Growth Hormone Replacement Therapy: Clinical and Economic Implications for Managed Care

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Talking Points

- Review clinical and economic data on recombinant human growth hormone (rhGH) therapy for adults and children with growth hormone deficiency (GHD) and related disorders, including:
  - Outcomes
  - Cost

Growth Hormone Deficiency in Adulthood

- Approximately 50,000 adults in the US have GHD
  - 6,000 new cases are reported each year, including GHD children who transition to GHD as an adult
- Categories based on the time GHD became manifest
  - **Adult-onset (acquired) GHD:** caused by trauma, central nervous system infection, hypothalamic or pituitary tumors, infiltrative or granulomatous disease, cranial irradiation, surgery, etc.
  - **Pediatric Organic GHD:** caused by genetic or acquired defects which continue into adulthood
  - **Child-onset idiopathic:** childhood GHD of unknown cause that may or may not continue into adulthood

Adult Growth Hormone Deficiency (AGHD). The Human Growth Foundation Web site. Available at: http://www.hgfound.org/res_aghd.explained.html#aghdexplained3. Accessed October 12, 2010.

Clinical and Emotional Impact of Growth Hormone Deficiency

Physical[1-4]	Metabolic[1-6]	Psychosocial[7]
• Reduced bone mineral density • Reduced lean body mass • Increased body fat • Excessive fatigue • Limited ability to perform daily activities	• Abnormal lipid profile • Increased cardiovascular risk • Abnormal body composition • Reduced bone density • Poor immune function	• Reduced quality of life • Emotional disturbances • Reduced self-confidence • Social isolation • Impaired memory and concentration

1. Boguszewski CL, et al. *Eur J Endocrinol*. 2005;152(1):67–75.
2. Hardin DS, et al. *Clin Pediatr (Phila).* 2007;46(4):279–286.
3. Saggese G, et al. *J Clin Endocrinol Metab.* 1996;81(8):3077–3083.
4. Underwood LE, et al. *J Clin Endocrinol Metab*. 2003;88(11):5273–5280.
5. Cook DM, et al. *Endocr Pract*. 2009;15(Suppl 2):1–29.
6. Boot AM, et al. *J Clin Endocrinol Metab*. 1997;82(8):2423–2428.
7. Kołtowska-Haggstrom M, et al. *Eur J Endocrinol*. 2009;161(Suppl 1):S51–S64.

GH-Deficient Adults Are at Greater Risk for CVD and Other Chronic Conditions

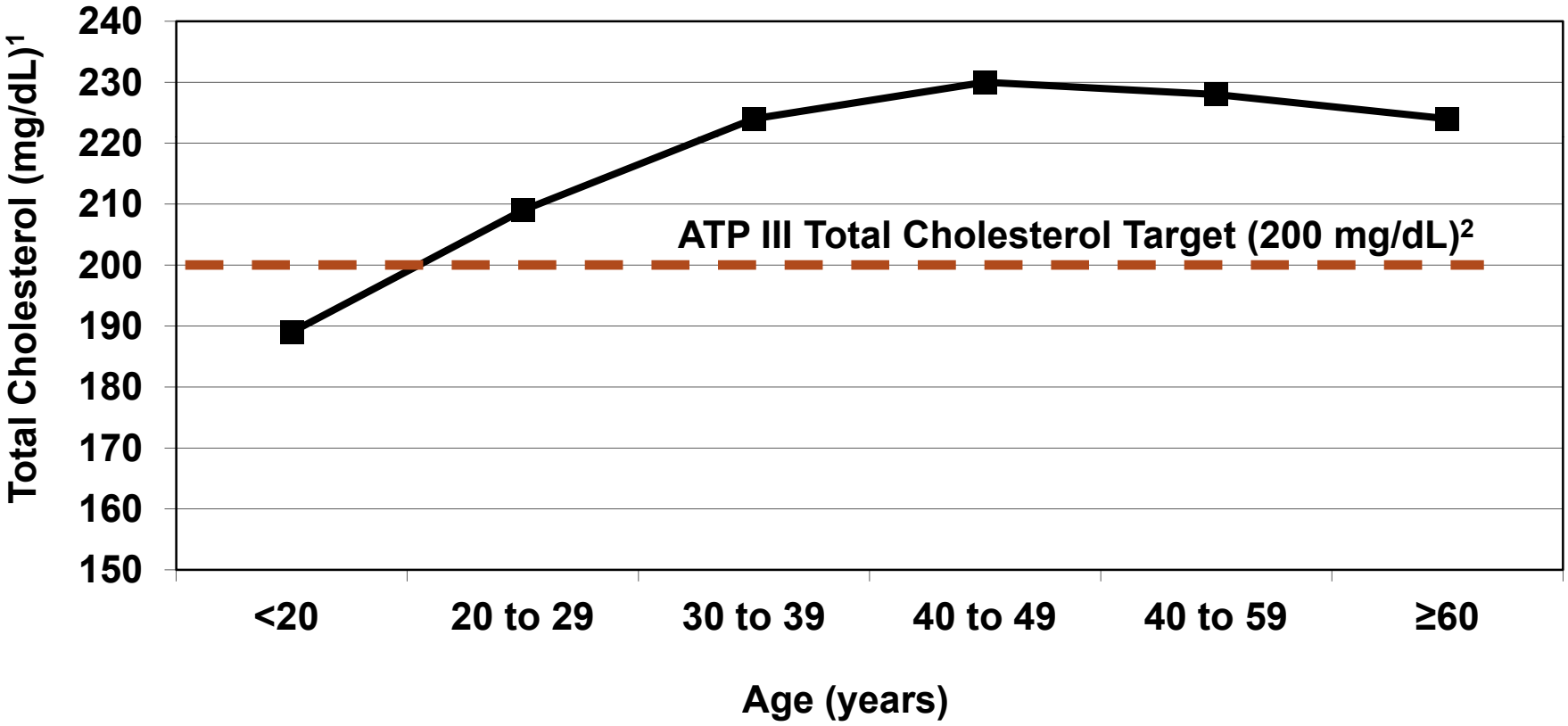
Parameter	Evidence of Morbidity
Bone density	Three-fold increase in bone fracture frequency[1]
Atherosclerosis	Over 20% increased carotid intima thickness[2]
Inflammation	Two-fold increase in inflammatory markers CRP and IL-6[3]
Body composition	Greater adiposity, lower muscle strength[4]
Quality of life	Impaired quality of life compared with the general population[5]

CVD=cardiovascular disease
CRP=C-reactive protein
IL=interluekin

1. Rosen T, et al. *Eur J Endocrinol*. 1997;137(3):240–245.
2. Sen F, et al. *Eur J Endocrinol*. 2008;158(5):615–622.
3. Leonsson M, et al. *Clin Endocrinol (Oxf)*. 2003;59(2):242–250.
4. Sartorio A, et al. *Arch Med Res*. 2008;39(1):78–83.
5. Blum WF, et al. *J Clin Endocrinol Metab*. 2003;88(9):4158–4167.

