (Fine 1994 (preD)) data were available for two years of treatment. Most of this growth acceleration occurred in the first year of rhGH therapy (Analysis 1.8.1). Treatment in the second year resulted in a small and not significant increase in HSDS (Analysis 1.8.2 (1 study, 82 children): MD 0.37, 95% CI -0.10 to 0.84). However treatment for two years with rhGH resulted in a persisting significant difference in HSDS between rhGH treated children and untreated children (Analysis 1.8.3 (1 study, 82 children): MD 1.36, 95% CI 0.86 to 1.86).

rhGH: 28 IU/m²/wk versus 14 IU/m²/wk

Three studies (Callis 1996 (preD); Hertel 2002 (preD/Dial); Kitagawa 1997 (Dial); Kitagawa 1997 (preD)) compared 28 IU/m²/wk with 14 IU/m²/wk and reported data on HSDS. There was no significant difference in the change in HSDS between baseline and one year (Analysis 2.1.1 (3 studies, 145 children): MD 0.20, 95% CI -0.09 to 0.48). Kitagawa 1997 (Dial) and Kitagawa 1997 (preD) showed no difference in HSDS between the two groups over six months (Analysis 2.1.2 (1 study, 40 children): MD 0.20, 95% CI -0.33 to 0.73) and between six months and one year (Analysis 2.1.3 (1 study, 40 children): MD 0.12, 95% CI -0.43 to 0.68). There was no obvious difference in the change in HSDS with rhGH according to the stages of CKD in one study (Kitagawa 1997 (Dial); Kitagawa 1997 (preD)).

rhGH: 28 IU/m²/wk versus 56 IU/m²/wk

One study (Hokken-K 1994 (TP)) compared 28 IU/m²/wk with 56 IU/m²/wk and showed no difference between groups in the change in HSDS at one year of treatment (Analysis 3.1 (1 study, 16 children): MD 0.30, 95% CI -1.00 to 1.60).

Change in height velocity

rhGH versus placebo/no treatment

Nine studies compared rhGH with placebo/no treatment and presented data on height velocity (Broyer 1996 (TP); Fine 1994 (preD); Fine 2002 (TP); Hokken-K 1991 (preD/Dial); Hokken-K 1996 (TP); Kuizon 1998 (Dial); Maxwell 1998a (TP); Maxwell 1998b (TP); Sanchez 2002 (TP); Santos 2010 (preD/Dial)). Two studies (Hokken-K 1991 (preD/Dial); Hokken-K 1996 (TP)) reported six month outcome data and showed an increase in height velocity of 2.85 cm over six months (Analysis 1.4 (2 studies, 27 children): MD 2.85 cm/6 mo, 95% CI 2.22 to 3.48). Seven studies (Broyer 1996 (TP); Fine 1994 (preD); Fine 2002 (TP); Kuizon 1998 (Dial); Maxwell 1998a (TP); Maxwell 1998b (TP); Sanchez 2002 (TP); Santos 2010 (preD/Dial)) showed an increase in height velocity over one year of 3.88 cm/y (Analysis 1.5 (7 studies, 288 children): MD 3.88, 95% CI 3.32 to 4.44).

Fine 1994 (preD) separately reported results for the second year of the study. Growth velocity fell from 4.2 cm/y in the first year (Analysis 1.8.4) to 2.3 cm/y in the second year of rhGH treatment (Analysis 1.8.5) and there was a greater decrease in height velocity in the rhGH-treated group relative to the untreated group (Analysis 1.8.6 (1 study, 82 children): MD -1.90 cm/y, 95% CI -3.04 to -0.76). However height velocity in the rhGH treated group still remained significantly higher than in the untreated group (Analysis 1.8.5 (1 study, 82 children): MD 2.30 cm/y, 95% CI 1.39 to 3.21) during the second year of treatment.

rhGH: 28 IU/m²/wk versus 14 IU/m²/wk

Four studies (Callis 1996 (preD); Hertel 2002 (preD/Dial); Ito 1997 (TP); Kitagawa 1997 (Dial); Kitagawa 1997 (preD)) comparing 28 IU/m²/wk with 14 IU/m²/wk of rhGH reported height velocity outcomes. Three studies showed a significant increase in height velocity with 28 IU/m²/wk compared with 14 IU/m²/wk for one year (Analysis 2.2.3 (3 studies, 150 children): MD 1.18 cm/y, 95% CI 0.52 to 1.84). One study (Kitagawa 1997 (Dial); Kitagawa 1997 (preD)) showed an increase in height velocity to six months with 28 IU/m²/wk compared with 14 IU/m²/wk (Analysis 2.2.1 (1 study, 80 children): MD 1.96 cm/6 mo, 95% CI 0.86 to 3.05), which waned during the second six months of intervention (Analysis 2.2.2 (1 study, 80 children): MD -0.53 cm/6 mo, 95% CI -1.65 to 0.59). Another study (Ito 1997 (TP)) reported a 2.7 cm/y (14 IU/m²/wk) and a 2.6 cm/y (28 IU/m²/wk) increase in height velocity but there was no statistical difference between treatment groups.

rhGH: 56 IU/m²/wk versus 28 IU/m²/wk

Hokken-K 1994 (preD/Dial) compared 56 IU/m²/wk with 28 IU/m²/wk of rhGH and showed no significant difference in mean height velocity (Analysis 3.2 (1 study, 16 children): MD 1.10 cm/y, 95% CI -1.30 to 3.50) during one year of treatment.

Change in height velocity standard deviation score

rhGH versus placebo/no treatment

Three studies comparing growth hormone treatment with placebo/no treatment reported data on height velocity SDS. Two studies (Hokken-K 1991 (preD/Dial); Hokken-K 1996 (TP)) reported an increase in height velocity SDS over six months duration (Analysis 1.7.1 (2 studies, 27 children): MD 7.80, 95% CI 6.09 to 9.51) and one study (Maxwell 1998a (TP); Maxwell 1998b (TP)) reported an increase over one year (Analysis 1.7.2 (1 study; 22 children): MD 6.14, 95% CI 3.41 to 8.86).

rhGH: 28 IU/m²/wk versus 14 IU/m²/wk

Three studies reported data on height velocity SDS. Height velocity SDS at one year was significantly higher in 28 IU/m²/wk compared with 14 IU/m²/wk of rhGH (Analysis 2.3.1 (2 studies, 106 children): MD 1.48, 95% CI 0.03 to 2.93). Height velocity SDS was significantly increased with 28 IU/m²/wk at six months (Analysis 2.3.2 (2 studies, 103 children): MD 2.05, 95% CI 0.82 to 3.28) but not between six months and one year (Analysis 2.3.3 (1 study; 40 children): MD -0.65, 95% CI -2.09 to 0.80).

Change in body proportions

Two studies (Hokken-K 1991 (preD/Dial); Hokken-K 1994 (preD/Dial)) provided additional information on body proportions (sitting height, arm span, lengths of body segments). Results were provided as changes in SDS but no standard deviations or confidence

intervals were provided so graphical analysis was not possible. Body proportions in children with CKD or ESKD did not differ from those seen in normal children. During rhGH therapy, body segments growth remained appropriate indicating that growth hormone did not influence body proportions during catch up growth.

Change in bone age

Seven studies (Broyer 1996 (TP); Fine 1994 (preD); Hokken-K 1991 (preD/Dial); Hokken-K 1996 (TP); Powell 1997 (preD); Sanchez 2002 (TP); Santos 2010 (preD/Dial)) all comparing rhGH treatment with placebo/no treatment, presented data on bone age. There was no significant difference in the change in bone age between the two groups over six months (Analysis 1.9.1 (2 studies, 27 children): MD -0.15, 95% CI -1.77 to 1.48), one year (Analysis 1.9.2 (4 studies, 202 children): MD 0.02, 95% CI -0.27 to 0.31 or between one and two years of treatment (Analysis 1.9.3 (1 study, 40 children): MD 0.40, 95% CI -0.99 to 1.79).

Other outcomes

Kidney function

Nine studies comparing rhGH therapy with placebo or no treatment provided some information on kidney function (Broyer 1996 (TP); Fine 1994 (preD); Fine 2002 (TP); Hokken-K 1991 (preD/Dial); Hokken-K 1996 (TP); Maxwell 1998a (TP); Maxwell 1998b (TP); Powell 1997 (preD); Sanchez 2002 (TP); Santos 2010 (preD/Dial)); the tenth study involved only dialysis patients (Kuizon 1998 (Dial)). All reported that kidney function did not differ between treated and control groups. Similarly in the six studies comparing different doses of rhGH, no differences in kidney function were identified among pre-dialysis or transplant patients.

