Clinical practice recommendations for growth hormone treatment in children with chronic kidney disease

Jens Drube, Mandy Wan, Marjolein Bonthuis, Elke Wühl, Justine Bacchetta, Fernando Santos, Ryszard Grenda, Alberto Edefonti, Jerome Harambat, Rukshana Shroff, Burkhard Tönshoff and Dieter Haffner, on behalf of the European Society for Paediatric Nephrology Chronic Kidney Disease Mineral and Bone Disorders, Dialysis, and Transplantation Working Groups

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Supplementary Box 1 | Cost-effectiveness analysis

Most pediatric CKD patients have advanced CKD at the time of initiation of GH treatment, and will undergo renal transplantation when GH treatment is terminated. The duration of GH treatment is mainly determined by the age at onset of CKD, its rate of progression and the availability of a renal transplant. Therefore, our cost-effectiveness analysis included two hypothetical scenarios: (i) case 1, a child with early-onset CKD requiring GH therapy at the age of 5 years, (ii) case 2, an adolescent with late onset or slowly progressive CKD requiring GH treatment at the age of 12 years. The mean duration of GH treatment in studies reporting on final height ranged between 2 and 5 years; therefore, we used this range to estimate the cumulative drug-related costs. In addition, the estimates for drug dose were based on daily GH doses of 0.045 mg/kg body weight and were calculated for the respective age- and sex-related 25th weight percentile using the WHO reference data, assuming that patients will have a height below the 3rd percentile at the time of initiation of GH treatment and will show catch-up growth into the lower normal range thereafter (Supplementary Table 5) [S1].

Since the costs for patient monitoring are less than 3% of total treatment-related costs, only drug-related costs were taken into account for this analysis [S2]. The cost for GH differs considerably among European countries, and a price of €22 per 1 mg GH, based on the median cost in eight representative European countries, was used (Supplementary Table 6).

In clinical studies the height standard deviation score (height SDS) is often used to compare growth in children differing in age and sex. Height SDS is a conversion of height (or length) that represents the number of standard deviations (SD) from the mean height for age and sex. A child with a height SDS less than -1.88, which corresponds to the 3rd percentile, has short stature. Therefore, the mean increase in final height in GH treated patients was calculated as the difference between standardized final height (height SDS) and standardized height at the start of GH therapy for all available studies reporting on adult height with treatment periods of at least 2 years (Supplementary Table 4). The median increase in standardized height in these studies (1.1 SDS) was converted to cm (7.4 cm in boys, 7.0 cm in girls) by use of European reference values. Thus, an expected gain in final height of 7.2 cm was used in the cost-effectiveness analysis; that is, a calculation of the incremental cost per centimeter gained in final height [S3].
Supplementary Table 1 | Inclusion and exclusion criteria used in 18 randomized clinical trials (RCTs) of GH treatment in children with chronic kidney disease.

| Ref. | Major inclusion criteria | Major exclusion criteria |
|------|--------------------------|--------------------------|
| Bacchetta et al. (2013) [S4] | CKD stage 5D | Poor medical adherence |
| | Age 2–21 yrs. | Parathyroidectomy |
| | No auxological inclusion criteria given | Epiphysial growth plate closure |
| | | Treatment with prednisone or any other immunosuppressive agent |
| Santos et al. (2010) [S5] | CKD stage 3–5D | Non-CKD related hormonal, genetic, neurologic, osseous conditions |
| | Well-nourished | Suspected allergy to the trial product |
| | Age 12 ± 3 months | Treatment with corticosteroids |
| | Length <–2.0 SDS and HV < 50th percentile | Inadequate metabolic control of CKD (severe sHPT, acidosis, sodium or water deficits) |
| Hertel et al. (2002) [S6] | CKD (eGFR <40 ml/min/1.73 m² or on dialysis) | Abnormal thyroid status |
| | Age 3–18 years | Endocrine or metabolic disease other than sHPT |
| | BA <12 yrs (girls), < 10 yrs (boys) | Growth retardation due to failure of other organs, or psychosocial dwarfism |
| | Height < –2.0 SDS and HV velocity SDS <0.0 | |
| Fine et al. (2002) [S7] | CKD stage 5T | Specific cause for the growth retardation other than those implicated in renal allograft recipients |
| | Height < –2.0 SDS | Active malignancy or treated for a malignancy within one year |
| | BA < 15 yrs (girls), < 16 yrs (boys) | Diabetes mellitus |
| | | Gonadotropin deficiency on estrogen/androgen therapy |
| | | Deformities obviating accurate height measurements |
| | | Other investigational drug within 6 months of the study |
| Sanchez et al. (2002) [S8] | CKD stage 5T | Willingness to undergo bone biopsy procedure |
| | Prepubertal | Histological evidence of sHPT |
| | Normal bone formation rate or adynamic bone disease on bone histomorphometric analysis | |
| | No auxological inclusion criteria given | |
| Kuizon et al. (1998) [S9] | CKD stage 5D on PD | Not given |
| | No auxological inclusion criteria given | |
| Maxwell et al., (1998) [S10] | CKD stage 5T | Height velocity > 75th percentile during the preceding 6 months |
| | At least 1 year after KTx | Treatment with any form of GH in the past year |
| | eGFR >20 ml/min/1.73m² | Previous malignancy |
| | Height <3rd percentile | Severe congenital abnormality |
| | or HV <25th percentile | Diabetes mellitus |
| | Normal thyroid function | Uncontrolled renal bone disease |
| Powell et al. (1997) [S11] | CKD (eGFR >5 and <75 ml/min/1.73 m²) | Serum albumin <2.5 g/dl |
| | Age > 2.5 years | Medications which influence growth |
| | Ability to stand for height measurement | Presence of illnesses affecting growth |
| | BA < 10 yrs (girls), < 11 yrs. (boys) | Diabetes mellitus |
| | Prepubertal | Present or past history of malignancy |
| Ito et al. (1997) | CKD (eGFR <40 ml/min/1.73 m² or on dialysis) | Not given |
| Reference                          | Criteria                                                                 | Additional Information                                      |
|-----------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------|
| Kitagawa et al. (1997) [S13]      | • CKD (eGFR < 40 ml/min/1.73 m²)                                         | • Not given                                                 |
|                                   | • BA < 12 yrs (girls), < 13 yrs (boys)                                    |                                                             |
|                                   | • Prepubertal                                                             |                                                             |
|                                   | • Height or HV < −2.5 SDS                                                 |                                                             |
| Broyer et al. (1996) [S14]        | • CKD stage 5T                                                           | • Not given                                                 |
|                                   | • Prepubertal                                                             |                                                             |
| Kawaguchi et al. (1996) [S15]     | • CKD (eGFR < 40 ml/min/1.73 m² or on dialysis)                           | • Not given                                                 |
|                                   | • BA < 12 yrs (girls), < 13 yrs (boys)                                    |                                                             |
|                                   | • Prepubertal                                                             |                                                             |
|                                   | • Height or HV < −2.5 SDS                                                 |                                                             |
|                                   | • CKD stage 5T (eGFR > 30 ml/min/1.73 m²)                                 |                                                             |
|                                   | • BA < 13 yrs (girls), < 14 yrs (boys)                                    |                                                             |
| Hokken-Koelega et al. (1996) [S16]| • CKD stage 5T                                                           | • Thyroid dysfunction                                       |
|                                   | • Height < −1.88 SDS and HV < 25th percentile                             | • Metabolic acidosis                                        |
|                                   | • Prepubertal                                                             | • Previous sex hormone treatment                             |
|                                   | • BA < 10 yrs (girls), < 12 yrs (boys)                                    | • Growth retardation due to other causes                    |
| Fine et al. (1995) [S17]          | • CKD (eGFR > 5 and < 75 ml/min/1.73 m²)                                 | • Specific cause of growth retardation other than CKD       |
|                                   | • Age < 2.5 yrs                                                           | • Inability to obtain accurate height measurements (e.g. severe scoliosis, meningomyelocele) |
|                                   | • BA < 10 yrs (girls), < 11 yrs (boys)                                    | • Medications that influence growth                         |
|                                   | • Prepubertal                                                             | • Diabetes mellitus                                         |
|                                   | • Height < 3rd percentile                                                 | • Active malignancy or treated for a malignancy within the past year |
| Hokken-Koelega et al. (1994) [S18]| • CKD (eGFR < 20 ml/min/1.73 m² or on dialysis)                           | • Specific cause of growth retardation other than CKD       |
|                                   | • Height < −1.88 SDS and HV < 50th percentile or                         | • Hypothyroidism                                            |
|                                   | • Height < 0.0 SDS and HV < 25th percentile                                | • Metabolic acidosis                                        |
|                                   | • Prepubertal                                                             | • Clinical or radiographic signs of osteodystrophy          |
|                                   | • BA < 10 yrs (girls), < 12 yrs (boys)                                    | • No previous treatment with anabolic or sex steroids       |
| Hokken-Koelega et al. (1994) [S19]| • > 12 months after KTx                                                   | • Specific cause of growth retardation other than CKD       |
|                                   | • > 6 months no history of rejections                                     | • Hypothyroidism                                            |
|                                   | • Height < −1.88 SDS and HV < 50th percentile or                         | • Metabolic acidosis                                        |
|                                   | • Height < 0.0 SDS and HV < 25th percentile                                | • No previous treatment with anabolic or sex steroids       |
|                                   | • Prednisone dosage < 0−0.25 mg per kg per day or 0.50 mg per kg every other day for 6 months |                                                             |
|                                   | • BA < 8 yrs (girls), < 10 yrs (boys)                                     |                                                             |
| Fine et al. (1994) [S20]          | • CKD (eGFR > 5 and < 75 ml/min/1.73 m²)                                 | • Specific cause of growth retardation other than CKD       |
|                                   | • Prepubertal                                                             | • Inability to obtain accurate height                      |
| Conditions                                                                 | Treatment                                                                 |
|----------------------------------------------------------------------------|---------------------------------------------------------------------------|
| BA <10 yrs (girls), <11 yrs (boys)                                         | Corticosteroids or other medications than influence growth                 |
| Height < 3rd percentile                                                     | Diabetes mellitus                                                         |
|                                                                             | Active malignancy or treated for a malignancy within the past year         |
|                                                                             | Other investigational drug within 2 months of assignment into the study   |
| Hokken-Ko elega et al. (1991) [S21]                                         | Specific cause of growth retardation other than CKD                        |
| CKD (eGFR < 20 ml/ min/1.73 m² or on dialysis)                             | Hypothyroidism                                                             |
| Height < -1.88 SDS and HV < 25th percentile                                | Metabolic acidosis                                                        |
| Prepubertal                                                                | Clinical or radiographic signs of osteodystrophy                           |
| BA < 10 yrs (girls), < 12 yrs (boys)                                       | Previous treatment with anabolic or sex steroids                            |