Total Cholesterol in GHD Patients Is Above Guideline-Recommended Levels

Elevated Cholesterol Adds to the CVD Risk in Adult GHD

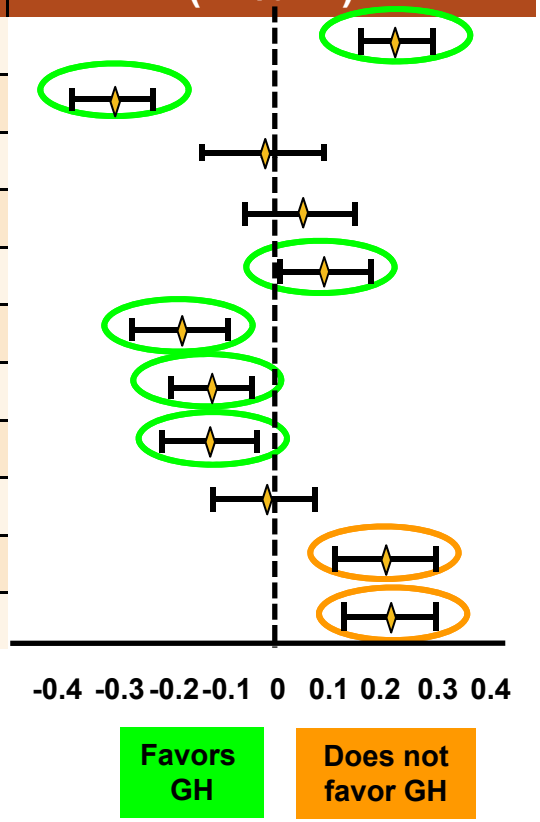


1. Abs R, et al. *Eur J Endocrinol*. 2006;155(1):79–90.
2. ATP III Guidelines At-A-Glance Quick Reference. National Heart Lung and Blood Institute Web site. Available at: http://www.nhlbi.nih.gov/guidelines/cholesterol/atglance.pdf. Accessed October 12, 2010.

GH Therapy Has Significant Beneficial Effects on Cholesterol, Blood Pressure

Factors	Treatment		Weighted mean change (GH-placebo)
	GH	Placebo	
Lean B mass	473	474	2.82 kg
Fat mass	352	345	3.05 kg
BMI	134	134	-0.12 kg/m^2
TG	202	203	2.71 mg/dL
HDL Chol.	267	261	2.32 mg/dL
LDL Chol.	255	248	-20.50 mg/dL
Total Chol.	310	306	-13.15 mg/dL
D.B.P.	200	201	-1.80 mmHg
S.B.P.	190	191	2.06 mmHg
Insulin	192	194	1.2 IU/mL
Glucose	254	257	8.51 mg/dL

Global Effect Size (95% CI)



GH=growth hormone
BMI=body mass index
TG=triglyceride
HDL=high density lipoprotein
LDL=low density lipoprotein
Chol=cholesterol
DBP=diastolic blood pressure
SBP=systolic blood pressure

Maison P, et al. *J Clin Endocrinol Metab*. 2004;89(5):2192–2199.

GH Therapy Alters Multiple Cardiometabolic Variables

	Baseline	After 6 Mo GH Therapy	Change from Baseline (%)
Fasting insulin (mU/mL)	3.5	3.1*	-11
HbA1c (%)	6.2	5.6*	-9.7
C-reactive protein (mg/dL)	7.02	4.81	-31.5
Fasting plasma glucose (mg/dL)	94.8	91.7	-3.3
Total cholesterol (mg/dL)	209.5	185.5†	-11.5
Triglycerides (mg/dL)	153.7	125.5	-18.3
Lp(a) (mg/dL)	15.3	21.3	40.2

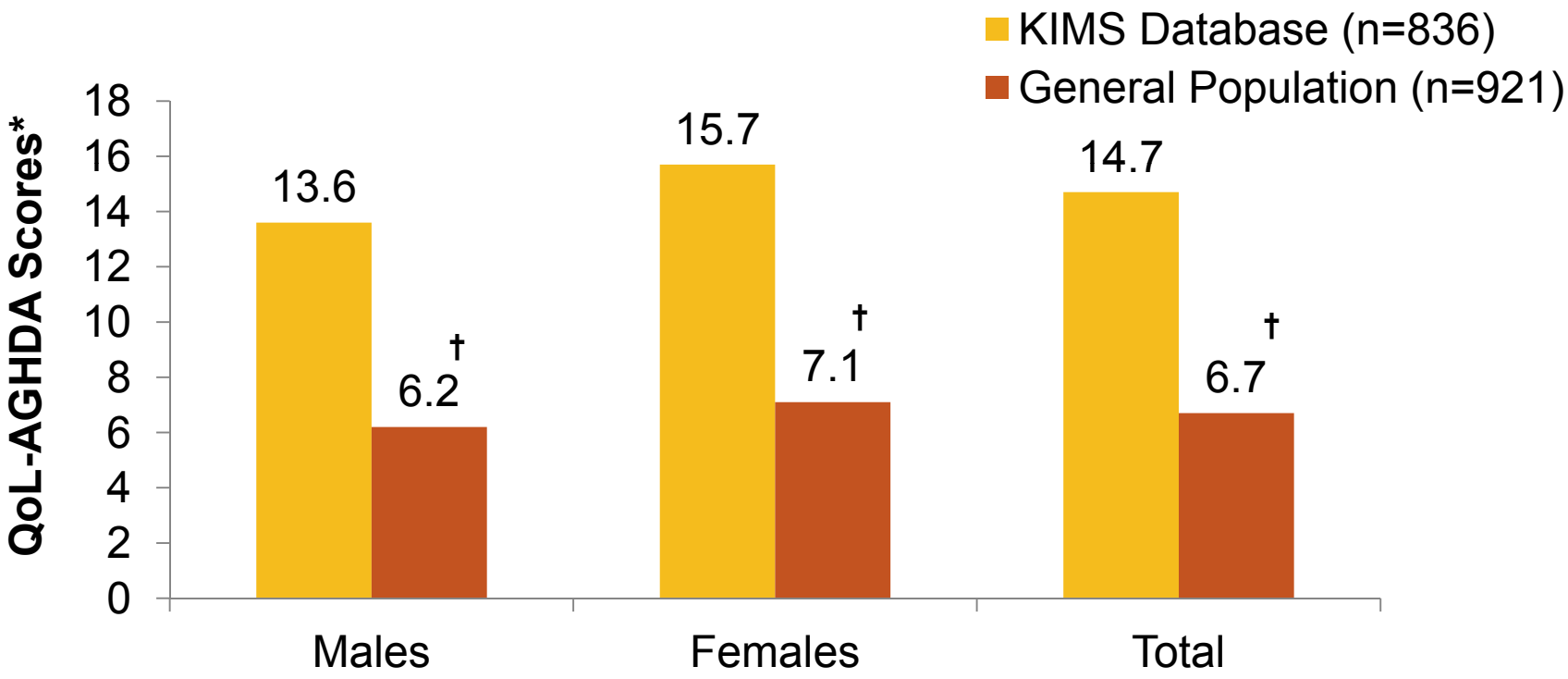
n=20 adult GHD patients
Mean age=46 years

Initial and final doses: 0.33 and 0.38 mg/kg (women, n=10)
0.25 and 0.35 mg/kg (men, n=10)

*Changes are not clinically significant
†$P<0.05$
Oliviera JL, et al. *J Clin Endocrinol Metab*. 2007;92(12):4664–4670.