Lipids

Hokken-K 1996 (TP) reported data on lipids and found no difference in cholesterol, triglycerides, apolipoproteins (Apo-A₁, Apo-B).

Glucose tolerance

Seven studies (Broyer 1996 (TP); Fine 1994 (preD); Hertel 2002 (preD/Dial); Hokken-K 1996 (TP); Maxwell 1998a (TP); Maxwell 1998b (TP); Powell 1997 (preD); Santos 2010 (preD/Dial)) reported data on fasting blood glucose, HbA_{1c} and insulin levels. Fasting blood glucose and HbA_{1c} remained generally within the normal range in both treatment groups but insulin levels were higher in rhGH treated patients. Individual patients developed glucose intolerance or frank diabetes mellitus (Table 1 - Reported adverse effects).

Acute rejection

Information on the incidence of acute rejection in kidney transplant recipients was reported in seven studies (Broyer 1996 (TP); Fine 2002 (TP); Hokken-K 1994 (TP); Hokken-K 1996 (TP); Ito 1997 (TP); Maxwell 1998a (TP); Maxwell 1998b (TP); Sanchez 2002 (TP)). Broyer 1996 (TP) reported that acute rejection episodes were more frequent in rhGH treated patients and that episodes were more frequent overall among recipients with more than one previous episode of acute rejection. The other studies noted no significant increase in rejection episodes in rhGH treated patients.

Benign intracranial hypertension

BIH was reported in one child treated with rhGH (Broyer 1996 (TP)) and one patient in the control group (Fine 1994 (preD)). The remaining studies did not provide any information on BIH.

Adverse effects

Reporting of adverse effects was generally scant. A number of papers reported adverse effects collectively without specifying the treatment group to which the subjects belonged. Reported side effects included asthma/whooping, acute rejection in transplantation, deterioration in kidney function, raised fasting glucose, papilledema, glucose intolerance, granuloma formation, lymph node swelling, claudication, hypertension and worsening of pre-existing idiopathic scoliosis (Table 1 - Reported adverse effects). Only one study (Fine 1994 (preD)) demonstrated a significant increase in adverse events in the rhGH group relative to the control group (using composite end-point data). A pooled estimate of rhGH-related adverse effects was not possible because of insufficient data in the primary studies.

DISCUSSION

Summary of main results

rhGH is effective in improving the growth of children with CKD during the first year of administration, with increases in all height indices. In children treated with rhGH, HSDS increases by 0.82 SDS, height velocity increases by 3.88 cm/y and height velocity SDS increases by 6 SDS above that of non-treated controls. It is likely that such growth will not be lost in later life and represents a long-term increase in growth potential. Within these short-term randomised studies, no variation in response to rhGH could be demonstrated between pre-pubertal and pubertal patients and between stage 3 and 4 CKD and stage 5 CKD treated by dialysis or by transplantation.

Available RCT data suggest that children with CKD should be treated with 28 IU/m²/wk of rhGH. Compared with a dose of 14 IU/m²/wk, the larger dose increases height by about 1.5 cm/y over one year but increasing the dose to 56 IU/m²/wk did not result in a statistically significant improvement in growth indices. However, these conclusions are based on only 18 patients. Using the 95% CI to quantify the uncertainty about the effect of the higher dose, relative to those patients given 28 IU/m²/wk, children given 56 IU/m²/wk may grow more than 3.43 cm/y taller in the first year or be 1.23 cm/y shorter.

Across all growth outcomes, there was a consistent pattern of waning effect with longer duration of treatment. This time-dependency could not be formally tested due to insufficient data points, however, observation of the study data is strongly suggestive of this relationship. For example, the differences in height velocity between the treated and untreated children were 2.85 cm/y (95% CI 2.22 to 3.48) for the first six months, 3.88 cm/y (95% CI 3.32 to 4.44) for the first year and -1.90 cm/y (95% CI -3.04 to -0.76) for the second year. The North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) registry found that HSDS improved by +0.5 SD following five years of rhGH therapy (Fine 2010).

Overall completeness and applicability of evidence

The identified studies only examined growth rates for a maximum of two years. No differences in efficacy were identified between pubertal and pre pubertal children or between different stages of CKD. However longer term cohort studies have demonstrated that response to rhGH therapy is better in prepubertal compared with pubertal children (Haffner 2000) and in stage 3 and 4 CKD compared with stage 5 CKD treated by dialysis or transplant (Berard 2008; Wühl 1996).

The most important height outcome is final or adult height. No RCTs have been published with final adult height as an outcome. However published study data do provide some indirect support that rhGH improves final adult height in children. During two years of rhGH treatment, there was no evidence that children grew less than their non-rhGH treated counterparts, even during the second year. There was no evidence that rhGH advanced the pubertal growth spurt, speeding up the normal growth process, or that it advanced bone age in the six studies in which this was evaluated. Data from children treated with rhGH, and followed till they achieved final adult height, indicate that treated children had sustained catch up growth whereas untreated matched children had progressive growth failure (Haffner 2000). Final adult height was 165 cm in boys and 156 cm in girls in treated children. The final adult height was -1.6 ± 1.2 SDS in treated children and -2.1 ± 1.2 SDS in untreated children. Improved final height in rhGH treated children has also been reported from the NAPRTCS registry (Fine 2005) and by the French Society of Pediatric Nephrology (Berard 2008) in children treated with rhGH.

Few adverse events were reported but the studies were underpowered to detect clinically important differences in adverse event rates. Several studies reported that adverse effects were minimal or did not report on adverse effects at all. In controlled studies for other indications and in observational studies of rhGH in children with or without CKD, adverse events (usually minor) are reported at a frequency of about 5/100 patient-years (Cowell 1995; Wilton 1999). BIH has been reported more commonly in rhGH treated patients than in the general population. Among different rhGH treated populations, BIH is most common in children with CKD and in children with Turner's Syndrome (Reeves 2002). Acute rejection episodes were seen more commonly in rhGH treated patients in one study (Broyer 1996 (TP)). However subsequent assessment demonstrated no consistent relationship between rhGH therapy and acute rejection in transplant recipients.

The benefits of rhGH on growth need to be balanced with the difficulty of adhering to a daily subcutaneous injection regimen. However no study addressed this outcome. In a case series of children with CKD treated with rhGH for two years, children who responded to rhGH reported they would choose treatment again, and those who did not respond generally reported they would not choose treatment again (Postlethwaite 1998). These data suggest that treatment response overrides concerns about injections.

Quality of the evidence

Sixteen RCTs were included in this review. Seven studies included only kidney transplant recipients, four studies included only predialysis patients while the remaining studies included both predialysis and dialysis patients. Risk of bias assessment indicated that the methodological quality of the studies was generally

poor with no study reporting the method of sequence generation and only four studies reporting adequate allocation concealment. Five studies were considered at low risk of performance bias as the control group received placebo injections. Although a single investigator undertook all the measurements in four studies, the risk of detection bias in these studies remained unclear as it was not clear whether the investigator was blinded to treatment groups. Studies without adequate allocation or blinding are considered to be at increased risk of bias (Moyer 1998; Schulz 1995). Eight and 12 studies respectively were considered at low risk of attrition bias or selective reporting. Fourteen studies reported pharmaceutical sponsorship.

The quality of evidence for the increase in HSDS and height velocity with rhGH compared with placebo/no specific therapy after one year of therapy was considered to be moderate, while the quality of evidence for the increase in height velocity after six months and the increase in height velocity SDS after one year was considered to be low (Summary of findings for the main comparison). The quality of evidence for the change in HSDS and height velocity after one year with rhGH 28 IU/m²/wk compared with 14 IU/m²/wk was considered to be moderate while that for height velocity SDS was considered to be low (Summary of findings 2).

Potential biases in the review process

This review identified 16 studies. Of these two were available in abstract form only (Callis 1996 (preD); Kuizon 1998 (Dial)) and three other studies were available in only limited reports (Broyer 1996 (TP); Ito 1997 (TP); Kitagawa 1997 (Dial); Kitagawa 1997 (preD)). Incomplete reporting of studies may result in inaccurate information being included in this systematic review. In particular the European multicentre study (Broyer 1996 (TP)) enrolled 203 children while the preliminary publication provided growth data only on 125 children and these data were related to pubertal status (Analysis 1.3). The only other publication identified from this study provided data on a subset of 85 French children and data from this subset is included in the overall analysis of HSDS (Analysis 1.1). It is possible that this subset of patients was not fully representative of the results seen in the larger group of children since the MD in HSDS was 0.3 SDS in the French children compared with MD of 0.5 to 0.7 SDS in the larger group of children (Analysis 1.3).

