Growth, puberty and growth hormone in children with CKD

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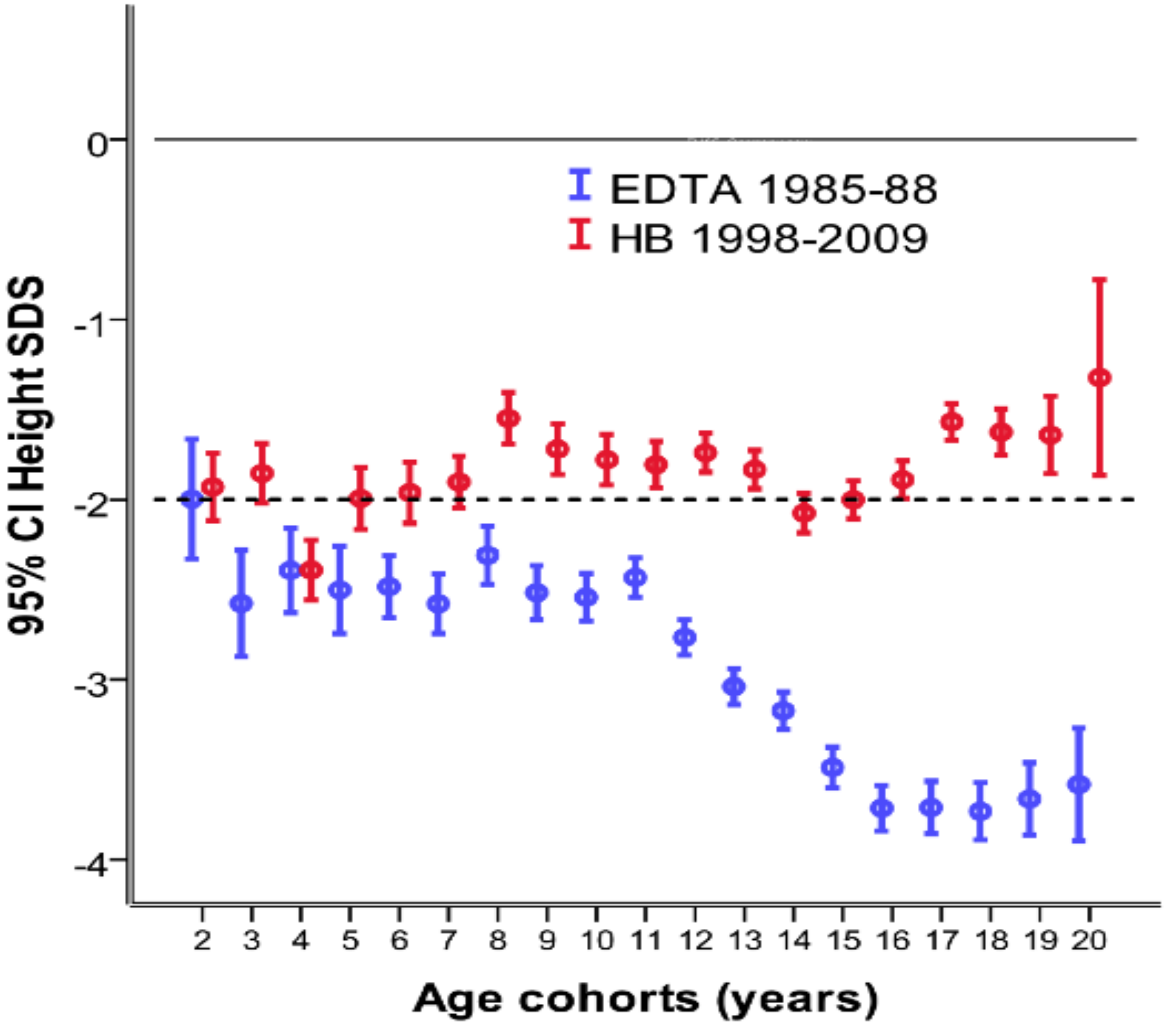
Egypt, 2018

The growth of our patients is improving:

Growth of children on RRT in 2 eras

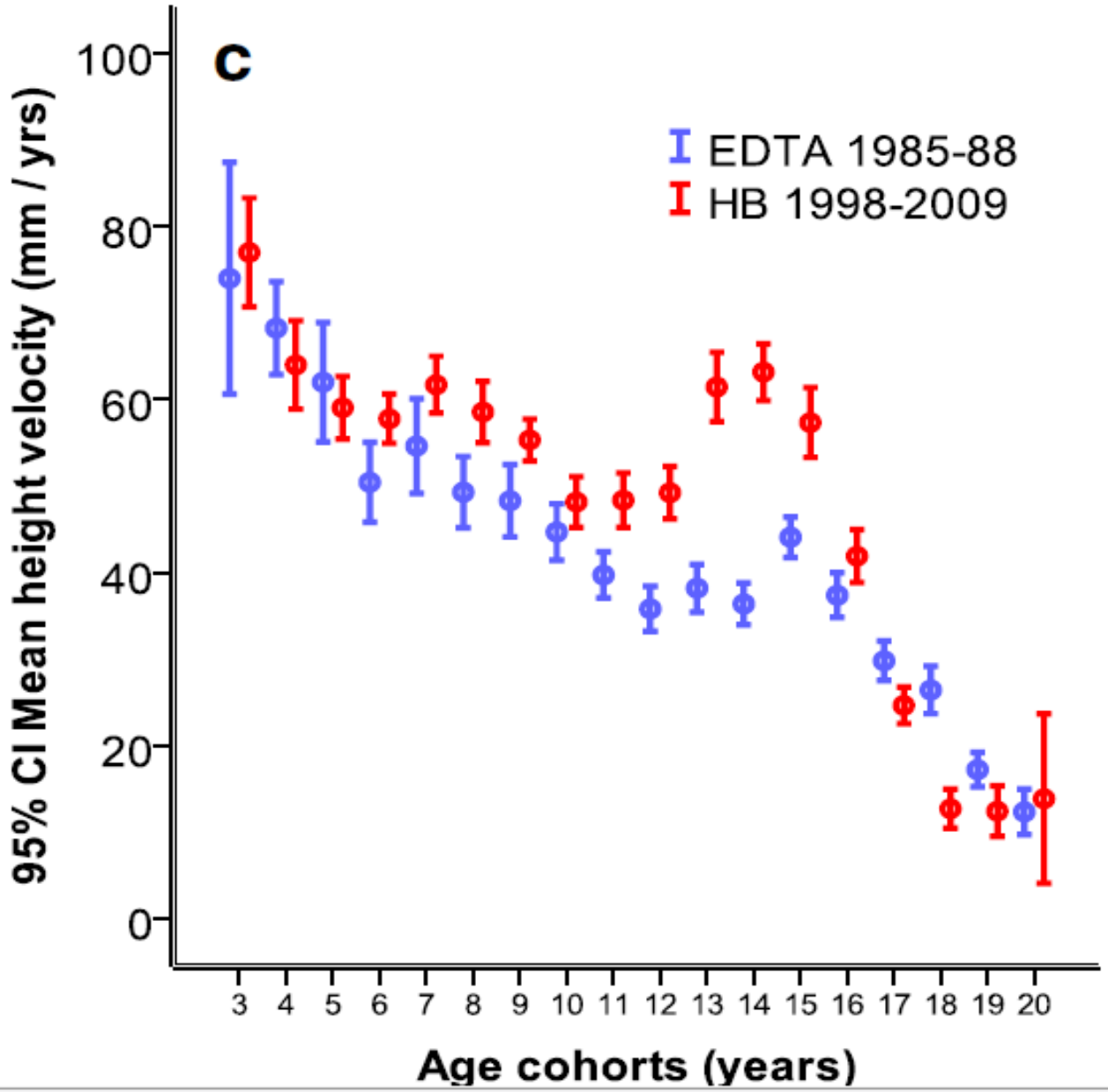


Puberty

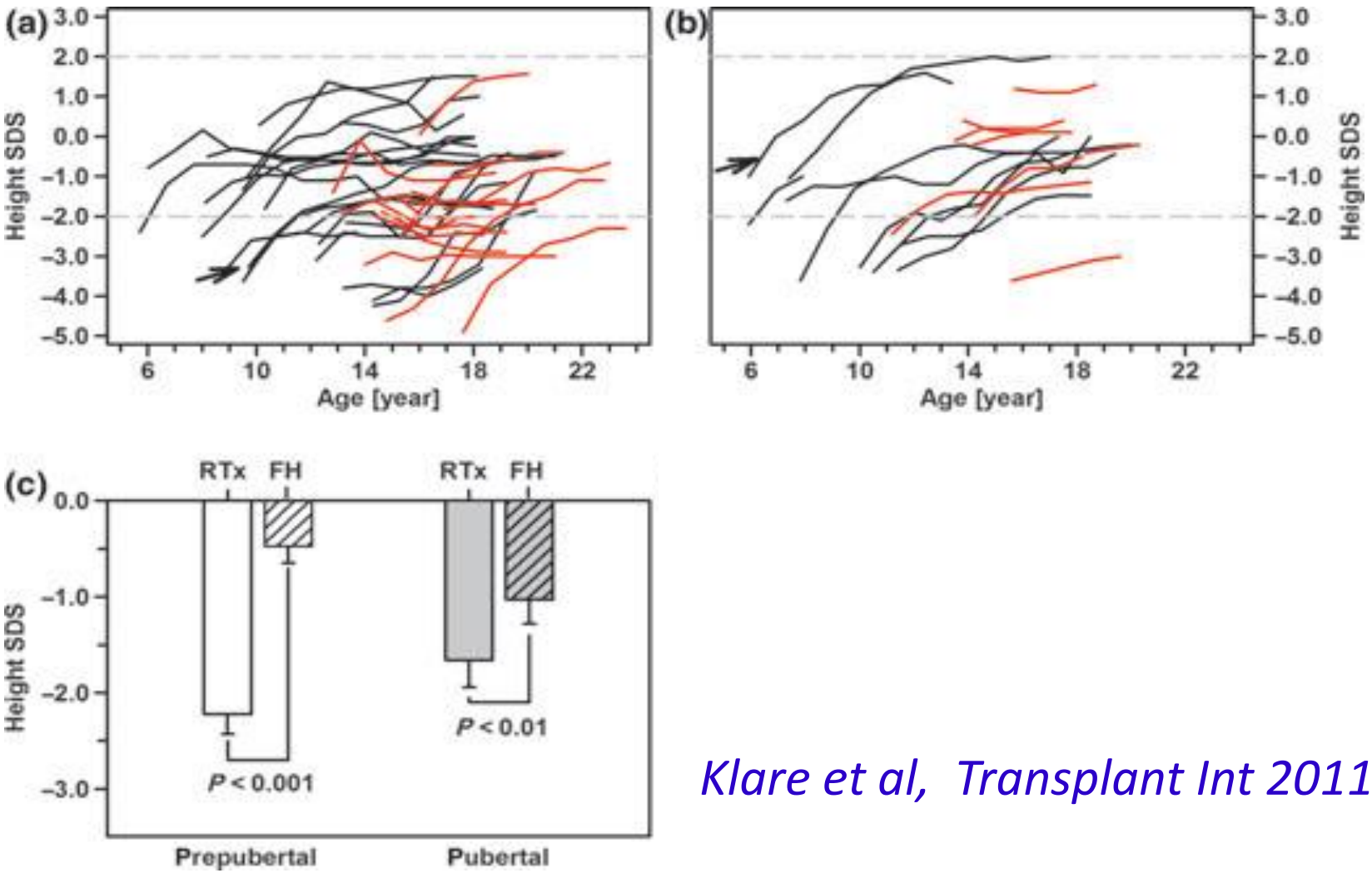
- Studies (now 20 years old) reported:
  - delayed puberty and attenuated growth spurt
  - low testosterone and oestradiol
  - raised LH/FSH.
- i.e. hypergonadotropic hypogonadism