Quality of Life in Adults With GHD Is Significantly Worse vs General Population

Data from the KIMS International Metabolic Database

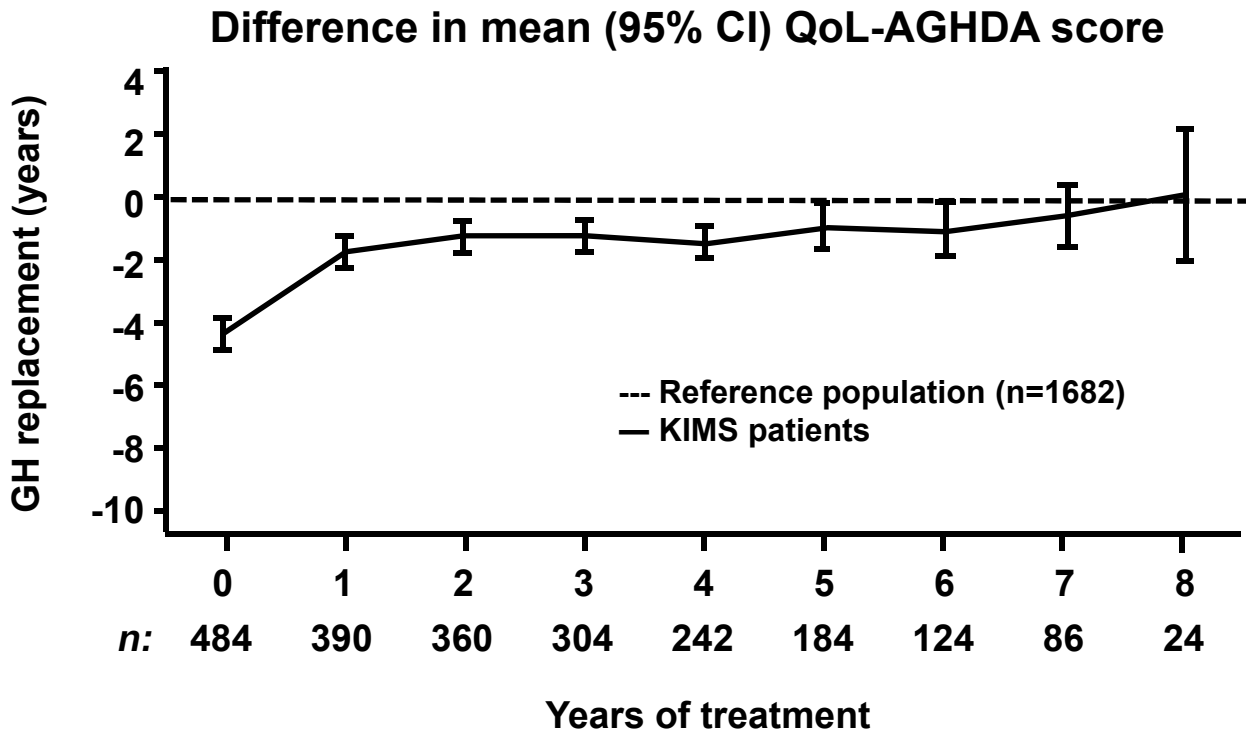


KIMS=Kabi International Metabolic Study
QoL-AGHDA=Quality of Life Assessment of Growth Hormone Deficiency in Adults

*Lower scores on the QoL-AGHDA indicate a higher quality of life
†*P*<0.001 vs patients in the KIMS database
Kołtowska-Haggstrom M, et al. *Horm Res*. 2005;64(1):46–54.

Quality of Life in GH-Deficient Adults Improves With GH Replacement Therapy

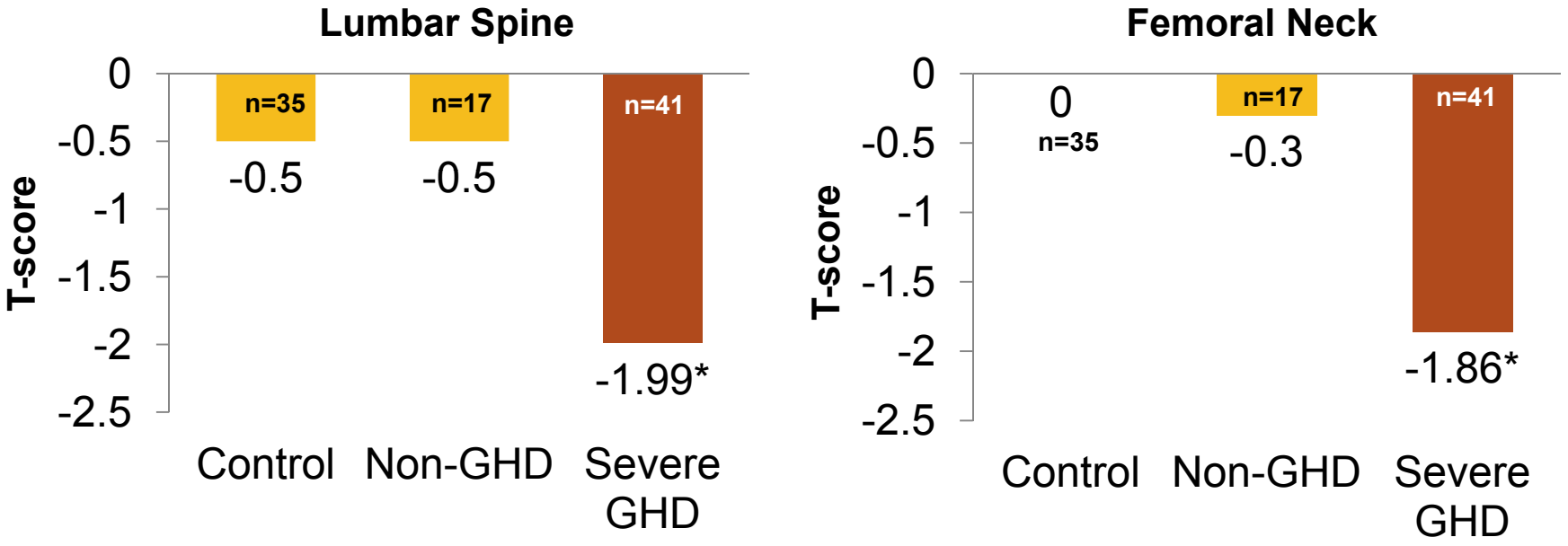
Data from the KIMS International Metabolic Database



KIMS=Kabi International Metabolic Study

Kołtowska-Haggstrom M, et al. *Eur J Endocrinol*. 2006;155(1):109–119.