The literature search was run several times up to December 2011 making it unlikely that any studies have been missed. Only two additional studies were identified since the last update of this review. Of these was a recent study while Callis 1996 (preD) was a conference abstract from 1996 identified by handsearching since the last update of this review. Of study reports in the Cochrane Renal Group's specialised register 40% have been identified by handsearching of conference proceedings. It remains possible that further studies examining rhGH therapy in children with CKD will be identified as conference proceedings from different congresses are searched.

Agreements and disagreements with other studies or reviews

The findings of increased HSDS and height velocity with short-term rhGH therapy in the RCTs included in this review are in keeping with longer duration non-randomised studies with concurrent or

historical control groups (Berard 2008; Haffner 2000) and with the NAPRTCS registry data (Fine 2005; Fine 2010). In larger studies and registry data, response to rhGH is greater in younger children and in children treated conservatively. This could not be demonstrated among the included studies but total patient numbers included in the studies were small. This review suggested that response to rhGH is attenuated in the second year of therapy and this has been confirmed in longer term studies (Fine 2005).

AUTHORS' CONCLUSIONS

Implications for practice

Based upon existing RCT data, one year of 28 IU/m²/wk rhGH in children with CKD, regardless of their pubertal and treatment status (pre-dialysis, dialysis, post-transplant), results in an average height increase of 3.88 cm/y. Data from cohort studies suggest that rhGH results in an increase in final adult height and that the response in pre-pubertal children and/or stage 3 or 4 CKD exceeds that in pubertal and/or stage 5 CKD. Side effects of rhGH are uncommon.

Implications for research

Available studies are few, are of short duration, and underpowered to detect differences in treatment effects across sub-groups of patients based upon plausible effect modifiers including the duration of treatment, age, pubertal status and stage of CKD. Although the studies did have some heterogeneity of children, the magnitude of treatment effect could not be related to age, pubertal status or stage of CKD. Longer term cohort studies have documented greater responses to rhGH in pre pubertal children not on dialysis. However rhGH is now well established as a therapy for children with CKD and growth retardation though its use varies widely throughout the world. Therefore further RCTs are unlikely to be performed as withholding rhGH from short children would now not be considered appropriate. In addition, dose regimens are now standardised so that studies comparing different dose regimens would also not be considered necessary.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Broyer 1996 (TP)

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Time frame: November 1990 to April 1994 Follow-up period: 12 months
Participants	<ul style="list-style-type: none"> Setting: multicentre tertiary centres Country: France, Belgium, Switzerland, Portugal, Sweden, United Kingdom, Hungary, Argentina, Australia, New Zealand Kidney transplant recipients at least 1 year post transplant with normal serum thyroid hormone levels; HSDS for CA below -2 or growth velocity < 25th percentile for age with 2 separate measurement

Broyer 1996 (TP) (Continued)

in ≥ 6 months before entry; GFR > 20 mL/min/1.73 m², pubertal (testicular volume $4 \leq 8$ mL, breast development B2 $\leq$ B3) (86) or prepubertal (testicular volume < 4 mL, breast development $< B2$) (86)

- Number
 - * Treatment group: 106 enrolled (67 prepubertal) (66 evaluated for height and 92 for GFR overall; 41/44 French children)
 - * Control group: 97 enrolled (51 prepubertal) (59 evaluated for height and 88 for GFR overall; 44/46 French children)
- Age (mean $\pm$ SD): treatment group (12.1 $\pm$ 3.1 years); control group (12.6 $\pm$ 3.3 years)
- Sex (M/F): treatment group (72/25); control group (71/35)

Exclusion criteria

- Other chronic illness; height velocity ≥ 75 th percentile; dialysis therapy; malignancy; treatment with rhGH in previous 12 months

Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • rhGH • Dose: 30 IU/m²/wk in divided daily doses SC <p>Control group</p> <ul style="list-style-type: none"> • No treatment <p>Co-interventions</p> <ul style="list-style-type: none"> • Prednisone, azathioprine, cyclosporin
Outcomes	<ul style="list-style-type: none"> • Change in HSDS • Change in height velocity • Change in BA • Adverse effects: change in GFR; acute rejection episodes • Follow-up at 1 year: 61% overall, 94% of 90 children included in report of French children
Notes	<ul style="list-style-type: none"> • Exclusions post randomisation but pre-intervention: none reported separately • Exclusions after intervention administered <ul style="list-style-type: none"> * 125/203 entered were evaluated for height and 180/203 entered evaluated for GFR * 23 excluded from kidney function analysis as GFR < 20, transplanted < 12 months, rhGH started without randomisation or therapy not complied with. * 49 excluded from growth analysis due to abnormal thyroid function, GV too high, HSDS at entry < -2 SDS, previous growth not documented. • Stop or end point/s: NS • Additional data requested from authors: no • Data on 90 patients from French centres, which took part in international multicentre study entering 203 patients, included in Analysis 1.1, Analysis 1.2, Analysis 1.4 and Analysis 1.7. Data from 125/203 patients included in Analysis 1.8 and Analysis 1.9

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not provided
Allocation concealment (selection bias)	Low risk	"Patients were randomised centrally"

Broyer 1996 (TP) *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding and outcome likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing data unlikely to influence true outcome (Guest) If include all data from Broyer - could influence as only 125/203 evaluated for growth and 180/203 for GFR. Unclear when these patients were excluded.
Selective reporting (reporting bias)	Unclear risk	Unclear whether all outcomes reported
Other bias	High risk	Funding by Pharmacia & Upjohn, Stockholm, Sweden

Callis 1996 (preD)

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Time frame: NS Follow-up period: 1 year
Participants	<ul style="list-style-type: none"> Setting: multicentre tertiary centres Country: Spain CKD with GFR < 50 mL/min/1.73 m²; height: SDS > - 2SDS or growth velocity < 50th percentile for CA; prepubertal using Tanner criteria; normal TSH levels and GH levels post stimulation ≥ 10 ng/mL Number: treatment group 1 (23); treatment group 2 (21) Age (mean ± SD): treatment group 1 (8.7 ± 2.8 years); treatment group 2 (8.7 ± 3.8 years) Sex (M/F): treatment group 1 (17/6); treatment group 2 (16/5) <p>Exclusion criteria: NS</p>
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> rhGH Dose: 28 IU/m²/wk in divided daily dose SC <p>Treatment group 2</p> <ul style="list-style-type: none"> rhGH Dose: 14 IU/m²/wk in divided daily dose SC <p>Co-interventions: NS</p>
Outcomes	<ul style="list-style-type: none"> Change in HSDS Height velocity (cm/y) Adverse effects Follow-up: 96%; 2 patients excluded from analysis because of protocol violation
Notes	<ul style="list-style-type: none"> Exclusions post randomisation but pre-intervention: NS

Callis 1996 (preD) (Continued)

- Exclusions after intervention administered
 - * 2/46 children not included in analysis because of protocol violation
 - * 34 completed 1 year of follow-up
- Stop or end point/s: NS
- Additional data requested from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding and outcome measurement could influence outcomes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Abstract only. 2/46 excluded for protocol violation
Selective reporting (reporting bias)	Unclear risk	Abstract only
Other bias	High risk	Pharmacia and Upjohn sponsored study

Fine 1994 (preD)

Methods	<ul style="list-style-type: none"> • Study design: parallel RCT • Time frame: April 1988 to June 1990 • Follow-up period: 24 months
Participants	<ul style="list-style-type: none"> • Setting: multicentre tertiary centres • Country: USA • CKD with CrCl > 5 and < 75 mL/min/1.73 m²; height: < 3rd percentile for CA; prepubertal (BA < 10 (girls), < 11 (boys)) • Number <ul style="list-style-type: none"> * Treatment group: 82 enrolled (69 completed 1 year and 55 completed 2 years). 55 included in results * Control group: 43 enrolled (30 completed 1 year, 27 completed 2 years). 27 included in results • Age (mean ± SD): treatment group (6.0 ± 3.9 years); control group (5.7 ± 3.6 years) • Sex (M/F): treatment group (61/21); control group (28/14; 1 patient unaccounted for) <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Cause for growth retardation not CKD; inability to measure accurately; steroid use; DM; malignant disease; other investigational drug

Fine 1994 (preD) (Continued)

Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> rhGH Dose: 28 IU/m²/wk (0.05 mg/kg/d SC). Dose adjusted for weight every 3 months <p>Control group</p> <ul style="list-style-type: none"> Placebo Dose: equivalent volume SC daily <p>Co-interventions</p> <ul style="list-style-type: none"> Vitamin D; phosphate binder; prophylactic antibiotics; antihypertensive agents
Outcomes	<ul style="list-style-type: none"> Change in HSDS Height velocity (cm/y) Change in BA Adverse effects Follow-up: at 1 year (80%); at 2 years (67%)
Notes	<ul style="list-style-type: none"> Exclusions post randomisation but pre-intervention: NS Exclusions after intervention administered <ul style="list-style-type: none"> * Treatment group <ul style="list-style-type: none"> ☐ Excluded in 1st year (13): adverse events (2); non compliance (4); transplant (2); request (5) ☐ Excluded in 2nd year (13): adverse events (2); lost to follow-up (1); transplant (9); request (1) * Placebo group <ul style="list-style-type: none"> ☐ Excluded in 1st year (12): adverse events (1); non compliance (2); transplant (4); request (3); protocol violation (1); precocious puberty (1) ☐ Excluded in 2nd year (3): transplant (2); request (1) Stop or end point/s: NS Additional data requested from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients said to be randomly assigned so that one third in placebo group and two thirds in treatment group but no method provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients received treatment or placebo in equivalent volumes & both provided by Genetech
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data likely to be related to true outcome
Selective reporting (reporting bias)	Low risk	All outcomes reported

Fine 1994 (preD) (Continued)

Other bias High risk Funding by Genetech Inc., South San Francisco, Calif..