- There may be additional defects of pituitary gonadotropin release and bioactivity

Improvement in growth spurt

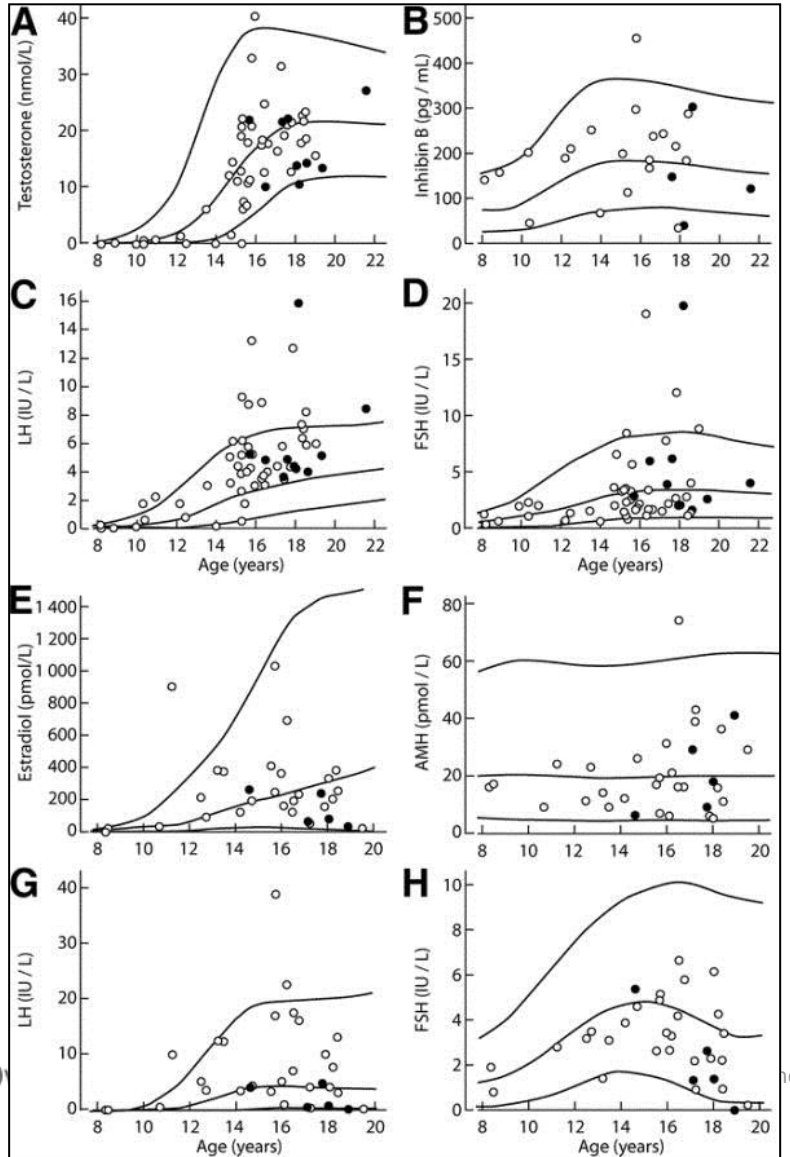


Renal transplantation normalises pubertal growth



Klare et al, Transplant Int 2011

Renal transplantation normalises pubertal hormones



Tainio, Transplantation. 2011

Factors independently associated with a better final HtSDS

- A more recent era for the start of RRT
- Older age at start of RRT
- Greater HtSDS at initiation of RRT
- Cumulative percentage time with a transplant
- Steroid free immunosuppression
- Less time on dialysis
- Absence of hyperoxaluria/cystinosis/syndromes
- rhGH