Very Low BMD in Adults With Severe GHD



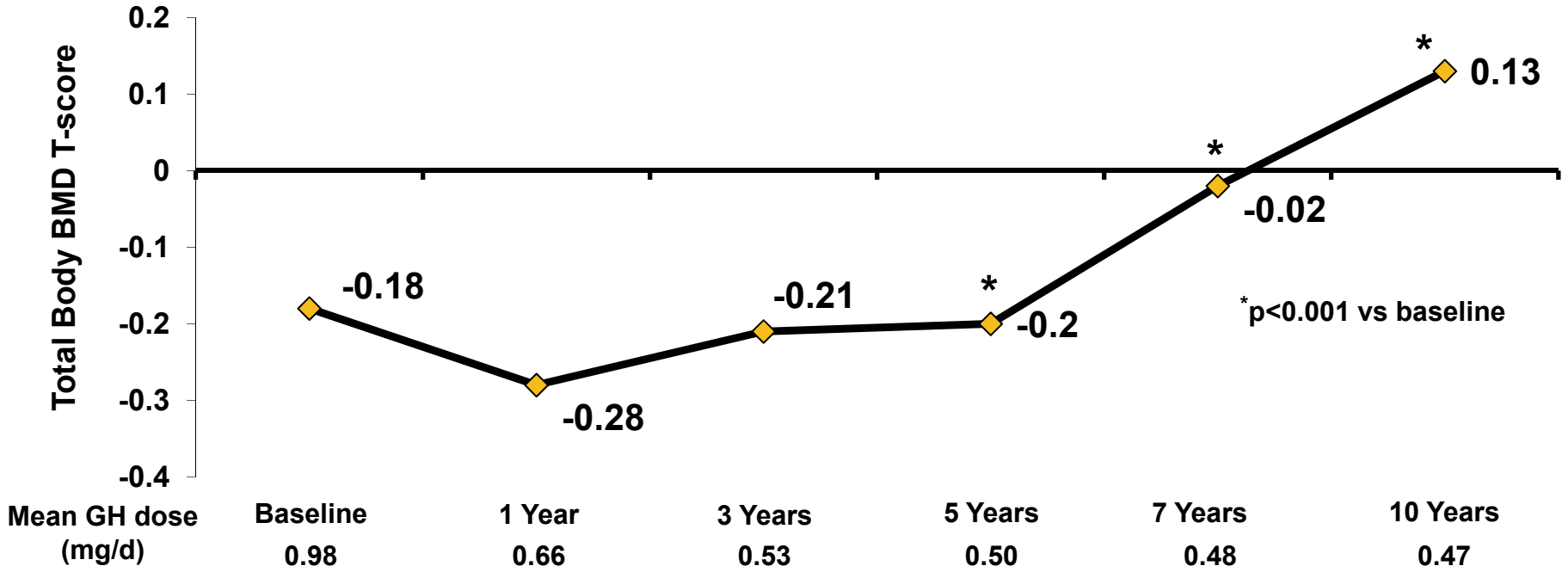
Mean GH (μ/L) 40.7, 28.3, and 0.9 for control, non-GHD, and severe GHD, respectively

******P*<0.01**

Colao A, et al. *J Clin Endocrinol Metab*. 1999;84(6):1919–1924.

Bone Mineral Density in GHD Adults Increases With GH Therapy

Effects of 10 Years of GH Therapy in GHD 87 Adults



BMD=bone mineral density

Gotherstrom G, et al. *Eur J Endocrinol*. 2007;156(1):55–64.

12 Months of GH Therapy Reduced the Need for Health Care

Data from the KIMS International Metabolic Database

	Baseline	12 Months
Sick leave days (number in previous 6 months)	9.5	3.8*
Hospital days (number in previous 6 months)	1.7	0.6*
Doctor visits (number in previous 6 months)	2.1	1.4†
Leisure time physical activity (visual analog scale score)	40.8	51.1‡
Satisfaction with leisure time activities (visual analog scale score)	41.6	48.8‡
Need for assistance with daily activities (%)	21	16*

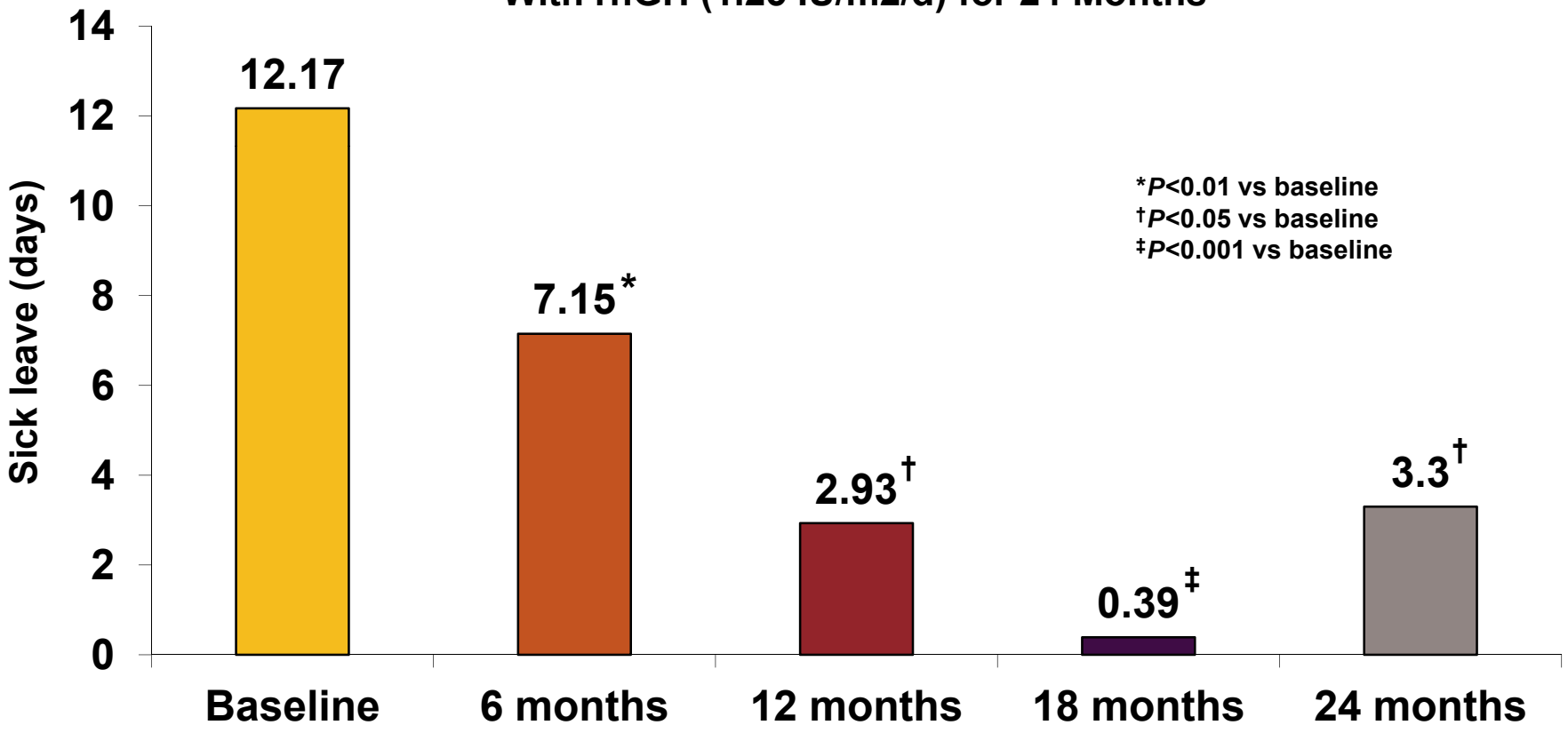
- n=150 and 154 adult men and women with GHD, respectively.
- Mean ages: Men 51 years; women: 49 years.
- None of the patients had received prior GH therapy in adulthood.
- GH dose ranged from 0.042 mg/kg/wk to 0.083 mg/kg/wk.