BA, bone age; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GH, growth hormone; KTx, kidney transplantation; HV, height velocity; SDS, SD score; sHPT, secondary hyperparathyroidism.
### Supplementary Table 2 | 18 RCTs and a meta-analysis on GH therapy in children with CKD included in the systematic review

| Ref. (country of origin) | Study design | Patients | Intervention and comparator | Outcomes |
|-------------------------|-------------|----------|-------------------------------|----------|
| Bacchetta et al. (2013) [S4] (USA) | Single center, RCT, open labeled | 33 patients with CKD stage 5D (all on PD) GH: n=15 (M/F 6/9), prepubertal: 8/15, low–normal bone turnover n=7, high bone turnover n=8 Controls: n=18 (M/F 9/9), prepubertal 9/18, low–normal bone turnover n=7, high bone turnover n=11 | GH: 0.05 µg/kg/d s.c. Controls: No GH In addition, patients with high bone turnover received 1µg calcitriol thrice weekly | Delta height SDS, GH vs. no- GH 0.32±0.08 (P<0.01). Bone formation rate increased in patients with low bone turnover and normalized (decreased) in patients with high bone turnover receiving GH therapy (each P <0.05) |
| Hodson et al. (2012) [S22] (Australia) | Cochrane Review comprising: 16 RCTs including 10 RCTs | n=809 (CT, dialysis, KTx) n=560 (CT, dialysis, KTx); most patients prepubertal or early pubertal | GH, 28 IU/m² per wk daily vs. placebo or no treatment | Delta height SDS at 1 year: 0.82 (95% CI 0.56–1.07) independent of pubertal status and CKD stage Increase in HV: at 6 months, 2.85 cm/6 mo (95% CI 2.22–3.84); at 12 months, 3.88 cm/yr (95% CI 3.32–4.44) HV greater by 2.3 cm/yr (95% CI 1.39–3.21) than in controls during the 2nd treatment year HV in higher GH dose group exceed that in the lower GH dose by 1.18 cm/yr (95% CI 0.52–1.84) The frequency of reported adverse effects of GH was generally similar to that in control groups |
| Santos et al. (2010) [S5] (Spain) | Multicenter, RCT, open labeled | n=16 (M/F 13/3, CKD stage 3-5D; 3 on PD) Age 12 ± 3 months GH: n=8 Controls: n=8 | GH: 0.33 mg/kg/wk for 12 months Controls: No GH treatment | Length gain in infants treated with GH was higher (P<0.05) than in controls (HV, 14.5 versus 9.5 cm/yr; change in height SDS, 1.43 versus -0.11); GH treatment increased forearm bone mass and serum concentrations of total and free IGF-I and IGFBP-3 |
| Hertel et al. (2002) [S6] (Denmark) | Multicenter, RCT, open labeled | CKD stage 3-5D GH 1: n=14 (M/F 12/2) GH 2: n=15 (M/F | GH 1: 28 IU/m²/wk daily GH 2: 14 IU/m²/wk daily | HV SDS was increased to 3.0 SDS in the 1st year in the low-dose, and to 3.8 SDS in the high-dose group (each P<0.05). In the 2nd year, HV SDS was increased to 1.3 SDS in the |
| Study                        | Design                     | n | Treatment  | Controls | Results                                                                 |
|-----------------------------|----------------------------|---|------------|----------|-------------------------------------------------------------------------|
| Fine et al. (2002) [S7] (USA) | Multicenter, RCT, open labeled | 68 (KTx) | GH: 0.05 mg/kg/d for 12 months | No GH treatment | Low-dose group and to 2.1 SDS in high-dose group (each P<0.05). |
| Sanchez et al. (2002) [S8] (USA) | Single center, RCT, open labeled | 21 (KTx) | GH: 28 IU/m²/wk for 24 months | No GH treatment | Delta height SDS, 0.49 vs. −0.10 (P<0.001); no increased rejection rates on GH; previous rejection was predictive for future rejections on GH treatment; adverse events similar. |
| Kuizon et al. (1998) [S9] (USA) | Multicenter, RCT, open labeled | 14 (CKD stage 5D; all on PD) | GH: 0.05 mg/kg/d (equivalent to 4 IU/m²/d) for 1st yr | No GH treatment | Height SDS after 1 year higher in GH group (−1.4 ± 0.6) compared to controls (−2.2 ± 1.1; P<0.05) |
| Maxwell et al. (1998) [S10] (UK) | Multicenter, RCT, open labeled | 22, CKD stage 5T; M/F 18/4 | GH: 0.05 mg/kg/d for 12 months | No GH treatment | GH: height SDS increased from -2.0±1.1 to −1.1±1.0 (P<0.02) after 12 months. Controls: no significant change; height velocity was greater in GH group versus controls (8.0±2.1 cm/year vs. 4.8±1.7 cm/year, P<0.01) |
| Powell et al. (1997) [S11] (USA) | Multicenter, RCT, open labeled | 44; CKD stage 3–5D; prepubertal 44/44 | GH: 0.05 mg/kg/d for 12 months | No GH treatment | GH: HV, 9.1 ± 2.8 cm; weight gain, 3.5 ± 1.5 kg (each P<0.01 GH vs. controls) |
| Ito et al. (1997) [S12] (Japan) | Multicenter, RCT, open labeled | 29 (M/F 5/24); CKD stage 3–5 n=21; dialysis n= 8 | GH: 0.5 IU/m²/d vs. 4 IU/m²/d for 12 months. Thereafter, 4 IU/m²/d for 12 months | No GH treatment | Significant increase in height SDS, HV and HV SDS in GH group compared to pre-treatment (each P<0.05); no significant difference between different treatment groups |
| Kitagawa et al. (1997) [S13] (Japan) | Multicenter, RCT, open labeled | CKD stage 5D, prepubertal | GH 0.5: 0.5 IU/kg/wk daily for 24 months | GH 1.0: 1.0 | Height SDS: GH 0.5: no significant increase during the 1st yr. GH 1.0: significant increase during the 1st yr (P<0.05). |