RhGH and growth in CKD

- The first studies showing the benefit of rhGH over 1 year were in the 1980s

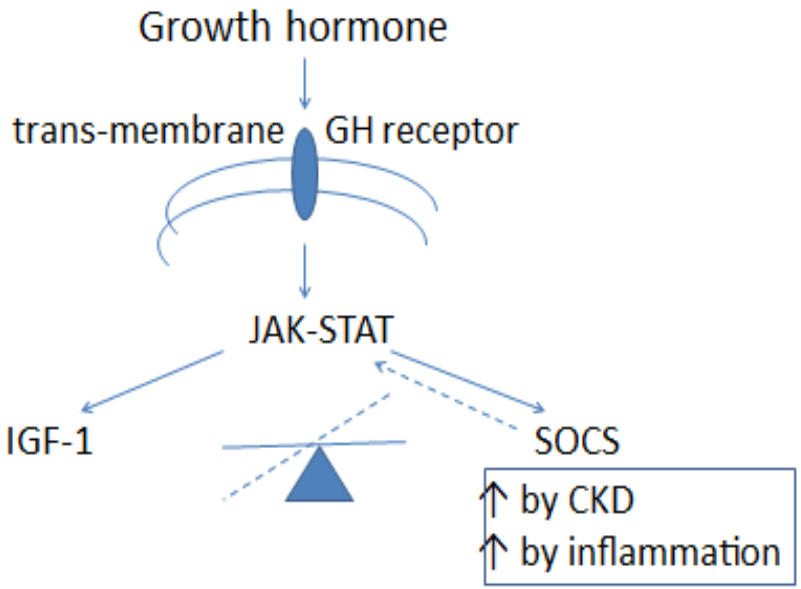
  (Koch, Rees, Tonshoff)

- Many publications show a benefit
  - 16 RCTs, not all fulfil the Cochrane criteria for evidence based medicine

- Problems:
  - Small numbers
  - Variable ages/pubertal stage
  - Variable diagnoses
  - Different treatment modalities
  - With or without retrospective control groups

Rationale for the use of rhGH in CKD and post transplant

- Imbalance of the JAK-STAT cascade
  - Uraemia
  - chronic inflammation
- ↓IGF-1 bioactivity
  - ↓synthesis
  - accumulation of inhibitors in plasma (IGFBPs)
- ↓GH secretion
  - metabolic acidosis
  - malnutrition
  - steroid therapy
- Resistance to GH
  - ↓GH receptor expression



How does rhGH exert its effect?

- By influencing the balance between growth stimulating IGFs and growth inhibitory IGFBPs
  - Principally ↑IGF1/IGFBP3
  - Maybe other IGFBPs

How much of this improvement is due to rhGH?

- Antenatal diagnosis allows early intervention
- Improved understanding and treatments for:
  - nutritional management
  - bone disease
  - metabolic abnormalities
  - anaemia
  - dialysis
  - post-transplant immunosuppressive therapy

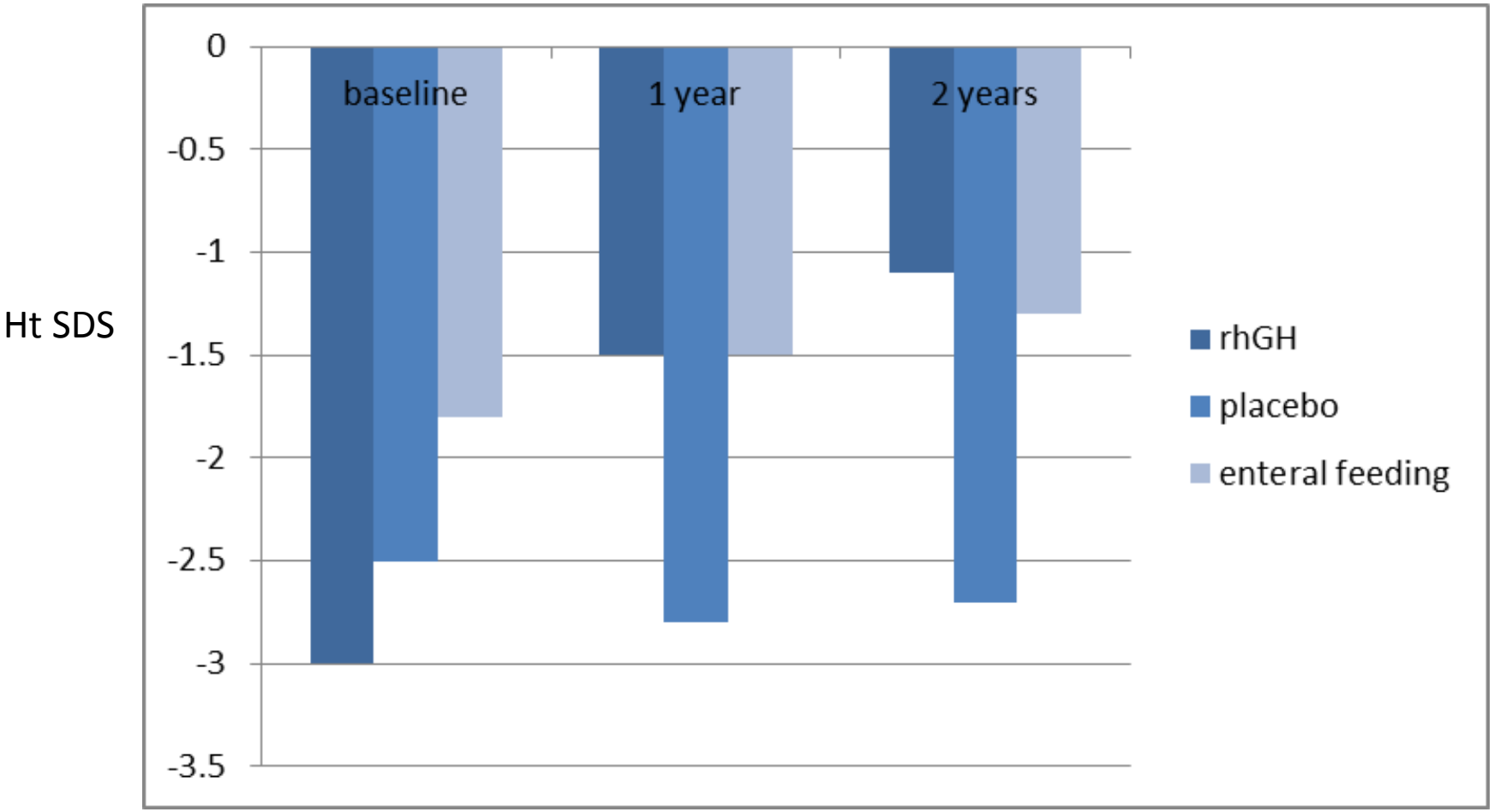
Improving growth with no increase in rhGH use:

US data for conservatively managed CKD

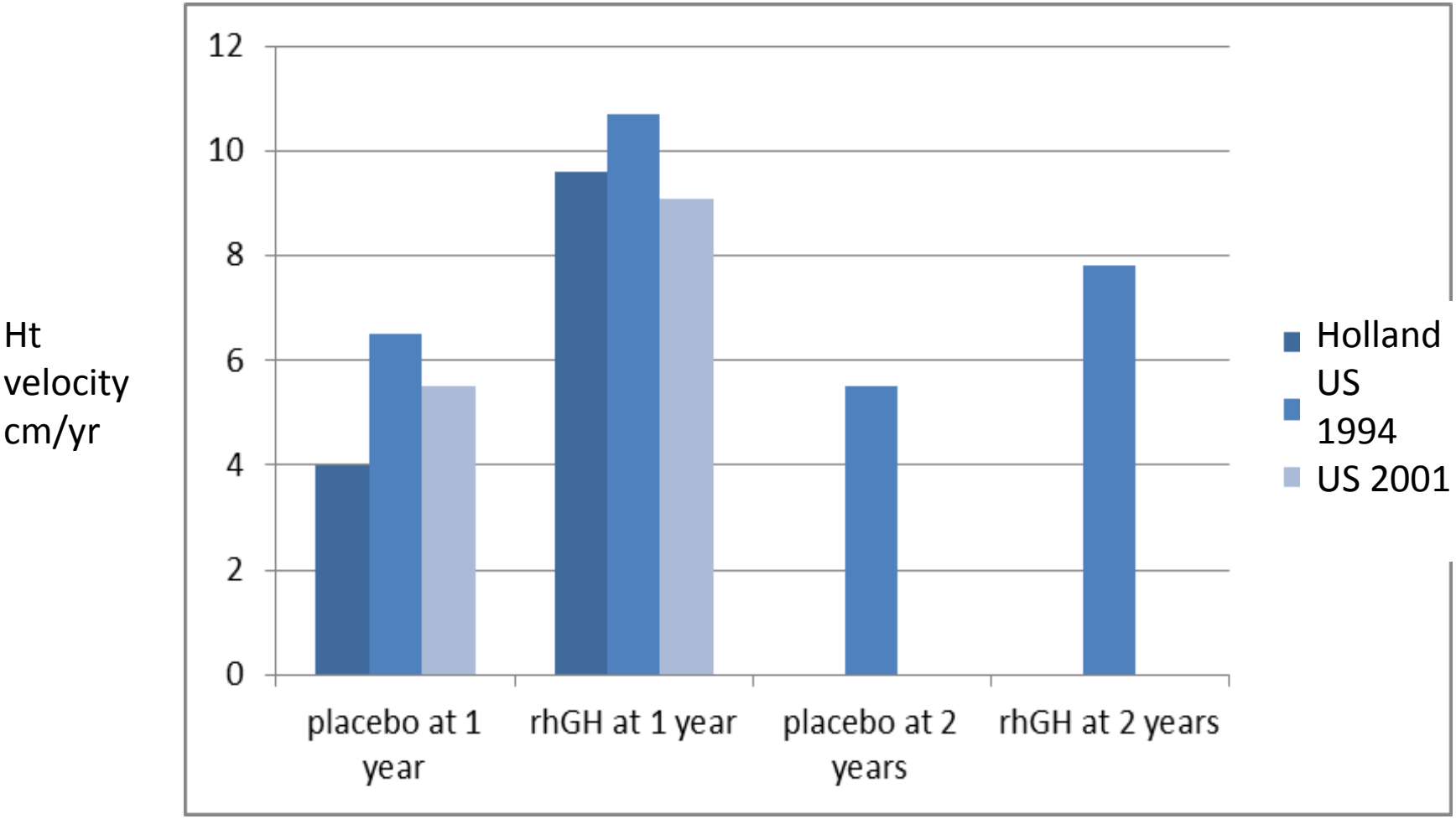
	NAPRTCS 2006	CKiD 2013
<3rd centile for height	33%	12%
rhGH if height <3rd centile	26%	23%
rhGH use in all children	7%	9%