*P<0.05 vs baseline
†P<0.01 vs baseline
‡P<0.001 vs baseline

Hernberg-Ståhl E, et al. *J Clin Endocrinol Metab*. 2001, 86(11):5277–5281.

24 Months of GH Replacement Reduced Sick Leave Days

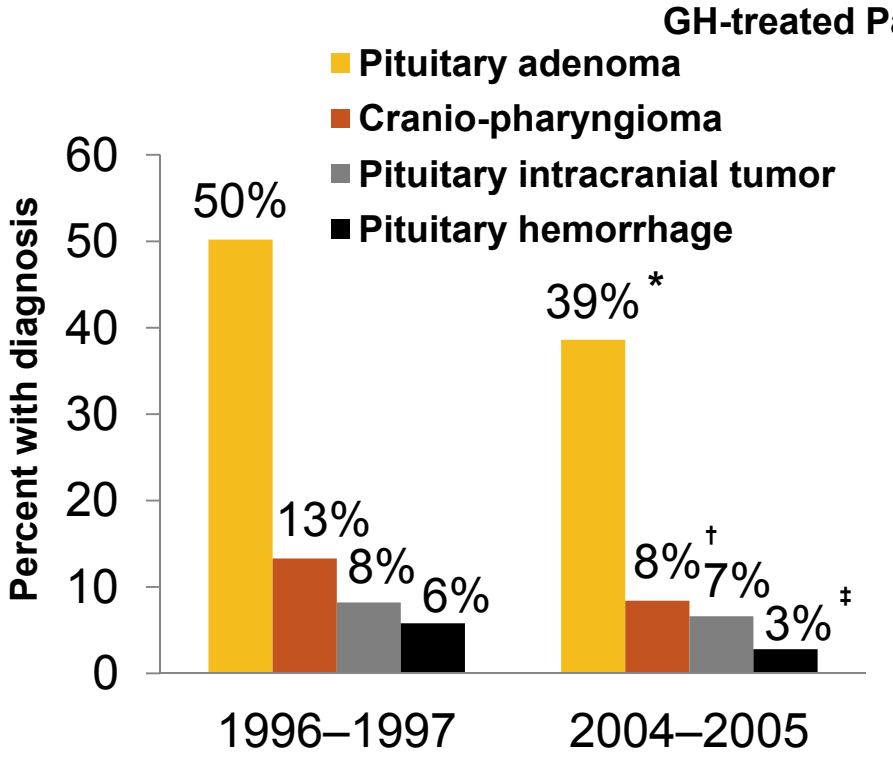
148 Adult GHD Patients (mean age = 43.5 yr) Treated With rhGH (1.25 IU/m2/d) for 24 Months



Verhelst J, et al. *Clin Endocrinol (Oxf).* 1997;47(4):485–494.

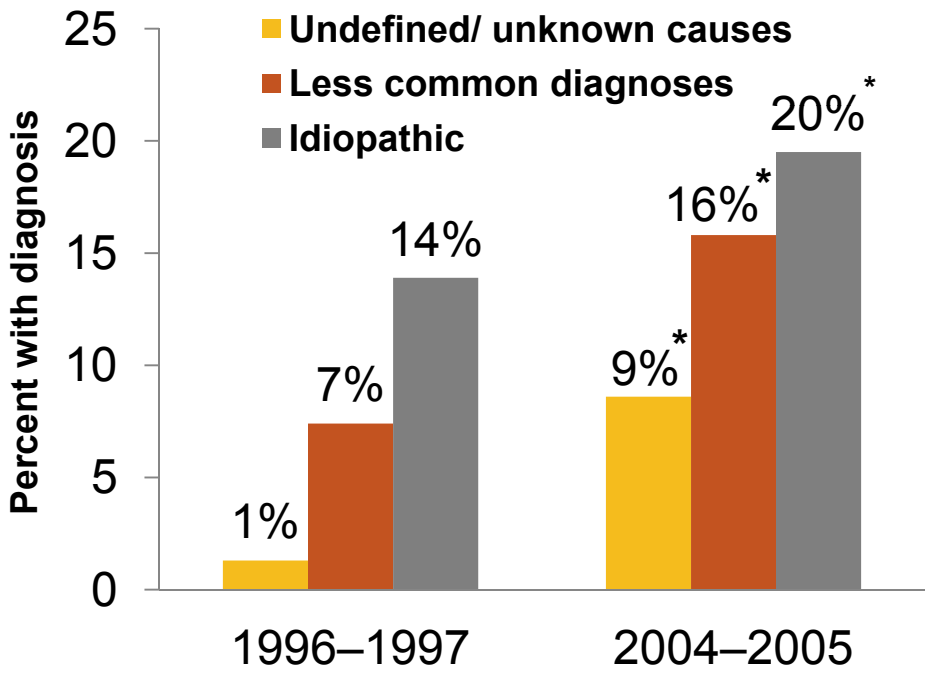
Shift in Use for GH Therapy Indicates a Trend Toward Less Severe Forms of GHD

Decreasing Trends



*P<0.001 vs 1996–1997
†P=0.005 vs 1996–1997
‡P=0.001 vs 1996–1997

Increasing Trends



*P<0.001 vs 1996–1997

Webb SM, et al. *J Clin Endocrinol Metab*. 2009;94(2):392–399.

Adult GHD: Summary

- Adults with GHD are at increased risk for cardiovascular disease, impaired physical function, and reduced quality of life
- It is recommended that GH be prescribed for adults with a history of hypothalamic-pituitary disease and biochemically proven GHD
  - GH therapy appears to have a beneficial effect on bone, muscle, cardiovascular risk, quality of life and other variables
  - However, data on the effect of GH therapy on endpoints such as cardiovascular events, fractures, and death are lacking

Growth Hormone Deficiency and Other Forms of Short Stature in Childhood

- Approximately 1 in 3,500 children in the US carries a diagnosis of growth hormone deficiency (GHD)[1]
  - 20% have organic GHD resulting from central nervous system tumors, radiation, infection, or traumatic brain injury
  - 80% have idiopathic GHD with no known cause

Additional FDA-approved Indications for GH Therapy in Children		
	Definition	**Maximum Estimated Prevalence***
ISS[2]	**Height ≥2.25 standard deviations *below* the mean for age and gender without evidence of underlying disease or GHD**	**400,000**
SGA[3]	**Birth weight and/or length at ≥2 standard deviations below the mean for gestational age and height below -2 SDS at age 4**	**90,000**