| Study | Design | Participants | GH | IU/kg/wk daily for 24 months | HV | Height SDS | Change in HV and delta height SDS during the 1st yr higher in GH group vs. controls (each \( P < 0.0001 \)). 2nd yr, HV remained greater in GH group compared to baseline resulting in further increase in height SDS |
|-------|--------|--------------|-----|---------------------------|----|------------|-------------------------------------------------------------|
| GH 1.0: n=28 (M/F 17/11) | IU/kg/wk daily for 24 months | GH 0.5: 0.5 IU/kg/wk daily for 24 months | GH 1.0: 1.0 IU/kg/wk daily for 24 months | Height SDS: Significant increase in both groups (each \( P < 0.05 \)). HV: Significant increase in both groups (each \( P < 0.05 \)). HV SDS: In both groups significant increase during the 1st and 2nd yr compared to baseline (each \( P < 0.01 \)) |
| CKD 3–5D, prepubertal GH 0.5: n=28 (M/F 19/9) GH 1.0: n=30 (M/F 22/8) | IU/kg/wk daily for 24 months | GH 0.5: 0.5 IU/kg/wk daily for 24 months | GH 1.0: 1.0 IU/kg/wk daily for 24 months | Height SDS: Significant increase in both groups (each \( P < 0.05 \)). HV: Significant increase in both groups (each \( P < 0.05 \)). HV SDS: In both groups significant increase during the 1st and 2nd yr compared to baseline (each \( P < 0.01 \)) |
| Broyer et al. (1996) [S14] (France) Multicenter RCT, open labeled | GH: n=106 (n=67 prepubertal, M/F 71/35, KTx 106/106) Control: n= 97 (n=51 prepubertal M/F 72/25, KTx 97/97) | Change in HV and delta height SDS during the 1st yr higher in GH group vs. controls (each \( P < 0.0001 \)). 2nd yr, HV remained greater in GH group compared to baseline resulting in further increase in height SDS |
| Kawaguchi et al. (1996) [S15] (Japan) Multicenter, RCT, open labeled | n=83; CKD stage 3–5D/T (including 23 KTx patients) GH 0.5: n=54 (CKD stage 3–5D n=28; M/F 34/20) GH 1.0: n=58 (CKD stage 3–5D n=30; M/F 39/19) GH: 30 IU/m²/ wk daily Control: no GH treatment | CKD stage 3–5: HV significantly increased in both groups, and was higher in GH 1.0 vs. GH 0.5 (each \( P < 0.01 \)). CKD stage 5D: HV significantly increased in both groups, and was higher in GH 1.0 vs. GH 0.5 (each \( P < 0.01 \)). CKD stage 5T: HV increased in both groups (each \( P < 0.05 \)) and did not differ between groups; 7/23 patients showed acute rejection episodes. |
| Hokken-Koelega et al. (1996) [S16] (Netherlands) Multicenter, RCT, open labeled | n=11; CKD stage 5T; prepubertal GH: n=6 (M/F 4/2) Controls: n=5 (M/F 4/1) GH: 28 IU/m²/ wk daily for 6 months Controls: placebo | HV exceeded that of placebo by 2.9 cm/6 months; no acceleration of bone maturation; no change in eGFR; increase in IGF-I and integrated insulin levels during GH |
| Fine et al. (1995) [S17] (USA) Multicenter, RCT, open labeled | n=30; age <2.5 yrs. GH: n=19 (M/F16/3); CKD stage 3–5 Controls: n=11 (M/F 7/4); CKD 3–5 GH: 0.05 mg/kg/day Controls: placebo | HV, 1st yr: 14.1 vs. 9.3 cm/yr; 2nd yr: 8.6 vs. 6.9 cm/yr (each \( P < 0.05 \)). Delta height SDS, 2.0 vs. –0.2 during 2 yrs. (\( P < 0.0001 \)) |
| Hokken-Koelega et al. (1994) [S18] (Netherlands) Multicenter, RCT, open labeled | n=23; CKD 4-5 n=8; CKD stage 5D n=15; prepubertual 23/23 GH 1: n=12 (M/F 11/1) GH 1: 28 IU/m²/ wk daily GH 2: 14 IU/m²/ wk daily | HV SDS comparable during 6 months; HV SDS higher at high dose in 2nd yr.; no further catch-up in 2nd year on low dose GH |
| Study | Design | GH 1: n=7 (M/F 4/3); prepubertal n=2, Tanner stage 2–3 n=5 | GH 2: n=9 (M/F 5/4); prepubertal n=4, Tanner stage 2–3 n=5 | GH 1: 56 IU/m²/wk daily | GH 2: 28 IU/m²/wk daily | Height increment during 2 yr. GH treatment was 15.7 (5.1) cm and 5.8 (3.4) cm in controls (P<0.0001). Similar results in both GH groups |
|-------|--------|--------------------------------------------------------|--------------------------------------------------------|--------------------------|--------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| Hokken-Koelega et al. (1994) [S19] (Netherlands) | Multicenter, RCT, open labeled | n=16, KTx | GH 1: n=7 (M/F 4/3); prepubertal n=2, Tanner stage 2–3 n=5 | GH 1: 56 IU/m²/wk daily | GH 2: 28 IU/m²/wk daily | Height SDS after 2 yrs: GH −1.55 vs. −2.94; Controls, −2.91 vs. −2.82 (P<0.0001). HV: GH, 10.7 cm/yr (1st yr), 7.8 cm/yr (2nd yr); controls, 6.5 cm/yr (1st yr), 5.5 cm/yr (2nd yr); each P<0.0001 |
| Fine et al. (1994) [S20] (USA) | Multicenter, RCT, double blinded | GH: n=82 (M/F 61/21); prepubertal 82/82 | Control: n=43 (M/F 28/14) prepubertal 43/43 eGFR <75 ml/min/1.73 m² | GH: 0.05 mg/kg/d Control: placebo | Height SDS after 2 yrs: GH −1.55 vs. −2.94; Controls, −2.91 vs. −2.82 (P<0.0001). HV: GH, 10.7 cm/yr (1st yr), 7.8 cm/yr (2nd yr); controls, 6.5 cm/yr (1st yr), 5.5 cm/yr (2nd yr); each P<0.0001 |
| Hokken-Koelega et al. (1991) [S21] (Netherlands) | Multicenter, RCT, double blinded crossover | GH: n=8 (M/F 6/2) Controls: n=8 (M/F 4/4) eGFR <20 ml/min/1.73 m² | GH: 28 IU/m²/wk for 6 months Controls: placebo | HV in GH group was significantly higher compared to controls by 2.9 cm per 6 months (P<0.05) |