Fine 2002 (TP)

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Time frame: December 1996 to June 2000 Follow-up period: 1 year
Participants	<ul style="list-style-type: none"> Setting: tertiary, multicentre Country: USA Kidney transplant recipients; no rejection requiring change of therapy in previous 6 months; transplant for > 1 year; HSDS: < -2; BA: < 16 years (M) < 15 years (F) Number: treatment group (36 enrolled; 5 withdrawn during study); control group (27 enrolled; 5 withdrawn during study) Age (range): treatment group (5-16 years); control group (5-16 years) Sex (M/F): treatment group (25/2); control group (29/7) Pubertal stage: treatment group (1 in 26; 2-3 in 10); control group (1 in 14; 2-3 in 13) <p>Exclusion criteria</p> <ul style="list-style-type: none"> Other protocols or investigational drugs; specific cause for growth retardation; malignancy; DM; oestrogen/androgen therapy; inability to measure
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> rhGH (Nutropin) Dose: 28 IU/m²/wk <p>Control group</p> <ul style="list-style-type: none"> No treatment <p>Co-interventions</p> <ul style="list-style-type: none"> Prednisone < 0.15 mg/kg/d or < 0.25 mg/kg on alternate days; centre-specific immunosuppression
Outcomes	<ul style="list-style-type: none"> Change in HSDS Change in growth velocity (cm/y) Adverse events Follow-up at 1 year: 84%
Notes	<ul style="list-style-type: none"> Exclusions post randomisation but pre-intervention: treatment group (3); control group (2) Exclusions after intervention: treatment group (5); control group (5) Stop or end point/s: NS Additional data requested from authors: additional information on HSDS obtained from authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Low risk	Randomisation into treatment and control groups was performed at the data co-ordinating centre (Emmes Corp.)

Fine 2002 (TP) (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding and outcome measurement could be influenced by blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data (16% rhGH group; 18% control) could introduce clinically relevant bias
Selective reporting (reporting bias)	Low risk	All outcomes appear to be reported. Information obtained from authors.
Other bias	High risk	Funding by EMMES Corporation

Hertel 2002 (preD/Dial)

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Time frame: NS Follow-up period: 1 year
Participants	<ul style="list-style-type: none"> Setting: tertiary, multicentre Country: Denmark, Sweden and Finland Pre-dialysis (GFR < 40 mL/min/1.73m²) and dialysis patients; CKD > 1 year; CA (3-18 years); HSDS (< -2) and HVSDS below mean for age/sex or HSDS below mean and HVSDS < 0.68 SD for CA; prepubertal (BA < 12 years (M), < 10 years (F)) Number: treatment group 1 (14 enrolled; 14 evaluated for 1+ outcomes); treatment group 2 (15 enrolled; 12 evaluated for 1+ outcomes) Age (mean; range): treatment group 1 (10.3 years; 3.6-15.1); treatment group 2 (9.7 years; 3.4-15.0) Sex (M/F): treatment group 1 (12/2); treatment group 2 (12/3) <p>Exclusion criteria</p> <ul style="list-style-type: none"> Abnormal thyroid function; endocrine/metabolic disease; growth retardation due to other physical disease or psychosocial
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> rhGH (norditrophin) Dose: 28 IU/m²/wk in divided daily dose SC <p>Treatment group 2</p> <ul style="list-style-type: none"> rhGH Dose: 14 IU/m²/wk in divided daily dose SC <p>Co-interventions: NS</p>
Outcomes	<ul style="list-style-type: none"> Change in HSDS Change in HVSDS Change in height velocity (cm/y) Carbohydrate metabolism Blood pressure and GFR

Growth hormone for children with chronic kidney disease (Review)

Hertel 2002 (preD/Dial) (Continued)

- Adverse events
- Follow-up at 1 year: 79%

Notes

- Exclusions post randomisation but pre-intervention: NS
- Exclusions after intervention: 6 (treatment groups NS)
- Stop or end point/s: NS
- Additional data requested from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not provided
Allocation concealment (selection bias)	Unclear risk	Information not provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding and outcome measurement could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	23/29 completed 1 year. 16/29 completed 2 years. Missing data unlikely to influence true outcome
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	High risk	Funding by Novo Nordisk

Hokken-K 1991 (preD/Dial)
Methods

- Study design: cross-over study
- Time frame: NS
- Follow-up period: 12 months (data taken from first 6 months)

Participants

- Setting: multicentre tertiary centres
- Country: Netherlands
- CKD (9) and ESKD (11; GFR < 20 mL/min/1.73 m²); HSDS for CA below -1.88; height velocity for CA < 25th percentile; prepubertal
- Number: treatment group (8); control group (8)
- Age (mean, range): treatment group (8.7 years, 4.4-11.3); control group (8.6, 4.4-16.0)
- Sex (M/F): treatment group (6/2); control group (4/4)

Exclusion criteria

- Thyroid disease; renal bone disease; previous anabolic steroids, sex steroids or erythropoietin

Interventions

Treatment group

Growth hormone for children with chronic kidney disease (Review)

Hokken-K 1991 (preD/Dial) (Continued)

- rhGH
- Dose: 28 IU/m²/wk in divided daily doses SC for 6 months

Control group

- Placebo
- Dose: equal volume of placebo preparation SC for 6 months

Co-interventions

- Vitamin D, phosphate binders, calcium supplements

Outcomes	<ul style="list-style-type: none"> • Change in height velocity • Change in height HVSDS • Change in bone age • Adverse effects • Follow-up: 80%; excluded because of kidney transplant at 6 months (3) and 7 months (1)
Notes	<ul style="list-style-type: none"> • Exclusions post randomisation but pre-intervention: none reported • Exclusions post intervention: excluded following kidney transplantation (4) • Stop or end point/s: NS • Additional data requested from authors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The children were blindly and randomly assigned to treatment with... or placebo". Trial said to be "double-blind".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The same investigator did all the measurements of the children but it was unclear whether this investigator was blinded to treatment groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data unlikely to be related to true outcome
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes reported
Other bias	High risk	Funding by Novo Nordisk

Hokken-K 1994 (preD/Dial)

Methods	• Study design: parallel RCT • Time frame: NS

Hokken-K 1994 (preD/Dial) (Continued)

- Follow-up period: 2.5 years

Participants	<ul style="list-style-type: none"> Setting: multicentre tertiary centres Country: Netherlands CKD (8) and ESKD (15; GFR < 20mL/min/1.73 m²); prepubertal; HSDS for CA < -1.88 with height velocity for CA < 50th percentile or HSDS for CA < 0.00 with height velocity for CA < 50th percentile; BA: < 10 (girls), < 12 (boys) Number: treatment group 1 (12); treatment group 2 (11) Age (mean, range): treatment group 1 (7.5 years, 1.6-14.1); treatment group 2 (6.6 years, 2.7-12.5) Sex (M/F): treatment group 1 (11/1); treatment group 2 (7/4) <p>Exclusion criteria</p> <ul style="list-style-type: none"> Renal bone disease; thyroid dysfunction; metabolic acidosis; previous anabolic steroids or sex steroids
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> rhGH Dose: 28 IU/m²/wk in divided daily dose SC <p>Treatment group 2</p> <ul style="list-style-type: none"> rhGH Dose: 14 IU/m²/wk in divided daily dose SC <p>Co-interventions</p> <ul style="list-style-type: none"> Vitamin D, phosphate binders, calcium supplements
Outcomes	<ul style="list-style-type: none"> Change in HVSDS Change in height velocity (cm/y) Adverse effects Follow-up: at 1 year (78%, 5/23 transplanted); at 2 years (57%, 4 transplanted, 1 died)
Notes	<ul style="list-style-type: none"> Exclusions post randomisation but pre-intervention: none reported Exclusions post intervention: excluded because of kidney transplant after 6 months (5); excluded in 2nd year because of transplant (4), death (1) Stop or end point/s: NS Additional data requested from authors: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients were randomly and blindly assigned to treatment groups. Trial reported to be "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The same investigator carried out all height measurements but it was unclear whether this investigator was blinded to treatment groups