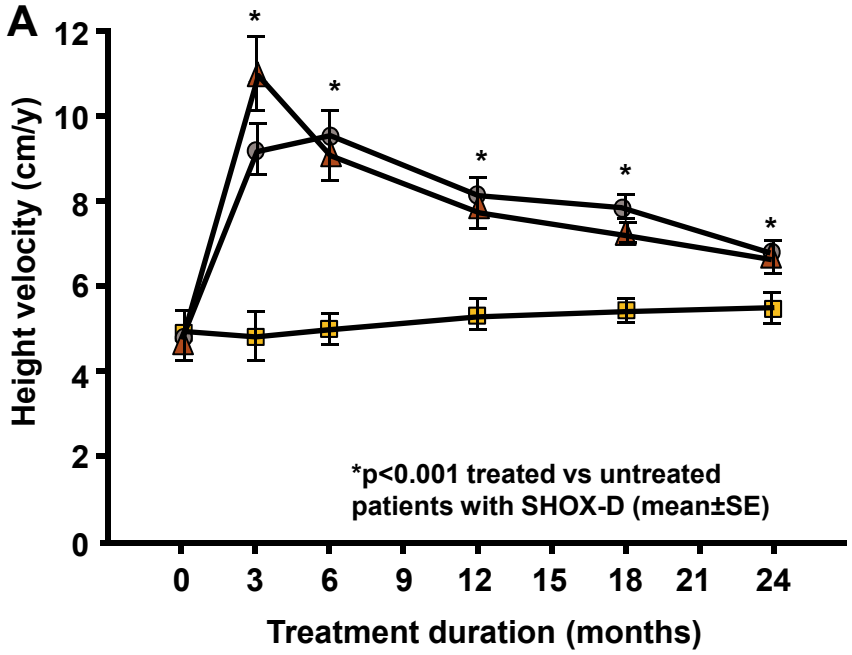
***Actual number of patients presenting to endocrinologists is approximately 10-fold lower.**

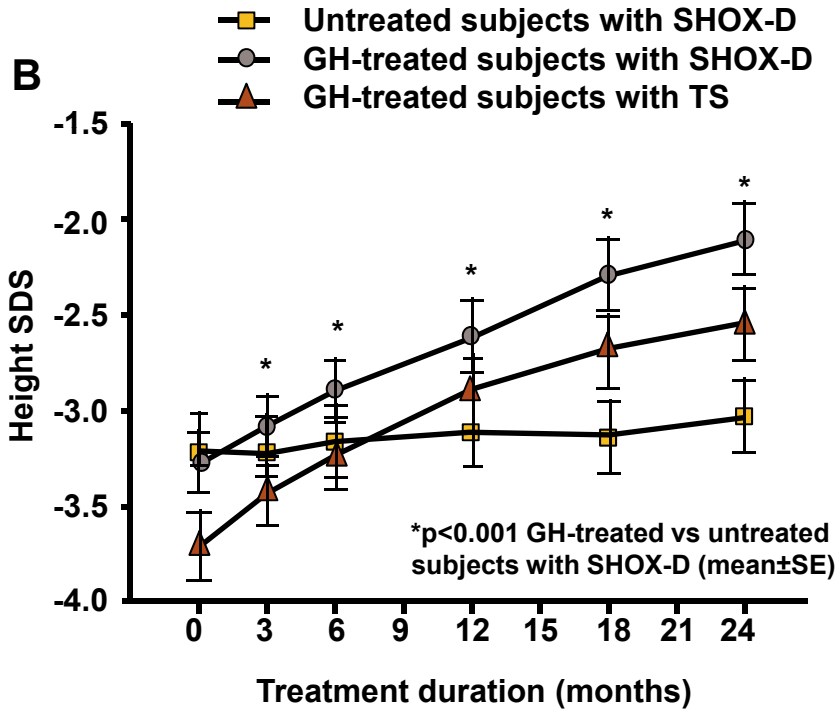
1. **Lindsay R, et al. *J Pediatr.* 1994;125(1):29–35.**
2. **Rekers-Mombarg LT, et al. *J Pediatr Endocrinol Metab.* 1999;12(5):611–622.**
3. **Lee PA, et al. *Pediatrics*. 2003;111(6 Pt 1):1253–1261.**

ISS=idiopathic short stature
SGA=small for gestational age

Long-term GH Therapy Is Beneficial to Patients With Genetically-Mediated Short Stature

24 Months of GH Effective for Treating Short Stature Associated With SHOX-D and Turner Syndrome





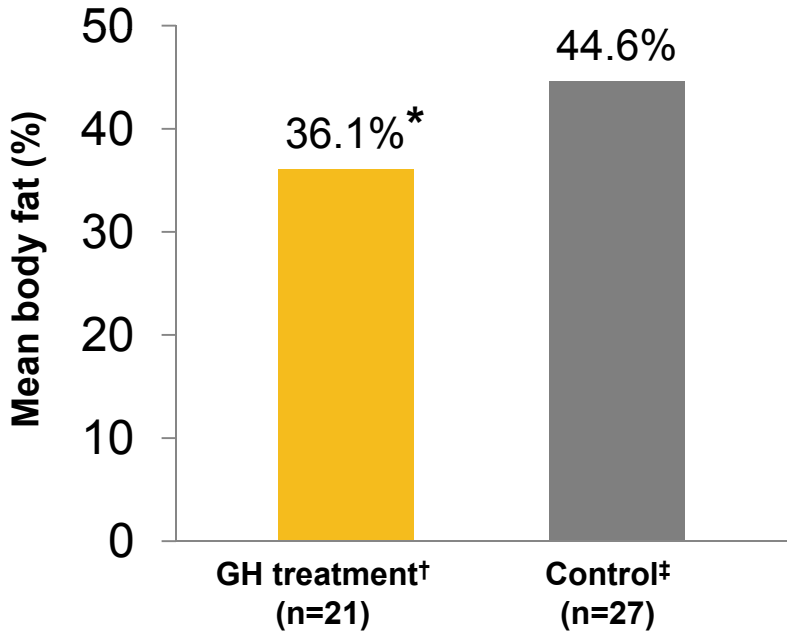
SHOX-D=short stature homeobox-containing gene deficiency

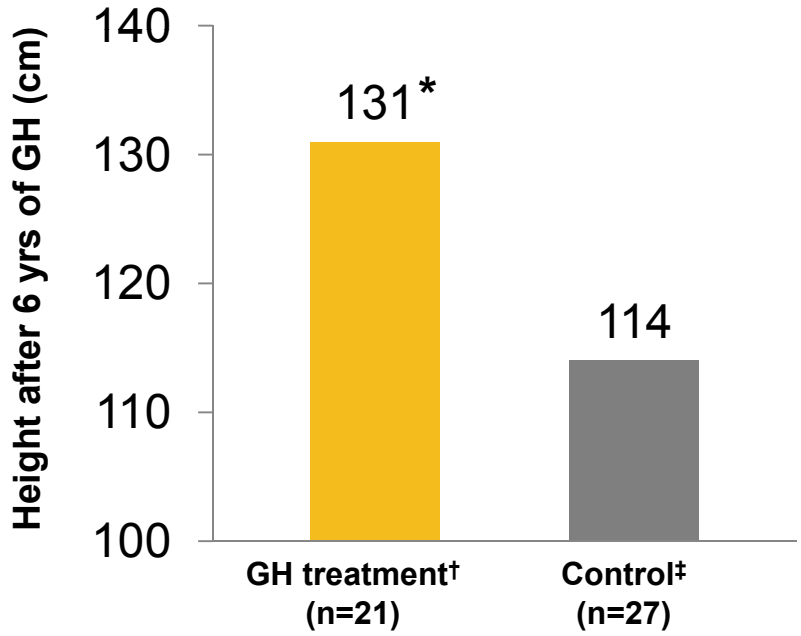
SHOX-D group: n=52 (aged 3.0–12.3 yrs)
Turner Syndrome group: n=26 (aged 4.5–11.8 yrs)
All patients received GH 50 mg/kg/day via sc injection

Blum WF, et al. *J Clin Endocrinol Metab.* 2007;92(1):219–228.