RhGH and enteral feeding in infants

Fine, RCT 1990, Mekahali CJASN 2010

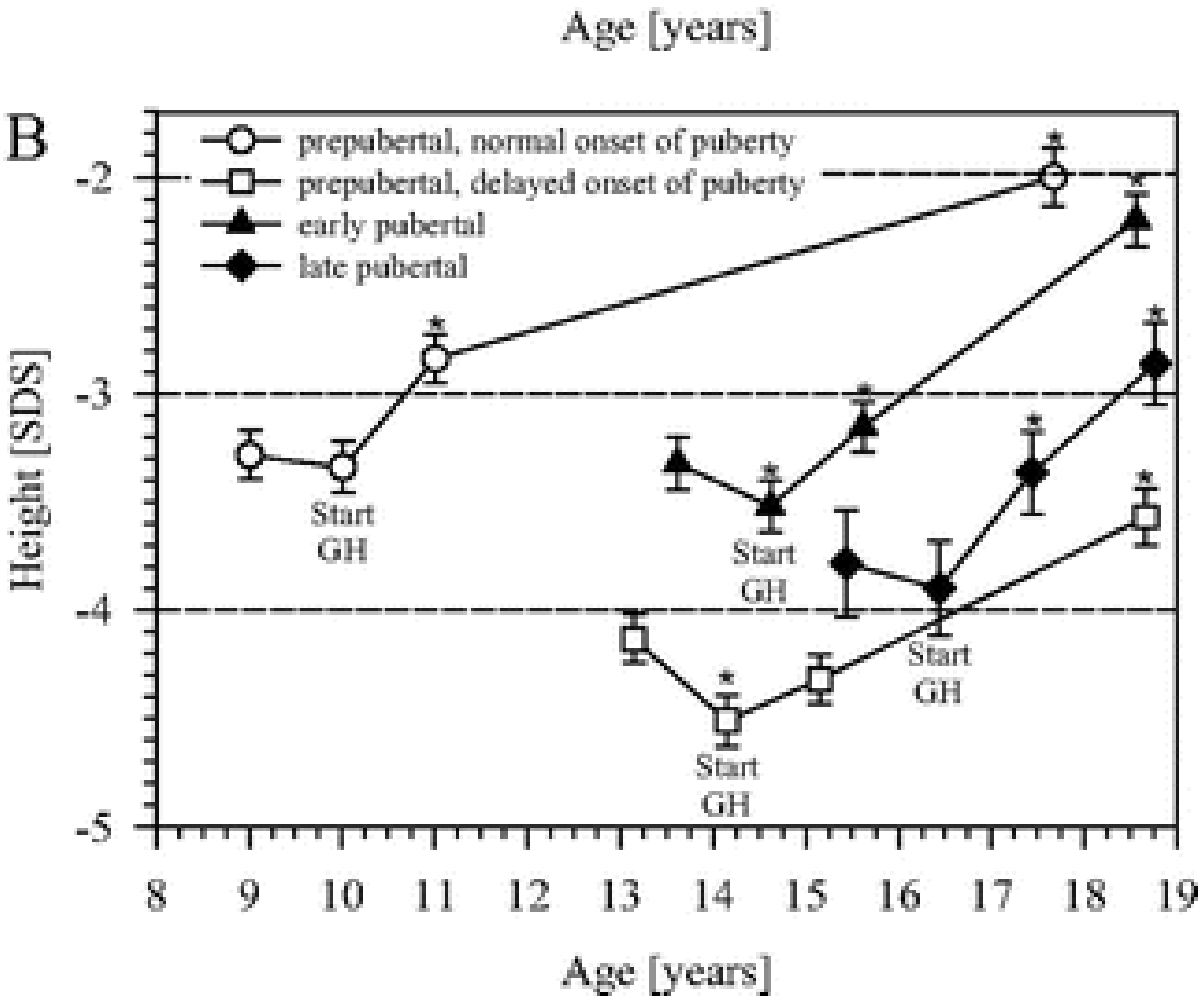


RhGH in prepubertal children with CKD 4



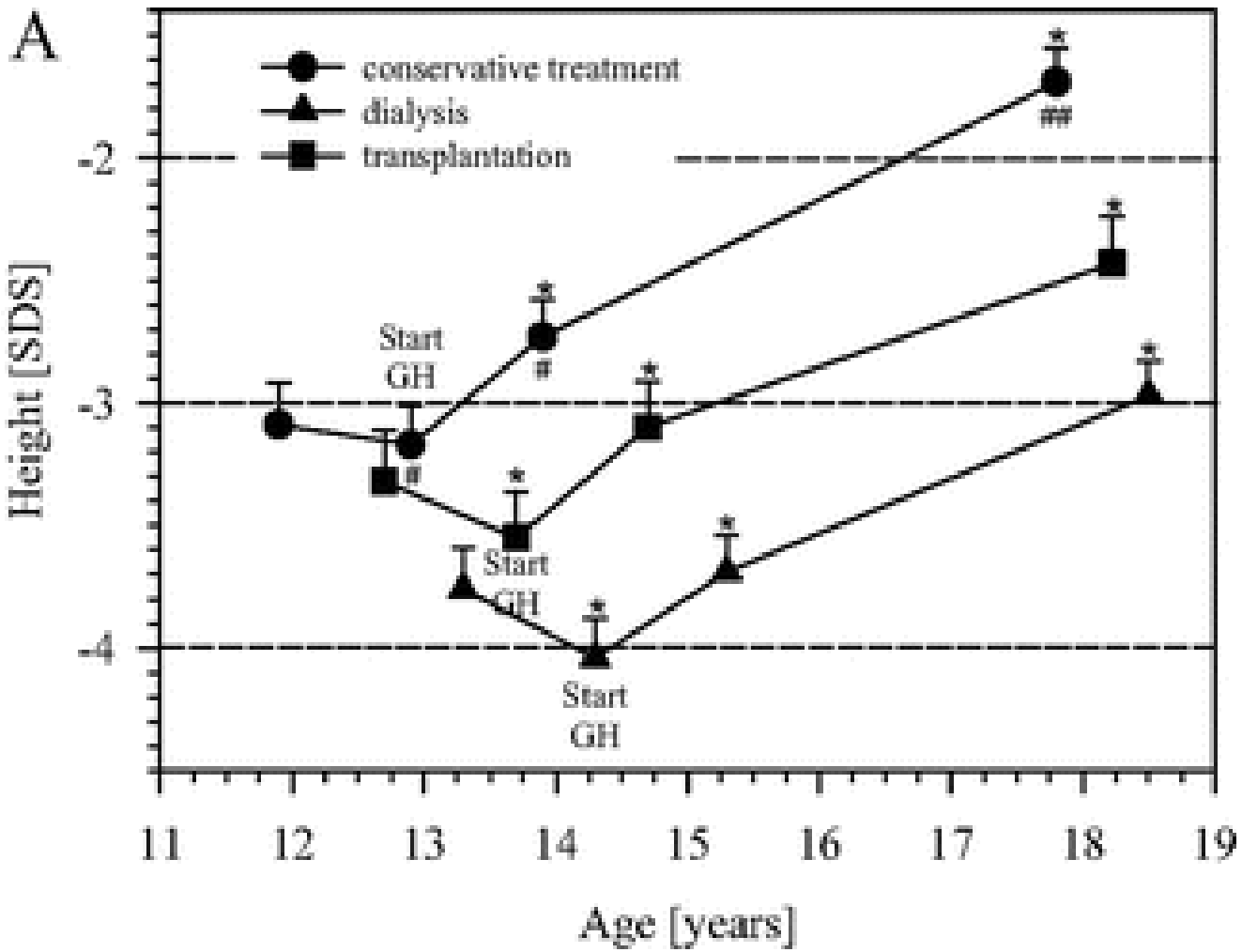
Effect of puberty on the response to rhGH

Nissel R, J Clin Endocrinol Metab 2008



Effect of treatment modality on the response to rhGH

Nissel R, J Clin Endocrinol Metab 2008



Effect of rhGH on final height

	number	Males, ht (cm) 2nd centile 163cm	Females, Ht(cm) 2nd centile 151cm
Belgium	17	162.7	151
Germany	38	161.8	147.7
Australia	183	161.8	149.5
France	102	162.2	152.9
GOSH infant ESKD	32	167	149

Median Δ HtSDS from start of rhGH to adult height in 11 studies of 313 patients was ***0.9 (0.3– 1.4) SD***

Dosage of rhGH

- 1 mg ≈ 3 IU
- 1 IU ≈ 0.33 mg
- Benefit of 1.18 cm/year with 28 IU/m²/week vs 14 IU/m²/week (3 studies, 150 children)
- No increase in side effects with the bigger dose
- No benefit from bigger doses during puberty
- Current recommended dose:
  - 45–50 micrograms/kg or 1.4 mg/m2 daily

Cochrane review 2011

16 RCTs of rhGH therapy, 809 children

28IU/m2/week

- ↑HtSDS of 0.82SD in first year
  (8 studies, 391 children)
- ↑height velocity of 3.88cm in first year
  (7 studies, 287 children)
- ↑height velocity of 2.3cm/year during the second year of therapy
  (1 study, 82 children)
- Side effects of rhGH were similar to controls
- Equal benefit in pubertal and pre pubertal children and different stages of CKD

Factors that influence the response to rhGH

Positive	Negative
• At the start of rhGH therapy: – Younger age – Lower HtSDS – Greater target-height deficit – Greater bone age retardation – Lower growth velocity • Target height • Response in the first year • Duration of rhGH therapy	• Increasing age • Delayed puberty • Increasing GFR • Duration of dialysis • Steroid therapy • Comorbid conditions

Side effects

No adverse effects

- Bone age
- Renal function
- Transplant rejection
- Glucose tolerance
- Lipids
- Bone

Benefits

- Body composition
- Psychosocial

Possible adverse effects

- Benign intracranial hypertension

Who should be treated with rhGH?