Hokken-K 1994 (preD/Dial) *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data unlikely to be related to true outcome
Selective reporting (reporting bias)	Low risk	Reported pre-specified outcomes
Other bias	High risk	Funding by Novo Nordisk

Hokken-K 1994 (TP)

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Time frame: NS Follow-up period: 2 years
Participants	<ul style="list-style-type: none"> Setting: multicentre tertiary centre Country: Netherlands Kidney transplant recipients > 1 year post-transplant; no rejection episodes for 6 months; HSDS < -1.88 and height velocity for CA < 50th percentile or HSDS > -1.88 and height velocity for CA < 25th percentile; prednisone (< 0.25 mg/kg/d or < 0.5 mg/kg/d on alternate days); pubertal Number: treatment group 1 (7 enrolled; 5 early puberty); treatment group 2 (9 enrolled; 5 early puberty) Age (mean ± SD): treatment group 1 (15.7 ± 1.9 years); treatment group 2 (15.5 ± 2.6 years) Sex (M/F): treatment group 1 (4/3); treatment group 2 (5/4) <p>Exclusion criteria</p> <ul style="list-style-type: none"> Thyroid dysfunction; metabolic acidosis; previous sex hormone treatment; growth retardation due to another cause
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> rhGH Dose: 56 IU/m²/wk divided into daily doses for 2 years <p>Treatment group 2</p> <ul style="list-style-type: none"> rhGH Dose: 28 IU/m²/wk divided into daily doses for 2 years <p>Co-interventions</p> <ul style="list-style-type: none"> Prednisone (alternate day 10, daily 7, none 1), azathioprine, cyclosporin
Outcomes	<ul style="list-style-type: none"> Change in HVSDS Change in height velocity (cm/y) Adverse effects Follow-up: did not complete 2 year study (3; returned to dialysis at 15 and 16 months (2)); entered late and completed 18 months (1))
Notes	<ul style="list-style-type: none"> Exclusions post randomisation but pre-intervention: none reported Exclusions post intervention: did not complete 2 years follow-up (3; 2 returned to dialysis, 1 entered late) Stop or end point/s: NS Additional data requested from authors: none

Hokken-K 1994 (TP) (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"16 were randomly and blindly assigned to one or other dosage"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	All measurements made by same investigator but unclear whether investigator was blinded to treatment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data not likely to be related to true outcome
Selective reporting (reporting bias)	Low risk	All outcomes addressed
Other bias	High risk	Funding by Novo Nordisk

Hokken-K 1996 (TP)

Methods	<ul style="list-style-type: none"> Study design: cross-over study Time frame: NS Follow-up period: 6 months
Participants	<ul style="list-style-type: none"> Setting: multicentre tertiary units Country: Netherlands Kidney transplant recipients > 1 year post transplant; no rejection episodes for 6 months; HSDS < -1.88 and height velocity for CA < 50th percentile or HSDS > -1.88 and height velocity for CA < 25th percentile; prednisone < 0.25 mg/kg/d for at least 6 months Number: treatment group (6); control group (5) Age (mean, range): treatment group (12.1 years, 9.1-18.7); control group (11.1 years, 8.3-14.9) Sex (M/F): treatment group (9/2), control group (4/1) <p>Exclusion criteria</p> <ul style="list-style-type: none"> Thyroid dysfunction; metabolic acidosis; previous sex hormone treatment; growth retardation due to another cause
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> rhGH Dose: 28 IU/m²/wk divided into daily doses for 6 months <p>Control group</p> <ul style="list-style-type: none"> Placebo

Hokken-K 1996 (TP) (Continued)

- Dose: divided into daily doses for 6 months

Co-interventions

- Prednisone, azathioprine, cyclosporin

Outcomes	<ul style="list-style-type: none"> • Change in HVSDS • Change in height velocity (cm/6 months) • Change in BA in years • GFR, effective renal plasma flow • Adverse effects • Follow-up: 100%
Notes	<ul style="list-style-type: none"> • Exclusions post randomisation but pre-intervention: none • Stop or end point/s: none reported • Additional data requested from authors: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients were randomly and blindly assigned". Placebo group received equal volume of injection. Trial reported to be double blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The same investigator undertook all measurements but it was unclear whether this investigator was blinded to the treatment groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	All children completed study period
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	High risk	Funding by Novo Nordisk

Ito 1997 (TP)

Methods	<ul style="list-style-type: none"> • Study design: parallel RCT • Time frame: NS • Follow-up period: 1 year
Participants	<ul style="list-style-type: none"> • Setting: single university centre • Country: Japan • Kidney transplant recipients; prepubertal or early puberty (BA <14 (boys), 13 (girls)); steroid dose < 0.5 mg/kg/d

Ito 1997 (TP) (Continued)

- Number: treatment group 1 (13); treatment group 2 (10)
- Age (years): NS
- Sex (M/F): NS

Exclusion criteria: NS

Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> • rhGH • Dose: 28 IU/m²/wk divided into daily doses for 1 year <p>Treatment group 2</p> <ul style="list-style-type: none"> • rhGH • Dose: 14 IU/m²/wk divided into daily doses for 1 year <p>Co-interventions: NS</p>
Outcomes	<ul style="list-style-type: none"> • Height velocity (cm/y) • Adverse effects • Follow-up: 85%
Notes	<ul style="list-style-type: none"> • Exclusions post randomisation but pre-intervention: NS • Exclusions post intervention: 27 children included initially, 4 excluded from analysis because of non compliance or poor response to rhGH • Stop or end point/s: none reported • Additional data requested from authors: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not provided
Allocation concealment (selection bias)	Unclear risk	Information not provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Outcome likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information not provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data likely to be related to true outcome
Selective reporting (reporting bias)	Unclear risk	No information in methods on outcomes
Other bias	Unclear risk	No information on sponsorship provided

Kitagawa 1997 (Dial)

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Time frame: NS Follow-up period: 24 months
Participants	<ul style="list-style-type: none"> Setting: multicentre tertiary units Country: Japan Children on dialysis; prepubertal (bone age < 13 years (boys), <12 years (girls)); HSDS or HVSDS < -1.5 Number: treatment group 1 (28); treatment group 2 (26) Age (mean $\pm$ SD): treatment group 1 (10.2 $\pm$ 4.3 years); treatment group 2 (9.9 $\pm$ 3.2 years) Sex (M/F): treatment group 1 (17/11); treatment group 2 (15/11) <p>Exclusion criteria: NS</p>
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> rhGH Dose: 28 IU/m²/wk divided into daily doses for up to 2 years <p>Treatment group 2</p> <ul style="list-style-type: none"> rhGH Dose: 14 IU/m²/wk divided into daily doses for up to 2 years <p>Co-interventions: NS</p>
Outcomes	<ul style="list-style-type: none"> Change in HSDS Change in height velocity (cm/y) Change in HVSDS Adverse effects Follow-up: at 1 year (88%); at 2 years (57%)
Notes	<ul style="list-style-type: none"> Exclusions post randomisation but pre-intervention: none reported Exclusions post intervention: did not complete 1 year of treatment (6); did not complete 2 years (additional 25) Stop or end point/s: NS Additional data requested from authors: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Outcome likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided

Kitagawa 1997 (Dial) (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data likely to be related to true outcome
Selective reporting (reporting bias)	Unclear risk	No details on pre-specified outcomes provided
Other bias	Unclear risk	No information on sponsorship provided

Kitagawa 1997 (preD)

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Time frame: NS Follow-up period: 24 months
Participants	<ul style="list-style-type: none"> Setting: multicentre tertiary units Country: Japan Children with CKD (GFR < 40 mL/min/1.73 m²); prepubertal (BA < 13 years (boys), < 12 years (girls)); HSDS or HVSDS < -1.5 Number: treatment group 1 (30); treatment group 2 (28) Age (mean ± SD): treatment group 1 (8.7 ± 2.9 years); treatment group 2 (8.6 ± 3.3 years) Sex (M/F): treatment group 1 (22/8); treatment group 2 (19/9) <p>Exclusion criteria: NS</p>
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> rhGH Dose: 28 IU/m²/wk divided into daily doses for up to 2 years <p>Treatment group 2</p> <ul style="list-style-type: none"> rhGH Dose: 14 IU/m²/wk divided into daily doses for up to 2 years <p>Co-interventions: NS</p>
Outcomes	<ul style="list-style-type: none"> Change in HSDS Change in height velocity (cm/y) Change in HVSDS Adverse effects Follow-up: at 1 year (83%); at 2 years (53%)
Notes	<ul style="list-style-type: none"> Exclusions post randomisation but pre-intervention: none reported Exclusions post intervention: did not complete 1 year (10); did not complete 2 years (additional 17) Stop or end point/s: NS Additional data requested from authors: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided

Growth hormone for children with chronic kidney disease (Review)

Kitagawa 1997 (preD) (Continued)

Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Outcome likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data likely to be related to true outcome
Selective reporting (reporting bias)	Unclear risk	No details on pre-specified outcomes provided
Other bias	Unclear risk	No information on sponsorship provided

Kuizon 1998 (Dial)

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Time frame: NS Follow-up period: 1 year (assumed)
Participants	<ul style="list-style-type: none"> Setting: tertiary centre Country: USA Children with ESKD on peritoneal dialysis Age (mean $\pm$ SE): 8.4 $\pm$ 1.5 years Number: treatment group (6); control group (8) Sex (M/F): NS <p>Exclusion criteria: NS</p>
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> rhGH Dose: 28 IU/m²/wk SC <p>Control group</p> <ul style="list-style-type: none"> No treatment <p>Co-interventions: NS</p>
Outcomes	<ul style="list-style-type: none"> Change in HSDS Growth velocity (cm/y) Loss to follow-up: not reported
Notes	<ul style="list-style-type: none"> Exclusions post randomisation but pre-intervention: none reported Stop or end point/s: NS Additional data requested from authors: additional information requested but not available

Kuizon 1998 (Dial) (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported to be randomly assigned but no methodology provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Control group received no treatment and outcome likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data only available from abstract
Selective reporting (reporting bias)	Unclear risk	Data only available from abstract
Other bias	Unclear risk	No information on sponsorship provided

Maxwell 1998a (TP)

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Time frame: NS Follow-up period: 1 year
Participants	<ul style="list-style-type: none"> Setting: multicentre tertiary units Country: UK Kidney transplant recipients for > 1 year; pubertal; height < 3rd percentile for CA or height velocity < 25th percentile for CA; GFR > 20 mL/min/1.73 m² (GFR 48 (23-78) mL/min/1.73 m²) Number: treatment group (4); control group (3) Mean age (range): 15.2 years, (12.4-19.8) Sex (M/F): 5/2 <p>Exclusion criteria</p> <ul style="list-style-type: none"> Thyroid dysfunction
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> rhGH Dose: 28 IU/m²/wk divided into daily doses for 1 year <p>Control group</p> <ul style="list-style-type: none"> No treatment <p>Co-interventions: NS</p>

Growth hormone for children with chronic kidney disease (Review)

Maxwell 1998a (TP) (Continued)

Outcomes	<ul style="list-style-type: none"> • Change in HSDS • Change in height velocity (cm/y) • Change in HVSDS • Change in BA • Adverse effects • Follow-up: 100%
Notes	<ul style="list-style-type: none"> • Exclusions post randomisation but pre-intervention: none reported • Stop or end point/s: NS • Additional data requested from authors: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients stratified according to pubertal stage but no information on method of sequence generation provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Open labelled" trial and outcome likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	All included patients included in analysis
Selective reporting (reporting bias)	Low risk	All outcomes specified in methods were reported
Other bias	High risk	Funding by Action Research and Pharmacia & Upjohn, Stockholm

Maxwell 1998b (TP)

Methods	<ul style="list-style-type: none"> • Study design: parallel RCT • Time frame: NS • Follow-up period: 1 year
Participants	<ul style="list-style-type: none"> • Setting: multicentre tertiary units • Country: UK • Kidney transplant recipients for > 1 year; prepubertal; height < 3rd percentile for CA or HV < 25th percentile for CA; GFR >20 mL/min/1.73 m² (GFR 51 (13-113) mL/min/1.73 m²) • Number: treatment group (9); control group (6) • Mean age (range): 13.0 years (9.4-16.5) • Sex (M/F): 13/2 • Age (years): NS

Maxwell 1998b (TP) (Continued)

- Sex (M/F): NS

Exclusion criteria

- Thyroid dysfunction

Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • rhGH • Dose: 28 IU/m²/wk divided into daily doses for 1 year <p>Control group</p> <ul style="list-style-type: none"> • No treatment <p>Co-interventions: NS</p>
Outcomes	<ul style="list-style-type: none"> • Change in HSDS • Change in height velocity (cm/y) • Change in HVSDS • Change in BA • Adverse effects • Follow-up: 100% (2/9 ceased rhGH after 9 and 11 months but included)
Notes	<ul style="list-style-type: none"> • Exclusions post randomisation but pre-intervention: none reported • Stop or end point/s: NS • Additional data requested from authors: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients stratified according to pubertal stage but no information on method of sequence generation provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Open labelled" trial and outcome likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	All included patients included in analysis
Selective reporting (reporting bias)	Low risk	All outcomes specified in methods were reported
Other bias	High risk	Funding by Action Research and Pharmacia & Upjohn, Stockholm

Powell 1997 (preD)

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Time frame: NS Follow-up period: 12 months
Participants	<ul style="list-style-type: none"> Setting: multicentre tertiary units Country: USA CKD with GFR 10-40 mL/min/1.73 m²; prepubertal with bone age <11 (boys), <10 (girls); age > 2.5 years; height: < 5th percentile for CA, able to stand for measurements Number: treatment group (46 enrolled; 30 analysed); control group (23 enrolled; 14 analysed) Age (mean ± SD): treatment group (5.6 ± 2.0 years); control group (5.7 ± 2.6 years) Sex (M/F): treatment group (25/5); control group (12/2) <p>Exclusion criteria</p> <ul style="list-style-type: none"> Serum albumin < 25g/L; receiving medications that influence growth; other illnesses that affect growth; DM; previous malignancy
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> rhGH 28 IU/m²/wk divided into daily doses for 1 year <p>Control group</p> <ul style="list-style-type: none"> No treatment <p>Co-interventions: NS</p>
Outcomes	<ul style="list-style-type: none"> Change in HSDS Change in BA Follow-up: completed study (64%)
Notes	<ul style="list-style-type: none"> Exclusions post randomisation but pre-intervention: none reported Exclusions post intervention: exited before 1 year (20; 1 death, 12 to ESKD, 1 allergy to rhGH, 6 entered puberty); excluded because of lack of data (5) Stop or end point/s: NS Additional data requested from authors: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not provided. Groups balanced for age, gender, height, GFR at baseline, primary kidney disease
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Stated to be "open label". Outcome could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided

Powell 1997 (preD) (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data likely to be related to true outcome
Selective reporting (reporting bias)	Unclear risk	Unclear whether all outcomes reported
Other bias	High risk	Funding by Genetech, San Francisco, Calif., USA

Sanchez 2002 (TP)

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Time frame: NS Follow-up period: 12 months
Participants	<ul style="list-style-type: none"> Setting: single tertiary unit Country: USA Kidney transplant recipient > 1 year post-transplant; prepubertal; stable kidney function; no previous rhGH; normal bone formation rate or adynamic bone disease on biopsy; agreement to undergo bone biopsy Number: treatment group (12 enrolled; 11 analysed; 1 withdrawn); control group (11 enrolled; 10 evaluated; 1 withdrawn) Age (mean $\pm$ SD): treatment group (9.7 $\pm$ 4.5 years); control group (11 $\pm$ 1.8 years) Sex (M/F): 18/5 <p>Exclusion criteria</p> <ul style="list-style-type: none"> Histological evidence of secondary hyperparathyroidism on bone biopsy
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> rhGH Dose: 28 IU/m²/wk (0.05 mg/kg/d given SC) for up to 24 months <p>Control group</p> <ul style="list-style-type: none"> No treatment <p>Co-interventions</p> <ul style="list-style-type: none"> Cyclosporin, azathioprine, prednisone (0.1 $\pm$ 0.04 mg/kg/d)
Outcomes	<ul style="list-style-type: none"> Change in HSDS Change in height velocity (cm/y) Change in BA GFR Adverse effects Follow-up: 91%
Notes	<ul style="list-style-type: none"> Exclusions post randomisation but pre-intervention: NS Exclusions post intervention: 1 patient withdrawn from each group and excluded from analysis Stop or end point/s: NS Additional data requested from authors: additional information on HSDS obtained from authors

Risk of bias

Sanchez 2002 (TP) (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided but apparently stratified for bone histology (normal bone formation rates or adynamic bone disease)
Allocation concealment (selection bias)	Low risk	"A statistician who had no information about the clinical or biochemical characteristics of the study participants randomised the qualified subjects according to initial bone histology finding"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding and outcome measurement likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data unlikely to be related to the true outcome
Selective reporting (reporting bias)	Low risk	Additional information on outcomes obtained from authors
Other bias	High risk	Funding by Genetech, San Francisco, Calif., USA