GH Therapy Reduces Body Fat and Increases Height in Patients With Genetically-Mediated Short Stature

Significantly Lower Body Fat and Greater Height Following 6 Years of GH Therapy in Children With Prader-Willi Syndrome

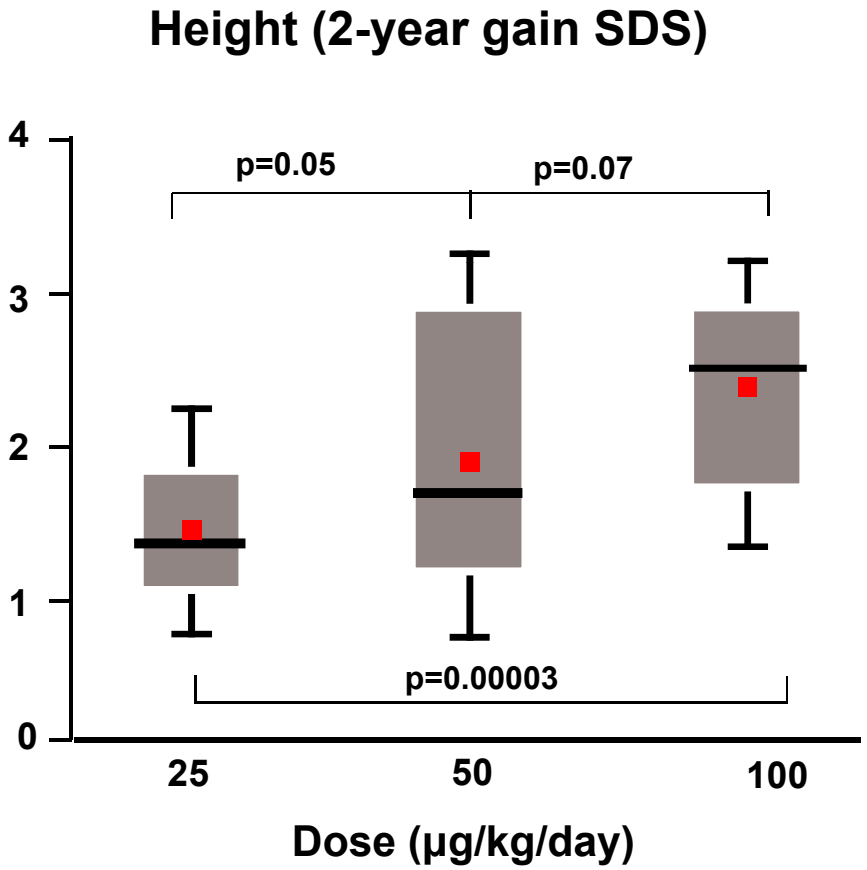


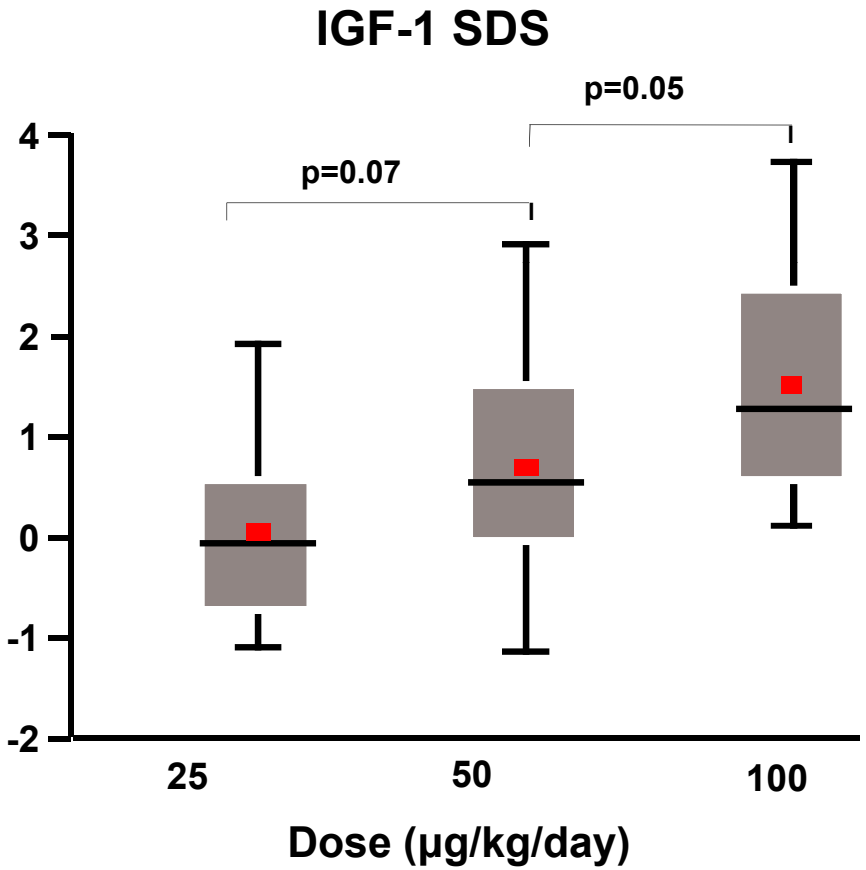


*P<0.01 vs control
†Aged 6–9 yrs at baseline
‡Aged 5–9 yrs at baseline

Carrel AL, et al. *J Clin Endocrinol Metab.* 2010;95(3):1131–1136.

Dose-related Responses of Height and IGF-1 to 2 Years of GH Therapy in GH-Deficient Boys





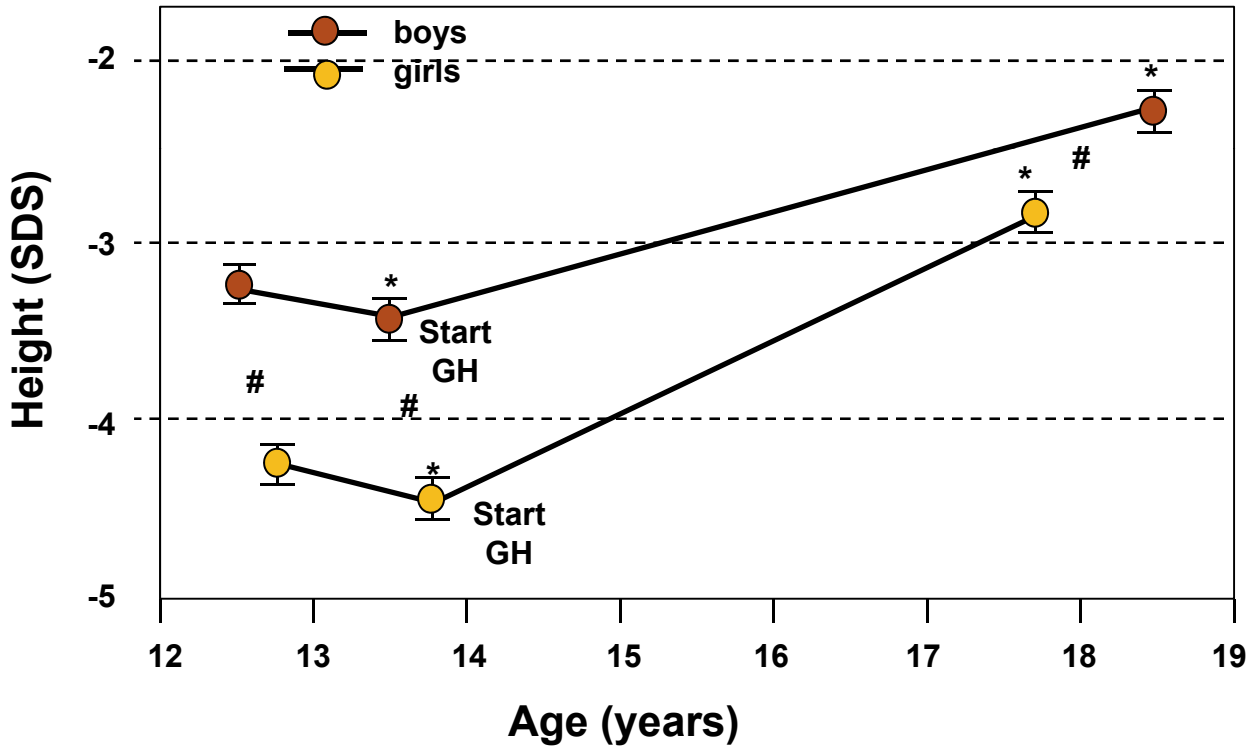
Plots represent +/- 2 SD (error bars), the 25 and 75% (box), the mean (red square), and the median (horizontal bar).