- HtSDS <3rd centile or with a HtVel SDS <-2SD

after

- metabolic and nutritional abnormalities have been corrected
- dialysis is optimised
- steroid prescription is reduced to the minimum possible

When to discontinue rhGH

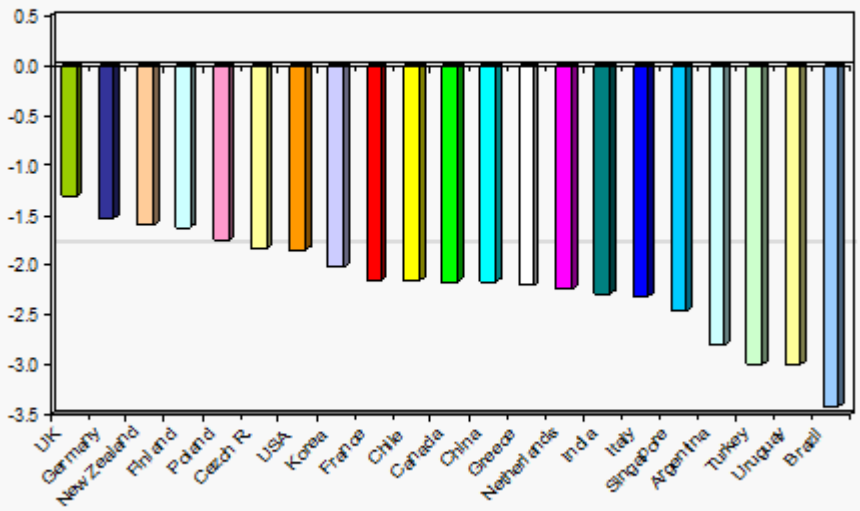
- Renal transplant
- Side effects
- Non-compliance
- If the height velocity
  - Does not increase after 1 year
  - Increase is <50% from baseline in the first year
  - falls to the pre rhGH value after the first year
  - is <2cm/year
- When the target height is approached
- Epiphyseal closure

Outcomes after stopping rhGH

- Reports are variable, some patients continuing to maintain improved growth, others needing to restart rhGH
- Discontinuation of rhGH at transplant does not have an adverse effect on growth

Fine, Pediatr 1996, Rees, Pediatr Nephrol 2000, Berard, Pediatr Nephrol 2008

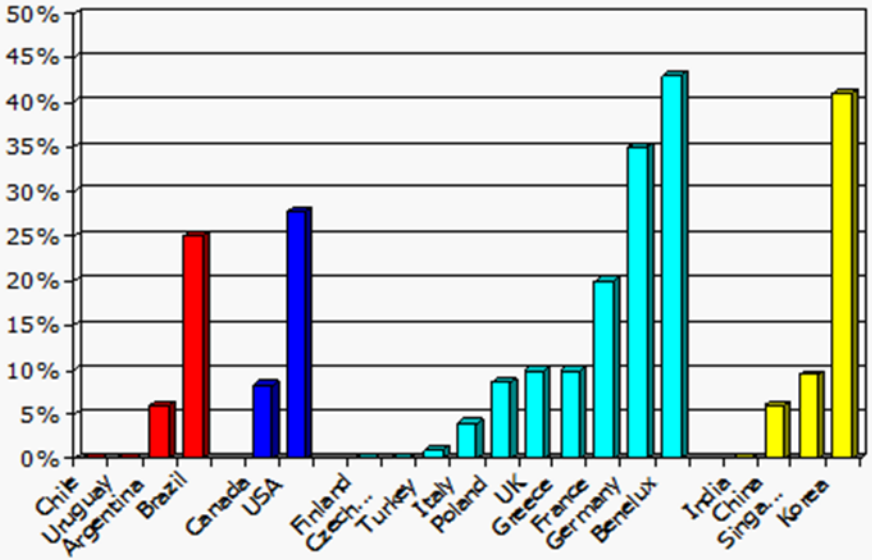
Statural Growth – Height SDS



International Pediatric Peritoneal Dialysis Network

Growth Hormone Utilization by Country

640 children with current height below 3rd pct



International Pediatric Peritoneal Dialysis Network

Relative costs of 1 year of rhGH and a dietician

- $1m^2$ child requires a 12mg cartridge per week = £278.20 per week
- £14,467 per year
- So 3 patients on rhGH or 1 dietician?

Conclusions

- RhGH is effective and safe in RCTs over 2 years of treatment
- It is unlikely that this height gain will be lost and is therefore expected to contribute to improved final height
- Response to rhGH is positively associated with:
  - Younger age
  - Lower HtSDS and growth velocity
  - Greater bone age retardation
  - Higher initial target height deficit and target height
  - Normal pubertal timing
  - Better GFR
- Final height correlates most strongly with height at start of RRT
- Final height is improving, although the part played by rhGH in this is unknown

Which is NOT true? In CKD:

a. GH levels may be increased

b. GH secretion is reduced by metabolic acidosis, malnutrition and steroids

c. SOCS dephosphorylate the GH-activated JAK-STAT cascade and so exert a GH-regulated negative feedback loop

d. GH decreases the ratio of IGF-1 to IGFBP3

Which is NOT true?

Better response to rhGH is associated with the following factors at the start of treatment:

a. Lower HtSDS
b. Greater target-height deficit
c. Better growth velocity
d. Greater bone age retardation

Which is true? rhGH is associated with:

a. Acceleration of bone age compared to chronological age

b. Increased rate of progression of CKD

c. Rejection episodes in transplant patients

d. Benign intracranial hypertension