Data are given as mean ± SD if not indicated otherwise. CKD, chronic kidney disease; CT, conservative treatment (CKD prior to dialysis); eGFR, estimated glomerular filtration rate; F, female; GH, growth hormone; HV, height velocity; KTx, kidney transplantation; M, male; PD, peritoneal dialysis; RCT, randomized controlled trial; s.c., subcutaneous; SDS, standard deviation score; SE, standard error
| Ref. (country of origin) | Study design | N | Population characteristics | GH dosage | Outcomes |
|-------------------------|--------------|---|---------------------------|-----------|----------|
| Nawrot-Wawrzynia et al. (2013) [S23] (Austria) |Observational study|18|CKD stage 5, n=18 (M/F 13/3) age 3.6–16 yrs. pubertal stage Tanner stage 1: n=15/18 Tanner stage 2: n=3/18 |1.0–1.1 IU/kg/wk daily for 12 months | • Bone mineralization density distribution: patients had low bone turnover (P<0.05); heterogeneity in mineralization.  
• After GH treatment, height increased by 9.1 cm (P <0.001) and bone turnover indices to normal values or beyond  
• Lower and more heterogeneous matrix mineralization compared to baseline |
| Youssef et al. (2012) [S24] (Egypt) |Crossover non-randomized controlled clinical trial|15|CKD stage 5, n=15 (M/F 7/8) age 10.6 ± 2.8 yrs (range 5–14 yrs.); pubertal stage not given |0.33 mg/kg/wk (0.8 IU/kg/wk) three times per wk for 1 year | • The year before therapy, increase of height was not statistically significant (P >0.05)  
• The year before therapy growth velocity was 0.6 cm/year  
• Under GH therapy, height increase was statistically not significant (P>0.05)  
• Under GH therapy: growth velocity, 4.1 cm/year |
| Müller-Wiefel et al. (2010) [S25] (Germany) |Open-label, international, multicenter study|81|CKD stage 3–5 n=37; CKD 5D n=27; KTx n=17 (M/F 58/23); age 8.6 ± 3.9 yrs; pubertal stage not given |0.35 mg/kg/wk daily for 12 months then extended to 2–5 yrs. |Change in HV and height versus baseline  
• After 12 months of treatment: HV: 4.6 ± 3.1 to 9.0 ± 3.6 cm/yr (P<0.001). Mean height SDS: –3.7 ± 1.7 to –3.0 ±1.7 (P<0.001). Mean HV SDS –2.4 ± 2.5 to 3.8 ± 4.5 (P< 0.001).  
• After 24 months of treatment: HV: 4.5 ± 3.3 to 7.5 ± 2.9 cm/yr (P<0.001). Mean height SDS: –3.6 ± 1.5 to –2.5±1.5 (P<0.001). Mean HV SDS: –2.4 ± 2.2 to 1.1 ± 0.8 (P<0.001).  
Normal height SDS was noted in 1% of children at baseline, 17% after 12 months and 43% after 24 months of GH therapy |
| Mencarelli et al. (2009) [S26] (Italy) |Retrospective study|27|CKD stage 3–5D Infants. GH: n=12 (M/F 9/3 Controls: n=15 (M/F 11/4). Higher frequency of ESRD in GH group |0.24 ± 0.07 mg/kg/wk daily |Height SDS: between the age of 0.5 and 2.5 years, the height SDS increased from –2.0 ± 1.2 to –0.9 ± 0.9 in the GH group (P < 0.005) and from –1.6 ± 1.6 to –1.0 ± 1.9 in the control group (P>0.05) |
| Kari et al. |Retrospective|32|CKD stage 3–5 |28 IU/m2/wk | CKD stage 3–5: height SDS |
| Reference | Study Type | N | CKD Stage | Gender Distribution | Pubertal Status | GH Dose | Mean HV Change | Significance | Additional Notes |
|-----------|------------|---|-----------|---------------------|----------------|---------|---------------|-------------|----------------|
| [S27] | study | n=21; CKD 5D n=11 (M/F 23/9); age: 8.3 ± 3.7 yrs; pubertal stage not given | daily until KTx over a mean period of 3.7 ± 2.0 years | improved from −2.5±1.4 to −2.1±0.7 at 1 yr, −2.0±0.7 at 2 yrs, and −1.6±0.6 at 3 yrs (each P<0.05). CKD stage 5D: height SDS improved from −2.7±0.5 to −2.3±0.5 at 1 yr (P<0.05). Thereafter, no further change. | |
| [S28] | Prospective study | 9 | CKD stage 5D n=9; gender distribution and age not given; all prepubertal | 0.05 mg/kg/d, intraperitoneal | Height SDS was −3.1 at baseline, −2.5 at 1 yr, and −2.3 at 2 yrs (P<0.05). Mean HV increased from 4.6 cm/yr to 8.5 cm/yr in the 1st yr (P<0.05) and 6.1 cm/yr during 2nd yr (P<0.05 vs. baseline). No increased peritonitis infection rates. | |
| [S29] | Multicenter, controlled, follow-up of previous trial: [S18, S21] | 45 | CKD stage 5D n=27 (PD:HD 18:9); CKD stage 3–5, n=18 (M/F 28/17); age 7.3 yrs; all prepubertal | 3.8 IU/m2/d for a maximum of 8 yrs | Significant increment in mean height SDS over baseline values (P<0.001), both in the total group of children with intermediate- and long-term GH therapy (n=45) as well as in those treated with GH for 6 (n=11) and 8 yrs (n=7). | |
| [S30] | Multicenter prospective study | 103 | CKD stage 3–5D n=74 (eGFR 26 ± 2 ml/min/1.73m²); CKD stage 5D n=29 (M/F 70/33) Age 8.5 yrs. all prepubertal | 28 to 30 IU/m²/wk daily up to 5 yrs. | Height SDS in CKD stage 3–5: Baseline −3.4 ± 0.1 1st yr −2.6 ± 0.1 2nd yr −2.1 ± 0.2 3rd yr −1.8 ± 0.3 4th yr −1.7 ± 1.5 5th yr −1.9 ± 1.5 (each P<0.05) Height SDS in CKD stage 5D Baseline −3.6 ± 0.2 1st yr −3.1 ± 0.3 2nd yr −3.0 ± 0.4 3rd yr −3.7 ± 0.8 (each P<0.05). Predicted adult height (+7.7 cm) after 3 yrs of GH treatment (P<0.001) | |
| [S31] | Multicenter prospective study | 42 | CKD stage 5D n=42 (M/F 26/16), age 10.4 ± 4.5 yrs. 34/42 prepubertal 8/42 early puberty | 1 IU/kg/wk daily for 1-5 yrs | 1st year of GH, HV increased from 3.5 to 7.0 cm/year (P<0.0001) and was always over 2.5 cm/year. Height SDS increased by 0.5 SDS. No significant adverse effects were observed | |
| [S32] | Multicenter prospective study | 36 | Cystinosis patients; only CKD stage 2–5D (eGFR 50 ± 27 ml/min/1.73m²) (M/F 20/16), age 7.3 ± 2.7 yrs; pubertal status not given | 1 IU/kg/wk daily for upto 5 yrs | During the 1st year HV increased from 4.1 ± 1.6 cm/yr to 8.8 ± 2.5 cm/yr. Height SDS improved within 1 yr from −4.2±1.0 to −3.3 ± 1.0 (each P<0.05) | |
| [S33] | Prospective study | 56 | CKD stage 3–5, eGFR 26 ± 17 ml/min/1.73m² (M/F 26/12), n=38, 28–30 IU/m²/wk for upto 2 yrs. | HV: CKD stage 3–5, 4.9 cm/yr to 9.5 cm/yr; CKD 5D: 4.6 cm/yr to 7.3 cm/yr (each P<0.05) | |
| Study                                      | Design          | Subjects                                                                 | Delta height SDS: CKD stage 3–5, 1.1 (1st yr), 0.5 (2nd yr); CKD stage 5D 0.5 (1st yr), 0.2 (2nd yr); each $P<0.05$ |
|-------------------------------------------|-----------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| Lanes et al. (1996) [S34] (Venezuela)     | Prospective     | age 6.5 ± 2.4 yrs. CKD stage 5D, n=18 (M/F 6/12), age 6.5 ± 2.0 yrs. all prepubertal | 1 IU/kg/wk daily for 12 months HV increased from 4.3 cm/yr to 9.1 cm/yr and height SDS from –3.5 to 2.6 (each $P<0.05$). GH treatment resulted in normalization of formally reduced bone mineral density. |