Santos 2010 (preD/Dial)

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Time frame: NS Follow-up period: Every 3 months up to 12 months
Participants	<ul style="list-style-type: none"> Setting: multicentre tertiary units Country: Spain, Portugal CA (12 ± 3 months); GFR (≤ 60 mL/min/1.73 m²) as calculated by Schwartz formula; length below -2 SDS for the same CA and growth velocity below the 50th percentile; conservative treatment or long-term peritoneal dialysis; euthyroid status; nutritional intake assessed by dietary records, providing a daily amount of at least 80% of recommended dietary allowances for calories and 10% of calories from high biologic value proteins Number: treatment group (8 enrolled; 7 completed); control group (8 enrolled; 7 completed) Age (mean $\pm$ SD): treatment group (14.0 ± 1.7 months); control group (14.4 ± 2.2 months) Sex (M/F): 13/3 <p>Exclusion criteria</p> <ul style="list-style-type: none"> Hormonal, neurologic, osseous, genetic, or nephrologic conditions, other than CKD, that are known to interfere adversely with growth; suspected allergy to the study product; treatment with corticosteroids; inadequate metabolic control of CKD (severe hyper-parathyroidism, sustained metabolic acidosis or sodium or water deficits)
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> rhGH Dose: 28 IU/m²/wk (0.33 mg/kg/wk) given daily SC at bedtime for up to 12 months

Santos 2010 (preD/Dial) (Continued)

Control group

- No treatment

Co-interventions: NS

Outcomes	<ul style="list-style-type: none"> • Change in HSDS • Change in height velocity (cm/y) • Adverse effects • Follow-up: completed the study (88%)
Notes	<ul style="list-style-type: none"> • Exclusions post intervention: 1 patient withdrawn from each group and excluded from analysis due to poor clinical and metabolic control • Stop or end point/s: NS • Additional data requested from authors: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients stratified for gestational age. No other information provided
Allocation concealment (selection bias)	Low risk	"The process of randomisation was centralized at Novo Nordisk"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding and outcome measurement could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data unlikely to influence outcome
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	High risk	Data Management by Novo Nordisk

BA - bone age; CA - chronological age; CKD - chronic kidney disease; CrCl - creatinine clearance; DM - diabetes mellitus; ESKD - end-stage kidney disease; GFR - glomerular filtration rate; HSDS - height standard deviation score; HVSDS - height velocity standard deviation score; NS - not stated; rhGH - recombinant human growth hormone; SC - subcutaneous

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Ghio 2002 (TP)	Not randomised
Jedrzejewski 2002	Not randomised

Study	Reason for exclusion
Laine 1995	Not randomised

DATA AND ANALYSES

Comparison 1. 28 IU/m²/wk versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HSDS after 1 year of rhGH	9	331	Mean Difference (IV, Random, 95% CI)	0.82 [0.56, 1.07]
1.1 Change in HSDS after 1 year of rhGH	6	247	Mean Difference (IV, Random, 95% CI)	0.84 [0.55, 1.13]
1.2 HSDS after 1 year of rhGH	3	84	Mean Difference (IV, Random, 95% CI)	0.84 [0.16, 1.52]
2 HSDS after 1 year according to treatment status	9	331	Mean Difference (IV, Random, 95% CI)	0.83 [0.57, 1.10]
2.1 Predialysis and dialysis patients	4	154	Mean Difference (IV, Random, 95% CI)	0.93 [0.69, 1.16]
2.2 Transplant patients	5	177	Mean Difference (IV, Random, 95% CI)	0.68 [0.21, 1.15]
3 Change in height SDS according to pubertal status	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 Prepubertal	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Entering puberty	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Pubertal	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Height velocity (cm/6 mo) after 6 months of rhGH	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Baseline to 6 months	2	27	Mean Difference (IV, Random, 95% CI)	2.85 [2.22, 3.48]
5 Height velocity (cm/y) after 1 year of rhGH	8	287	Mean Difference (IV, Random, 95% CI)	3.88 [3.32, 4.44]
5.1 Change in height velocity (cm/y) after 1 year of rhGH	3	107	Mean Difference (IV, Random, 95% CI)	4.07 [2.57, 5.58]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.2 Growth velocity (cm/y) after 1 year of rhGH	5	180	Mean Difference (IV, Random, 95% CI)	4.01 [3.28, 4.74]
6 Height velocity (cm/y) according to pubertal status	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6.1 Prepubertal	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Entering puberty	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.3 Pubertal	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7 Change in height velocity SDS	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 Baseline to 6 months	2	27	Mean Difference (IV, Random, 95% CI)	7.80 [6.09, 9.51]
7.2 Baseline to 1 year	2	22	Mean Difference (IV, Random, 95% CI)	6.14 [3.42, 8.86]
8 Growth after 2 years of rhGH	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
8.1 Change in height SDS after 1 year of rhGH	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 Change in height SDS between 1 and 2 years of rhGH	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8.3 Height SDS after 2 years of rhGH	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8.4 Growth velocity (cm/y) after 1 year of rhGH	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8.5 Growth velocity (cm/y) in second year of rhGH therapy	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8.6 Change in growth velocity (cm/y) between 1 and 2 years of rhGH	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9 Change in bone age	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 Baseline to 6 months	2	27	Mean Difference (IV, Random, 95% CI)	-0.15 [-1.77, 1.48]
9.2 Baseline to 1 year	4	202	Mean Difference (IV, Random, 95% CI)	0.02 [-0.27, 0.31]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.3 1 to 2 years	1	82	Mean Difference (IV, Random, 95% CI)	0.40 [-0.99, 1.79]

Analysis 1.1. Comparison 1 28 IU/m²/wk versus placebo/no treatment, Outcome 1 HSDS after 1 year of rhGH.

Analysis 1.2. Comparison 1 28 IU/m²/wk versus placebo/no treatment, Outcome 2 HSDS after 1 year according to treatment status.

Analysis 1.3. Comparison 1 28 IU/m²/wk versus placebo/no treatment, Outcome 3 Change in height SDS according to pubertal status.

Analysis 1.4. Comparison 1 28 IU/m²/wk versus placebo/no treatment, Outcome 4 Height velocity (cm/6 mo) after 6 months of rhGH.

Analysis 1.5. Comparison 1 28 IU/m²/wk versus placebo/no treatment, Outcome 5 Height velocity (cm/y) after 1 year of rhGH.

Analysis 1.6. Comparison 1 28 IU/m²/wk versus placebo/no treatment, Outcome 6 Height velocity (cm/y) according to pubertal status.

Analysis 1.7. Comparison 1 28 IU/m²/wk versus placebo/no treatment, Outcome 7 Change in height velocity SDS.

Analysis 1.8. Comparison 1 28 IU/m²/wk versus placebo/no treatment, Outcome 8 Growth after 2 years of rhGH.

Analysis 1.9. Comparison 1 28 IU/m²/wk versus placebo/no treatment, Outcome 9 Change in bone age.

Comparison 2. 28 IU/m²/wk versus 14 IU/m²/wk

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Final or change in HSDS	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Baseline to 1 year	4	145	Mean Difference (IV, Random, 95% CI)	0.20 [-0.09, 0.48]
1.2 Baseline to 6 months	2	80	Mean Difference (IV, Random, 95% CI)	0.20 [-0.33, 0.73]
1.3 6 months to 1 year	2	80	Mean Difference (IV, Random, 95% CI)	0.12 [-0.43, 0.68]
2 Final/change in height velocity (cm/ time period)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Baseline to 6 months	2	80	Mean Difference (IV, Random, 95% CI)	1.96 [0.86, 3.05]
2.2 6 months to 1 year	2	80	Mean Difference (IV, Random, 95% CI)	-0.53 [-1.65, 0.59]
2.3 Baseline to 1 year	4	150	Mean Difference (IV, Random, 95% CI)	1.18 [0.52, 1.84]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Final/change in height velocity SDS	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Baseline to 1 year	3	106	Mean Difference (IV, Random, 95% CI)	1.48 [0.03, 2.93]
3.2 Baseline to 6 months	3	103	Mean Difference (IV, Random, 95% CI)	2.06 [0.81, 3.31]
3.3 6 months to 1 year	2	80	Mean Difference (IV, Random, 95% CI)	-0.65 [-2.09, 0.80]

Analysis 2.1. Comparison 2 28 IU/m²/wk versus 14 IU/m²/wk, Outcome 1 Final or change in HSDD.