| Maxwell et al. (1996) [S35] (Canada)      | Prospective     | age 6.5 ± 2.0 yrs. all prepubertal | 0.14 IU (0.05 mg)/kg/d Height SDS improved from −3.3 to −2.2 ($P<0.01$). HV SDS improved from −1.3 to 1.1 ($P<0.01$). No Change in eGFR |
| Schwartz et al. (1995) [S36] (USA)        | Prospective     | CKD stage 5D n=6 (M/F 4/2); KTx n=9 (M/F 8/1); age 9.1 ± 2.5 yrs. pubertal stage not given | HV SDS increased in both groups compared to baseline (each $P<0.05$); no significant increase in height SDS |
| Fine et al. (1994) [S37] (USA)            | Prospective     | CKD stage 2–5 (eGFR 5–75 ml/min/1.73m²) (M/F 11/0), age 2.5–16.3 yrs.; pubertal stge not given | 8 patients: 0.125 mg/kg thrice weekly for 6 months, then 0.053 mg/kg daily for up to 60 months. 3 patients: 0.053 mg/kg daily for up to 60 months |
| Jabs et al. (1993) [S39] (USA)            | Prospective     | KTx: age 7.4 to 17.7 yrs; prepubertal and pubertal pts | HV increased from 1.7±0.7 to 7.1±1.2 cm/yr during the 1st yr. Height SDS increased from −3.9±1.5 to −3.4±1.3 (each $P<0.001$) |
| Wühl et al. (1993) [S40] (Germany)       | Prospective     | CKD stage 3–5D; KTx; all prepubertal | 28 Prospective study 30 IU/m2/week daily for 12 months Predictors of growth response to GH: 
  - HV inversely correlated with age ($r = −0.63$); and positively correlated with pretreatment HV ($r = 0.65$) 
  - Increment in HV SDS was negatively correlated with pretreatment HV SDS ($r = −0.58$) each $P<0.001$ HV was highest in pts. on CT and lowest on dialysis |
| Reference | Study Details | Participants | Dose Details | Outcomes |
|-----------|---------------|--------------|--------------|----------|
| Tönshoff et al. (1993) [S41] (Germany) | Multicenter, prospective study | 15 KTx (M/F 12/3), age 13.2 yrs; 10/15 pre-pubertal | 30 IU/m² per week daily for 36 months | HV in prepubertal pts (cm/yr): baseline 2.2; 1st yr 7.9; 2nd yr 7.2; 3rd yr 5.5 (each P<0.05) |
| Van Renen et al. (1992) [S42] (Australia) | Prospective study | 9 CKD stage 3–4; eGFR 11–60 ml/min/1.73m² (M/F 9/0), age 4.8–15.6 yrs; prepubertal 5/9 | 30 IU/m²/wk daily for 12 months | Prepubertal: HV increased from 4.6±1.3 to 9.0±1.3 cm/yr (P<0.001); height SDS increased from –2.2±0.7 to –1.5±0.5 (P<0.01). Pubertal: HV increased from 5.4±1.4 to 10.4±1.8 cm/yr (P<0.01). |
| Fine et al. (1992) [S43] (USA) | Prospective study | 13 KTx (M/F 11/2), age 7.6 to 17.7 yrs; prepubertal and pubertal pts. | 0.375 mg/kg per week given daily for 12-36 months | HV SDS increased from 2.7 to 6.3 (12 mo.) and to 5.2 (24 mo.); each P<0.05. eGFR was 66±26 ml/min/1.73m² at baseline, 55±30 ml/min/1.73m² at 1 yr and 52±28 ml/min/1.73m² at 2 yrs. (each P>0.05). |
| Van Dop et al. (1992) [S44] (USA) | Prospective study | 9 KTx, age 12.6±4.0 yrs; 7/9 prepubertal | 0.3 to 0.35 mg/kg/wk given daily, three times per wk or six times per wk | HV: 1.9 ± 1.1 cm/yr to 7.2 ± 1.8 cm/yr (P<0.01) |
| Bartosh et al. (1992) [S45] (USA) | Prospective study | 5 KTx (M/F 4/1), age 15.2±2.0 yrs; all prepubertal | 0.05 mg/kg/day for 1 to 3 yrs | HV (cm/yr): baseline 3.5, 1st yr 8.5 (P<0.05). Height SDS: –4.3 vs. –4.9 (P<0.05) |
| Fine et al. (1991) [S46] (USA) | Prospective study | 9 CKD stage 2–5 eGFR 5–75 ml/min/1.73m² (M/F 9/0), age 2.8–16.3 yrs; pubertal stage I–II | 0.05 mg/kg/day for 1 to 3 yrs | HV increased significantly during GH compared to baseline. No significant change in eGFR |
| Van Es et al. (1991) [S47] (Sweden) | Prospective study | 74 CKD stage 3–5 n=31; prepubertal 31/31 KTx n=43; 26/43 prepubertal | 28–30 IU/m2 per week daily for 24 months | HV (cm/yr): CKD stage 3–5, 9.8 (6.8, 2nd yr) vs. 4.2. Prepubertal KTx: 8.4 (5.4 2nd yr) vs. 3.6. Pubertal KTx: 6.6 (4.5 2nd yr) vs. 3.2. (each P<0.05) |
| Tönshoff et al. (1991) [S48] (Germany) | Prospective study | 43 CKD stage 3–5 n=17; prepubertal 7/17 CKD stage 5D n=13; prepubertal, n=10 KTx n=13; prepubertal 10/13 | 28-30 IU/m² per week daily for 12-24 months | Prepubertal pts. HV (cm/yr): CKD 3–5 10.0 (9.3, 2nd yr) vs. 4.3 (each P<0.05). CKD stage 5D 7.3 vs. 4.2. KTx, 7.9 (8.6, 2nd yr) vs. 2.3 (each P<0.05) |
| Rees et al. (1990) [S49] (UK) | Prospective study | 18 CKD stage 4–5 n=6; all prepubertal; age 7.7 yrs (5.0–10.4) (M/F 5/1) | 30 IU/m² per wk. daily for 12 months | HV: CKD stage 4–5: 4.8 to 10.1 cm/yr KTx (prepubertal): 2.3 to 6.1 cm/yr |
| Study | Study Type | Sample Size | CKD Stage | Treatment | Outcome |
|-------|------------|-------------|-----------|-----------|---------|
| KTx n=6; majority prepubertal; age 12.1 yrs (9.5–15.8) (M/F 3/3) | KTx (pubertal): 3.2 o 6.0 cm/yr (each P<0.05) |
| | | | | | |
| | | | | | |
| | Prospective study | 9 | CKD stage 5 n=1; CKD 5D n=8 (M/F 7/2); age 5.8 yrs; all prepubertal | 4 IU/m2 per day for 12 months | HV (cm/yr): 8.0 vs. 4.4 (each P<0.05) |
| Tönshoff et al. (1990) [S50] (Germany) | Johansson et al. (1990) [S51] (Belgium) | | | | |
| | | | | | |
| | | | CKD stage 4–5 n=22; all prepubertal; age 8.4 yrs (3.1–12.8) | 28-30 IU/m2 per wk. daily for 12 months | CKD stage 4-5: HV increased from 4.8 cm/yr to 10.0 cm/yr (HV SDS from –1.3 to 5.1) |
| | | | | | |
| | | | KTx n=15, all prepubertal | | KTx prepubertal children: HV increased from 2.6 cm/yr to 6.2 cm/yr (HV SDS from –2.8 to 2.3) |
| | | | KTx n=13, all pubertal | | KTx pubertal children: HV increased from 3.8 cm/yr to 6.7 cm/yr (each P<0.05) |
| | | | | | |
| | Prospective study | 5 | CKD stage 5D (PD), age 1.2 to 17.7 yrs; prepubertal and pubertal patients | 0.125 mg/kg 3 times weekly for 12 months | Significant increase in HV compared to pretreatment year (P<0.05) |
| Fine et al. (1990) [S52] (USA) | Tönshoff et al. (1989) [S53] (Germany) | | | | |
| | | | | | |
| | | | CKD stage 5D (M/F 7/2); all prepubertal | 4 IU/m2 per day for 6–9 months | HV SDS changed from –2.8 to 2.5 (P<0.05) |
| | | | | | |
| | | | | | |
| | Prospective study | 5 | CKD stage 3–5D (eGFR 18±6 ml/min/1.73 m²); (M/F 5/0); age 4.6±1.8 yrs; all prepubertal | 0.125 mg/kg 3 times weekly for 12 months | HV (cm/yr) increased from 4.9±1.4 to 8.9±1.2, and height SDS from –3.0± 0.7 to –2.4±0.8 (each P<0.05) |
| Koch et al. (1989) [S54] (USA) | | | | | |
| | | | | | |
| | Prospective study | 5 | CKD stage 3–5 age 35–91 months all prepubertal | 0.125 mg/kg 3 times weekly for 6 months and 6 months follow-up without GH | HV (cm/yr) increased from 4.9±1.4 to 10.1±2.0 (P<0.01) |
| Lippe et al. (1988) [S55] (USA) | | | | | |
| | | | | | |
| | Prospective study | 5 | CKD stage 3–5 | | |

Data are given as mean ± SD if not indicated otherwise. CKD, chronic kidney disease; CPD, continuous peritoneal dialysis; CT, conservative treatment (CKD prior to dialysis); eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; F, female; HD, haemodialysis; HV, height velocity; GH, growth hormone; KTx, kidney transplantation; M, male; NS, nonsignificant; SDS, standard deviation score; SE, standard error.
Table 4: Synopsis of 11 studies reporting adult height or near adult height data after GH treatment of growth failure in CKD patients.

| 1st author, year, origin [Ref.] | Study design | Patients | Age at start of GH (years) | Pre-pubertal (%) | Duration of follow-up (years) | GH dosage | Duration of GH Tx (years) | Initial height SDS | Adult height SDS | Change in height SDS |
|---------------------------------|--------------|----------|--------------------------|-----------------|-------------------------------|-----------|----------------------------|------------------|----------------|-------------------|
| Gils S 2018, Argentina [S56]    | Prospective study | KTx; n=23 (only boys) GH, n=13 no GH, n=10 | 15.5 | 0 | 3.1 | 9.33 mg/m²/wk daily | 2.3 | -3.1 ± 1 | -1.8 ± 0.8 | 1.2 ± 0.3 |
| Gils S 2012, Argentina [S57]    | Prospective study | KTx, n=47 GH, n=33, no GH, n=14 | 13.2 | 45 | 30 | 10 mg/m²/wk daily | 3.5 | -3.3 ± 1.2 | -1.9 ± 1.1 | 1.2 ± 0.7 |
| Berard E 2008, France [S58]    | Prospective study | CKD stage 3-5, n=35 | n.i. | n.i. | n.i. | n.i. | 1 IU/kg/wk daily | n.i. | -3.0 ± 0.9 | -1.8 ± 0.9 | 1.2 |
| Nissel R 2008, Germany [S59]   | Registry | CKD 3-5, n=108 dialysis, n=67 KTx, n=65 n=240 regular pubertal onset delayed puberty in early puberty in late puberty | 12.8 | n.i. | 4.9 | 0.33 mg/kg/wk daily | > 2 | -3.6 (each p<0.05<sup>a</sup>) | -3.3 | 1.1 (each p<0.002) |
| Seikaly MG 2007, USA            | Registry | n=91 | 14.2 | n.i. | 4.0 | | | | | |

<sup>a</sup>GH dosage includes daily and weekly administration.
| Reference                          | Study Type          | GHR 1997, Belgium [S66] | 2000, Germany [S65] | 2004, Australia [S62] | 2005, USA [S61] | 2000, USA [S64] | 2004, The Netherlands [S63] |
|-----------------------------------|---------------------|-------------------------|---------------------|-----------------------|-----------------|-----------------|-------------------------|
| CKD 3-5, n=30                     | n.i.                | ca. 60                  | n.i.                | n.i.                  | > 2             | -2.6           | n.i.                    | 0.8                     |
| dialysis, n=20                    | n.i.                | ca. 60                  | n.i.                | n.i.                  | > 2             | -2.7           | n.i.                    | 0.5                     |
| KTx, n=41                         | n.i.                | ca. 60                  | n.i.                | n.i.                  | > 2             | -2.4           | n.i.                    | 0.19 (each p<0.05)      |
| Fine RN 2005, USA [S60]           | Registry            | KTx, n=676 GH, n=71     | n.i.                | ca. 60                | n.i.            | > 2             | -2.7 (p>0.05)          | -1.8 (p<0.001)          |
|                                   |                     | non-GH, n=669           |                     |                      |                 |                 | -2.5 (p<0.001)         | -0.1 (p>0.05)           |
| Crompton C 2004                   | Registry            | n=39 CT, dialysis, KTx  | 12.8                | ca. 50                | 5.4             | 27 IU/m²/wk daily | 3.3         | 2.65  | 2.3  | 0.35  | (p<0.001)                 |
| Australia                         |                     |                         |                     |                      |                 |                 |                         |                         |
| Hokken-Koelega AC 2004, The      | Prospective study   | n=65 CT, dialysis       | n.i.                | 100                   | 4 IU/m²/d       | 5.8             | -2.8 n.i.              | -1.4 n.i.               | 1.4 (p<0.001) height gain 19 cm |
| Netherlands [S63]                 |                     |                         |                     |                      |                 |                 |                         |                         |
| Fine RN 2000, USA [S64]           | Registry            | CT, GH, n=9 CT, non-GH, n=335 | n.i.                | n.i.                  | < 3.2           | -3.0           | -1.0                    | 0.7 (p<0.05)            | -0.02 (p<0.05)          |
|                                   |                     | dialysis, GH, n=22      | n.i.                | n.i.                  | < 4.1           | -3.6           | -1.88                   | 0.4 (p<0.09)            | 0.06 (p=0.09)           |
|                                   |                     | dialysis, non-GH, n=377 | n.i.                | n.i.                  | < 4.1           | -3.2           | -1.82                   |                         |                         |
|                                   |                     | KTx, GH, n=72 KTx, non-GH, n=1480 | n.i.                | n.i.                  | < 3.7           | -3.0           | -1.7                    | 0.5 (p<0.01)            | 0.04 (p<0.01)           |
| Haffner D 2000, Germany [S65]     | Prospective study   | GH, n=38 47% CKD 3-5, 24% dialysis, 29% KTx | 10.4                | 100                   | 7.6             | 0.33 mg/kg /wk daily | 5.3         | -3.1  | -1.6 ± 1.2 | 1.4 (p<0.001)          |
|                                   |                     | non-GH, n=50 53% CKD 3-5, 20% dialysis, 27% KTx | 9.7                   | 100                   | 8.3             | -            | -1.5 (p<0.05)          | -2.1 ± 1.2 (p<0.05)     | -0.6 p<0.001           |
| Janssen F 1997, Belgium [S66]     | Retrospective study | KTx, n=17               | n.i.                | n.i.                  | 4 IU/m²/d       | 3.4             | -3.0                    | -1.8                   | 1.2 (p<0.005)           |

a1 IU = 0.33 mg; b follow up / subanalysis of Gils S, 2012; c in the studies of Gils et al [S56] and Nissel et al [S59] near adult height data were reported; d vs. baseline; e published only in abstract form; f percentage distribution of patient years spent in each treatment category; Tx = treatment; CT = conservative treatment (CKD prior to dialysis); KTx = Kidney transplantation; n.i. = no information given
### Supplementary Table 5 | Model parameters, values and data sources for cost-effectiveness of GH in CKD.

| Scenario | Parameter | Value and source | Mean total cost of GH therapy | Incremental cost per cm gained |
|----------|-----------|------------------|-------------------------------|------------------------------|
| **Population data** | | | | |
| All scenarios | Sex distribution of patients | 50% males | NA | NA |
| **Investigation and treatment parameters** | | | | |
| All scenarios | Drug doses condition based on age- and sex-related weight at 25th percentile and not adjusted during puberty. | 0.045 mg/kg per day | NA | NA |
| All scenarios | Median cost per mg | €22 | NA | NA |
| **Effectiveness data** | | | | |
| Scenario 1A<sup>a</sup> | Length of treatment | 2 years | €12,966 | €1,805 |
| | Final height gain | 7.2 cm | | |
| Scenario 1B<sup>b</sup> | Length of treatment | 5 years | €37,905 | €5,265 |
| | Final height gain | 7.2 cm | | |
| Scenario 2A<sup>a</sup> | Length of treatment | 2 years | €27,075 | €3,760 |
| | Final height gain | 7.2 cm | | |
| Scenario 2B<sup>b</sup> | Length of treatment | 5 years | €80,142 | €11,131 |
| | Final height gain | 7.2 cm | | |