Analysis 2.2. Comparison 2 28 IU/m²/wk versus 14 IU/m²/wk, Outcome 2 Final/change in height velocity (cm/time period).

Analysis 2.3. Comparison 2 28 IU/m²/wk versus 14 IU/m²/wk, Outcome 3 Final/change in height velocity SDS.

Comparison 3. 56 IU/m²/wk versus 28 IU/m²/wk

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in HSDS	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Change in height velocity (cm/y)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Baseline to 1 year	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 3.1. Comparison 3 56 IU/m²/wk versus 28 IU/m²/wk, Outcome 1 Change in HSDS.

Study or subgroup	56 IU rhGH		28 IU rhGH		Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)		
Hokken-K 1994 (TP)	7	1 (1.1)	9	0.7 (1.6)		0.3[-1.1,1.6]

Analysis 3.2. Comparison 3 56 IU/m²/wk versus 28 IU/m²/wk, Outcome 2 Change in height velocity (cm/y).

Study or subgroup	56 IU rhGH		28 IU rhGH		Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)		
3.2.1 Baseline to 1 year						
Hokken-K 1994 (TP)	7	7.8 (2.1)	9	6.7 (2.7)		1.1[-1.23,3.43]

ADDITIONAL TABLES

Table 1. Reported adverse effects

Studies	Adverse effects
Broyer 1996 (TP)	One patient on rhGH developed BIH. There were 22 episodes of acute rejection in 10 treated patients and 9 episodes in 7 control patients.
Fine 1994 (preD)	Asthma/wheezing was reported in 8/55 children in the rhGH group and 0/27 children in the control group (RD 0.15, 95% CI 0.01 to 0.26). There were 3 episodes of acute rejection in control patients and none in rhGH treated children.
Fine 2002 (TP)	During 1 year study, 3 control and 0 rhGH treated patients had rejection episodes. No graft loss in 1 year study. Other reported adverse effects: PTLD (1 control); Hodgkin's Lymphoma (1 treated); BIH (1 control); headache with normal CSF pressure (1 treated); DM (1 in each group); infection (3 treated, 2 control); TIA (1 treated), genu valgum (1 treated).
Callis 1996 (preD)	Kidney function fell in 9/21 and 11/23 respectively of the treatment groups

Table 1. Reported adverse effects (Continued)

Hertel 2002 (preD/Dial)	14 IU group: DM (1); hypertension (1); injection pain (1). 28 IU group: injection pain (2)
Hokken-K 1991 (preD/Dial)	Reported 'no adverse effects.'
Hokken-K 1994 (preD/Dial)	Acute rejection and deterioration of kidney function reported - group not specified.
Hokken-K 1994 (TP)	Reported 'no adverse effects.'
Hokken-K 1996 (TP)	Reported 'no acute rejection or serious deterioration of kidney function during rhGH therapy.'
Ito 1997 (TP)	Episodes of rejection were reported in 5/13 children in the 1.0 IU group and 2/10 children in the 0.5 IU group (RD 0.18, 95% CI -0.21 to 0.51). Glucose intolerance in 2/13 in 1.0 IU group.
Kitagawa 1997 (Dial); Kitagawa 1997 (preD)	More patients in the 1.0 IU than in the 0.5 IU group showed signs of deterioration in kidney function. Glucose intolerance (2), granuloma formation at the exit site of the Tenckhoff catheter, lymph node swelling in the groin, claudication, and hypertension reported - group not specified.
Kuizon 1998 (Dial)	Not addressed
Maxwell 1998a (TP); Maxwell 1998b (TP)	Eight presumed rejection episodes in 13 patients in the treatment group and in 9 patients in the control group. One patient on rhGH had raised fasting glucose. One patient in the control group developed worsening of a pre-existing idiopathic scoliosis.
Powell 1997 (preD)	None reported.
Sanchez 2002 (TP)	Not addressed
Santos 2010 (preD/Dial)	There were 29 adverse events: 9 in the rhGH group and 20 in the untreated group, none were considered related to rhGH therapy.

BIH - benign intracranial hypertension; DM - diabetes mellitus; PTLD - post-transplant lymphoproliferative disease; rhGH - recombinant human growth hormone; TIA - transient ischaemic attack:

APPENDICES

Appendix 1. Electronic search strategies

Database	Search strategy
CENTRAL	<ol style="list-style-type: none"> 1. GROWTH HORMONE 2. SOMATOTROPIN 3. (growth next hormone) or (rhGh) or (hGH) 4. somatotropin 5. (#1 or #2 or #3 or #4) 6. KIDNEY FAILURE CHRONIC 7. ((chronic next kidney next failure) or (chronic next renal next failure)) 8. DIALYSIS EXTRACORPOREAL 9. dialysis 10. KIDNEY TRANSPLANTATION 11. ((kidney next transplant) or (renal next transplant)) 12. ((end next stage next renal next disease) or (end next stage next renal next failure) or (end next stage next kidney next disease) or (end next stage next kidney next failure))

(Continued)

	13. (#6 or #7 or #8 or #9 or #10 or #11 or #12)
	14. (#5 and #13)
MEDLINE	<ol style="list-style-type: none"> 1. exp somatotropin/ or "growth hormone".mp. 2. exp kidney failure, chronic/ or "chronic kidney failure".mp. 3. exp dialysis/ or exp peritoneal dialysis/ or exp peritoneal dialysis, continuous ambulatory/ or "dialysis".mp. 4. exp hemodialysis/ or exp hemodialysis units, hospital/ or exp hemodialysis, home/ or "hemodialysis".mp. 5. exp kidney transplantation/ or "kidney transplantation".mp. 6. "END-STAGE RENAL DISEASE".mp. 7. or/2-6 8. 1 and 7
EMBASE	<ol style="list-style-type: none"> 1. exp growth hormone/ or "growth hormone".mp. 2. exp chronic kidney failure/ or "chronic kidney failure".mp. 3. exp continuous ambulatory peritoneal dialysis/ or exp dialysis/ or exp home dialysis/ or exp peritoneal dialysis/ or "dialysis".mp. 4. exp hemodialysis/ or "hemodialysis".mp. 5. exp kidney transplantation/ or "kidney transplantation".mp. 6. "END-STAGE RENAL DISEASE".mp. 7. 1 or 2 or 3 or 4 or 5 or 6

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	<p><i>Low risk of bias:</i> Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).</p> <p><i>High risk of bias:</i> Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.</p> <p><i>Unclear:</i> Insufficient information about the sequence generation process to permit judgement.</p>
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	<p><i>Low risk of bias:</i> Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).</p> <p><i>High risk of bias:</i> Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.</p> <p><i>Unclear:</i> Randomisation stated but no information on method used is available.</p>

(Continued)

Blinding of participants and personnel

Performance bias due to knowledge of the allocated interventions by participants and personnel during the study

Low risk of bias: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.

High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.

Unclear: Insufficient information to permit judgement

Blinding of outcome assessment

Detection bias due to knowledge of the allocated interventions by outcome assessors.

Low risk of bias: No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.

High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.

Unclear: Insufficient information to permit judgement

Incomplete outcome data

Attrition bias due to amount, nature or handling of incomplete outcome data.

Low risk of bias: No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.

High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.

Unclear: Insufficient information to permit judgement

Selective reporting

Reporting bias due to selective outcome reporting

Low risk of bias: The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Unclear: Insufficient information to permit judgement

Other bias

Bias due to problems not covered elsewhere in the table

Low risk of bias: The study appears to be free of other sources of bias.

(Continued)

High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.

Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

WHAT'S NEW

Date	Event	Description
30 January 2012	Review declared as stable	This review is no longer being updated

HISTORY

Protocol first published: Issue 3, 1999

Review first published: Issue 4, 2001

Date	Event	Description
9 January 2012	New citation required but conclusions have not changed	No change to conclusions
9 January 2012	New search has been performed	New studies added; flow chart added; summary of findings tables added; risk of bias assessment has replaced quality assessment
1 October 2008	Amended	Converted to new review format.
22 May 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

- EH and NW screened titles and abstracts of new searches, independently extracted data and updated the review in 2006 and 2011.
- JC resolved any disagreement through discussion and consultation.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Small Grants Scheme of the Children's Hospital at Westmead, Australia.

External sources

- Cochrane Child Health Field Bursary, Canada.
- Australian Kidney Foundation, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Risk of bias assessment tool has replaced quality assessment checklist.

INDEX TERMS

Medical Subject Headings (MeSH)

Body Height [drug effects]; Growth Disorders [*drug therapy] [etiology]; Human Growth Hormone [adverse effects] [*therapeutic use]; Kidney Failure, Chronic [*complications] [therapy]; Randomized Controlled Trials as Topic; Recombinant Proteins [adverse effects] [therapeutic use]

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant; Infant, Newborn