<sup>a</sup>Assumes a child aged 5 years and benefit uniformly spread over treatment period. <sup>b</sup>Assumes a child aged 12 years and benefit uniformly spread over treatment period. NA, not applicable.
Supplementary Table 6 | Costs of GH in eight representative European countries in 2018

| Country       | Median cost for 1 mg of GH reference (somatotropin) | Median cost for 1 mg of GH biosimilar | Median cost for 1 mg GH |
|---------------|-----------------------------------------------------|---------------------------------------|-------------------------|
| Belgium       | €23                                                 | €20                                   | €22                     |
| France        | €30                                                 | €25                                   | €28                     |
| Germany       | €60                                                 | €48                                   | €54                     |
| Italy         | €29                                                 | €15                                   | €22                     |
| Netherlands   | €30                                                 | €30                                   | €30                     |
| Poland        | €10                                                 | €4                                    | €7                      |
| Spain         | €16                                                 | n.a.                                  | €16                     |
| United Kingdom| €22                                                 | €17                                   | €20                     |
| **Median**    |                                                     |                                       | **€22**                 |

Costs were obtained from national data sources or local pharmacies; n.a., not available.
## Supplementary Table 7 | Adverse events in parallel RCTs comparing GH versus control group

| Reported adverse effects | Studies [Ref.] | N (GH, control) | Control group | GH group | Between groups comparison | rhGH discontinuation |
|--------------------------|----------------|----------------|----------------|----------|--------------------------|---------------------|
| Benign intracranial hypertension (ICH) | Fine 2002 (KTx) [S10] | 68 (29, 39) | At 1st year: 1 patient | At 1st year: 1 report of headache with normal cerebrospinal fluid pressure. | - | Both patients discontinued from study. |
| | Broyer 1998 (KTx) [S20] | 90 (46, 44) | 1 patient developed papilledema while on GH – group not specified | - | Papilledema resolved after discontinuation of GH. |
| Bone histology changes | Sanchez 2002 (KTx) [S15] | 23 (11, 12) | At 1st year, 1 patient developed mild lesion of secondary hyperparathyroidism on bone biopsy (n=8) | At 1st year, 2 patients developed adynamic bone and 2 patients developed mild secondary hyperparathyroidism (N=8) | - | None reported |
| Glucose intolerance | Fine 2002 (KTx) [S7] | 68 (29, 39) | At 1st year (no treatment): 0 report At 2nd year (GH): 1 patient developed hyperglycaemia | At 1st year: 1 patient developed diabetes mellitus. | - | GH discontinued in the patient with diabetes mellitus; reintroduction of GH with no problem. |
| | Broyer 1998 (KTx) [S14] | 90 (46, 44) | At year 1: increase in mean fasting glucose concentrations, fasting plasma insulin, mean values of insulin during OGTT. (N=19) 1 children developed diabetes during 1st year (before GH) | At year 1: increase in mean fasting glucose concentrations, fasting plasma insulin, mean values of insulin during OGTT. (n=20) | NS | None reported |
| | Maxwell 1998 (KTx) [S10] | 22 (9, 13) | No report | At 9 months of GH therapy, 1 patient with partial pancreatectomy had raised fasting glucose, insulin, and HbA1c concentrations. | GH was discontinued and values returned to normal. |
| Reported adverse effects | Studies                  | N (GH, control) | Control group                                      | rhGH group                                      | Between groups comparison | rhGH discontinuation |
|--------------------------|--------------------------|----------------|---------------------------------------------------|-------------------------------------------------|----------------------------|---------------------|
| Graft rejection          | Broyer 1998 (KTx) [S14]  | 90 (46, 44)    | Acute, biopsy-proven rejection: 1st year (no treatment): 4 patients 2nd year (GH): 6 patients | Acute, biopsy-proven rejection: 1st year: 9 patients 2nd + 3rd year: 12 patients | 1st year: NS           | 4 pts. discontinued GH, recovered and maintain stable renal function. A total of 13 cases of discontinuation. |
|                          | Fine 2002 (KTx) [S7]     | 68 (29, 39)    | Rejection episodes: At 1st year (no treatment): 3 patients At 2nd year (GH): 2 patients Allograft failure: 1 patient at 2nd year while on GH | Rejection episodes: At 1st year: 0 report At 2nd year: 3 patients Allograft failure: 2 patients | -                         | None reported       |
|                          | Sanchez 2002 (KTx) [S8]  | 23 (11, 12)    | No report                                         | 2 patients had biopsy confirmed acute rejection after 3 and 12 months of GH therapy. | -                         | None reported       |
|                          | Maxwell 1998 (KTx) [S10] | 22 (9, 13)     | Presumed rejection episodes: At 1st year: 9 patients | Presumed rejection episodes: At 1st year: 8 patients | NS                        | None reported       |
| Renal function deterioration | Fine 2002 (KTx) [S7]     | 68 (29, 39)    | At 1st year (no treatment): 0 report At 2nd year (GH): 2 patients with elevated serum creatinine | None reported                                   | -                         | None reported       |
|                          | Broyer 1998 (KTx) [S14]  | 90 (46, 44)    | At 1st year: Moderate but significant decrease in GFR. | At 1st year: Moderate but significant decrease in eGFR | NS                        | 7 cases discontinued due to increased serum creatinine level |
|                          | Fine 1994 (CT) [S20]     | 125 (43, 82)   | At 2nd year: Serum creatinine levels rose (n=24) | At 2nd year: Serum creatinine levels rose (n=48) | NS                        | None reported       |
Supplementary Table 7 – continued

| Reported adverse effects | Studies | N (GH, control) | Control group | rhGH group | Between groups comparison | rhGH discontinuation |
|--------------------------|---------|----------------|---------------|------------|---------------------------|---------------------|
| Others                   | Sanots 2010 (CT/CKD VD) [S5] | 14 (7, 7) | 20 unspecified adverse events | 9 unspecified adverse events. None were considered related to rhGH therapy. | P=0.065 | None reported |
|                          | Fine 2002 (KTx) [S7] | 68 (29, 39) | At 1st year (no treatment): 2 cases of infection; 1 case of septic arthritis; 1 patient developed post-transplant lymphoproliferative disease | At 1st year: 2 cases of infection; 1 case of transient ischemia attack; 1 case of genu valgum; 1 patient developed post-transplant lymphoproliferative disease. | - | None reported |
|                          | Maxwell 1998 (KTx) [S10] | 22 (9, 13) | No report | 1 patient developed worsening of a pre-existing idiopathic scoliosis. | - | None reported |
|                          | Fine 1994 (CT) [S20] | 125 (43, 82) | At 2nd year: 0 report of asthma/wheezing (n=27) | At 2nd year: 8 reports of asthma/wheezing (n=55) | P=0.048 | None reported |
| Reported "no adverse effects" | Bacchetta 2013 (CKD VD) [S4] | | | | | |
|                          | Hokken-K 1991 (CT/CKD VD) [S21] | | | | | |
|                          | Hokken-K 1996 (KTx) [S16] | | | | | |
| Adverse effects not addressed | Powell 1997 (CT) [S11] | | | | | |
|                          | Kuizo 1998 (CKD VD) [S9] | | | | | |

KTx, Kidney transplant; CT, conservative treatment (CKD prior to dialysis); CKD 5D, dialysis; N, total no. of patients randomized (no treatment group, GH group); NS, Non-significant; OGTT, Oral glucose tolerance test.
### Supplementary Table 8 | Adverse events in parallel RCTs comparing two doses of GH

| Reported adverse effects | Studies | N (low dose, high dose) | GH group (2 IU/m²/day) | GH group (4 IU/m²/day) | GH discontinuation |
|--------------------------|---------|-------------------------|------------------------|------------------------|-------------------|
| Claudication             | Kitagawa 1997 (CT/CKD VD) [S13] | 122 (54, 58) | Number of cases not specified | None reported |
| Graft rejection          | Ito 1997 (KTx) [S12] | 23 (10, 13) | Acute, biopsy confirmed rejection At 1st year: 2 patients | Acute, biopsy confirmed rejection At 1st year: 5 patients | None reported |
| Glucose intolerance      | Hertel 2002 (CT/CKD VD) [S6] | 29 (15, 14) | 1 patient developed diabetes mellitus after 34 months of therapy. At 2nd year (4 IU/m²/day): significant increase in fasting insulin levels | 0 reports At 2nd year (4 IU/m²/day): significant increase in fasting insulin levels | Patient with diabetes mellitus discontinued GH |
|                          | Kitagawa 1997 (CT/CKD VD) [S13] | 102 (54, 58) | 2 cases reporteda | None reported |
| Granuloma formation      | Kitagawa 1997 (CT/CKD VD) [S13] | 102 (54, 58) | 2 cases reporteda | None reported |
| Hypertension             | Hertel 2002 (CT/CKD VD) [S6] | 29 (15, 14) | 1 patient after 6 months of therapy | 0 reports | Hypertensive patient discontinued GH |
|                          | Kitagawa 1997 (CT/CKD VD) [S13] | 102 (54, 58) | Number of cases not specified | None reported |
## Supplementary Table 8 - continued

| Reported adverse effects | Studies | N (low dose, high dose) | GH group (2 IU/m²/day) | GH group (4 IU/m²/day) | GH discontinuation |
|--------------------------|---------|------------------------|------------------------|------------------------|-------------------|
| Injection pain           | Hertel 2002 (CT/CKD VD) [S16] | 29 (15, 14) | 1 patient | 1 patient | None reported |
| Lymph node swelling      | Kitagawa 1997 (CT/CKD VD) [S13] | 102 (54, 58) | Number of cases not specified | None reported |
| Renal function deterioration | Hertel 2002 (CT/CKD VD) [S6] | 29 (15, 14) | At 1st year: 1 patient | At 1st year: 0 reports | None reported |
| Renal function deterioration | Kitagawa 1997 (CT/CKD VD) [S13] | 102 (54, 58) | More patients in the 4 IU/m²/day than in the 2 IU/m²/day group showed signs of deterioration in renal function | None reported |
| Callis 1996 (CT) [S67] | 43 (21, 23) | At 6 months: 9 patients | At 6 months: 11 patients | None reported |

N, Total no. of patients randomised (low dose, high dose); *It is not possible to determine whether these patients were from the low or high dose GH group.
## Supplementary Table 9 | Summary of recommendations

| Recommendation                                                                                                                                                                                                 | evidence quality, strength of recommendation |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| 1.1  We recommend that height (or supine length for patients below 2 years of age) is regularly measured depending on age and chronic kidney disease (CKD) stage (Table 1). Height velocity should be calculated over a minimum period of 6 months, and both height and height velocity should be compared to standardized growth charts. | A, strong                                      |
| 1.2  We recommend that growth potential is assessed by calculation of genetic target height on the basis of parental height and the extent to which the epiphysis of the left wrist is open on radiography (grade A, strong recommendation). We do not recommend application of adult height prediction methods for children with CKD. | A, strong                                      |
| 1.3  Age, primary renal disease, systemic disorders, stage of CKD, dialysis adequacy (for patients on dialysis) and graft function and glucocorticoid therapy (in children post-transplantation) should be taken into account when considering growth hormone (GH) therapy. | B, moderate                                    |
| 1.4  CKD-associated growth-limiting factors such as protein-calorie malnutrition, metabolic acidosis, electrolyte disturbances (hyponatremia), dehydration and mineral dysregulation, including secondary hyperparathyroidism, should be adequately controlled before considering GH therapy (grade A, strong recommendation). | A, strong                                      |
| 1.5  The following assessments should be performed prior to starting GH:  
- Serum creatinine (and estimated glomerular filtration rate), urea, calcium, phosphorus, total alkaline phosphatase, bicarbonate, parathyroid hormone, 25(OH) vitamin D, albumin, fasting glucose and glycosylated hemoglobin levels  
- Serum thyroid hormone (TSH and free T3) and insulin-like growth factor 1 concentrations  
- Fundoscopic examination  
- Radiography of the left wrist  
- Pubertal status according to Tanner | C, moderate                                    |
| 2.1  We recommend that pros and cons of growth hormone (GH) treatment are discussed with individual patients and their families before GH treatment is initiated. Such discussion is of particular importance for immobilized patients and those with syndromic kidney diseases. | no grading                                     |
| 2.2  We recommend that children with stage 3-5 chronic kidney disease (CKD) or on dialysis aged above 6 months should be candidates for GH therapy if they have persistent growth failure, defined as a height below the third percentile for age and sex and a height velocity below the twenty-fifth percentile, once other potentially treatable risk factors for growth failure have been adequately addressed and provided the child has growth potential. | B, moderate                                    |
| 2.3  We recommend that GH therapy is considered for children with stage 3-5 CKD or on dialysis aged above 6 months who present with a height between the third and tenth percentile but persistent low height velocity (below the twenty-fifth percentile) once other potentially treatable risk factors for growth failure have been adequately addressed. | D, weak                                        |
| 2.4  In children who have received a kidney transplant and have persistent growth failure, defined as a height below the third percentile for age and sex and a height velocity below the twenty-fifth percentile, we recommend initiating GH therapy 1 year after transplantation if spontaneous catch-up growth does not occur and steroid-free immunosuppression is not a feasible option. | B, moderate                                    |
| 2.5  In children with CKD due to nephropathic cystinosis who have persistent growth failure, defined as a height below the third percentile for age and sex and a height velocity below the twenty-fifth percentile, we recommend that GH therapy is considered at all stages of CKD. | C, moderate                                    |
| 2.6  GH therapy should not be started  
- In patients with closed epiphyses  
- In patients with known hypersensitivity to the active substance or to any of the excipients  
- In the case of unwillingness of the patient or their family  
- In patients with severe secondary hyperparathyroidism (parathyroid hormone > 500 pg/ml) | X, strong                                      |
| 3.1 | We suggest considering the cost–benefit ratio before initiating growth hormone treatment in short children with chronic kidney disease. | D, weak |
| 4.1 | We recommend that growth hormone (GH) is given at a dose of 0.045–0.05 mg/kg body weight per day by subcutaneous injections in the evening. | B, moderate |
| 4.2 | We suggest that parents and physicians encourage children from about 8–10 years of age to do the GH injections on their own if adequate training and adherence is ensured. | D, weak |
| 4.3 | We recommend both GH reference and GH biosimilar products for use in short children with chronic kidney disease (CKD). | B, moderate |
| 4.4 | We suggest clinic visits every 3–6 months or more frequently for young patients and those with advanced CKD to monitor stature, height velocity, pubertal development, skeletal maturation on wrist radiography, renal function, thyroid hormone levels (TSH and free T3), serum glucose, calcium, phosphate, bicarbonate and parathyroid hormone levels. | D, weak |
| 4.5 | If height velocity in the first year of GH treatment is less than 2 cm per year over baseline, we recommend assessment of patient adherence to GH therapy, including measurement of serum insulin-like growth factor 1 levels, weight-adjusted GH dosage and assessment of nutritional and metabolic factors, as recommended before initiation of GH therapy. | B, moderate |
| 4.6 | We recommend stopping GH  
- When epiphyseal closure is demonstrated  
- At the time of renal transplantation  
- In patients with persistent severe secondary hyperparathyroidism (parathyroid hormone (PTH) >500 pg/ml). GH may be re instituted when levels return to the desired PTH target range  
- With occurrence of intracranial hypertension  
- In patients with slipped capital femoral epiphysis  
- If the patient does not adequately respond to GH treatment despite optimal nutritional and metabolic control  
- In patients with accelerated bone maturation  
- In case of an unexplained decrease in estimated glomerular filtration rate | X, strong  
X, strong  
X, strong  
X, strong  
X, strong  
X, strong  
X, strong  
X, strong  
X, strong  
X, strong  
X, strong  
X, moderate  
X, moderate  
X, moderate |
| 4.7 | We suggest that cessation of GH treatment is considered  
- When the patient reaches his or her genetic target height percentile. GH may be re instituted if catch-down growth occurs  
- When the patient reaches his or her genetic target height | X, moderate  
X, moderate |
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