SDS=standard deviation score
IGF-1=insulin-like growth factor 1

Cohen P, et al. *J Clin Endocrinol Metab*. 2002;87(1):90–98.

Long-term GH Therapy in Children With CKD Results in an Increased Adult Height

Data From the Pfizer International Growth Database (KIGS)



CKD=chronic kidney disease

Boys: n=193; aged 4.7–19.7 years; Girls: n=47; aged 8.1–18.0 years.
All patients received GH (target dose 0.33 mg/kg/week) for at least 1 year.

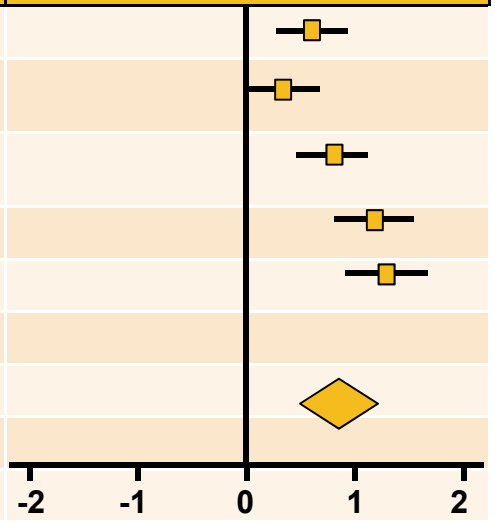
#*P*<0.01 boys vs girls
**P*<0.01 vs previous time point

Nissel R, et al. *J Clin Endocrinol Metab*. 2008;93(4):1359–1365.

GH Therapy in Children Born Small for Gestational Age Increases Adult Height

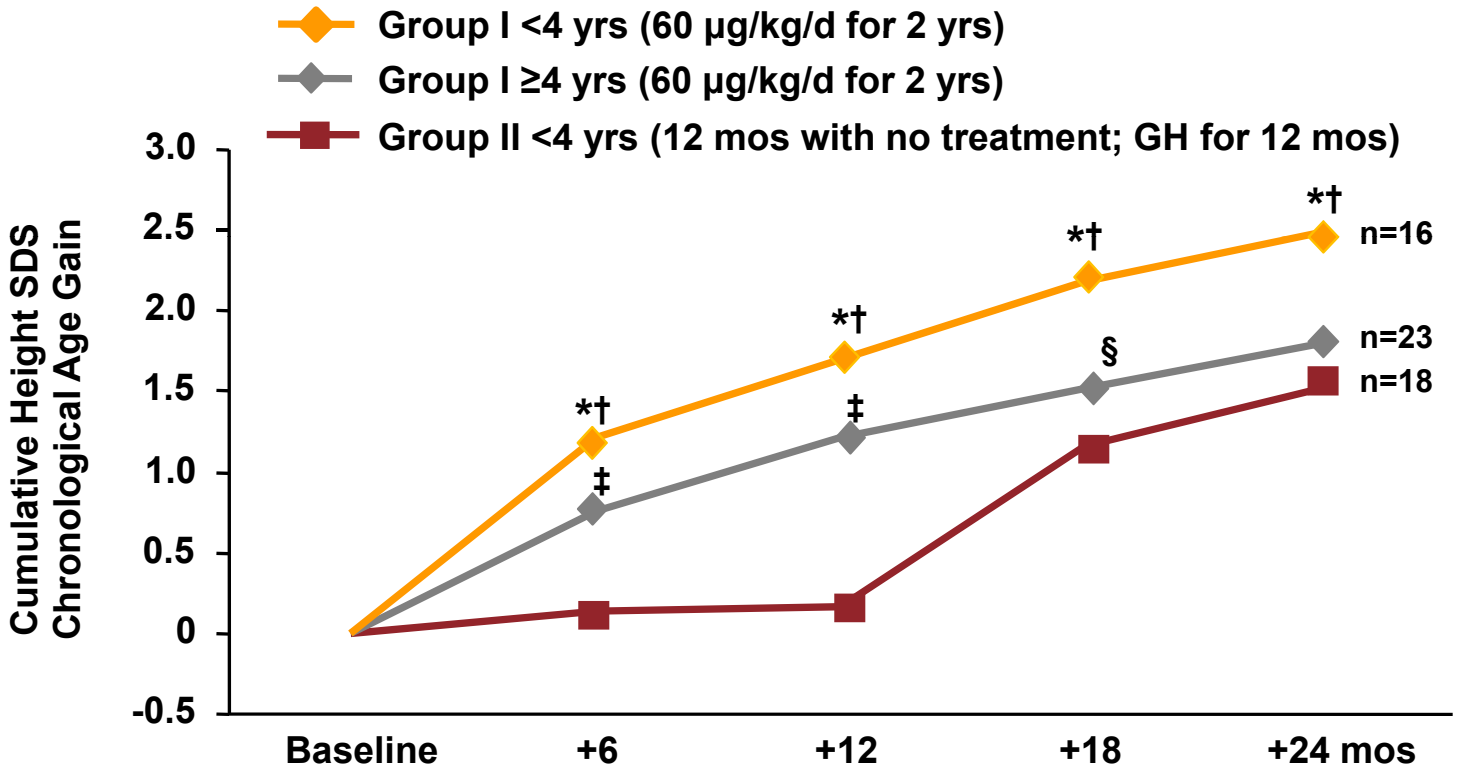
Meta-analysis of 5 Randomized Controlled Clinical Trials

Study or Subgroup	Treated			Untreated			Weight	Mean Difference	Mean Difference
	Mean	SD	Total	Mean	SD	Total		IV, Random [95% CI]	IV, Random, 95% CI
Carel et all[11] (2003)	-2.1	1.0	102	-2.7	0.9	47	21.3%	0.60 [0.28–0.92]	
Dahlgren and Wikland[10] (2005) <2 y	-1.6	0.8	41	-2.0	0.8	34	20.2%	0.40 [0.04–0.76]	
Dahlgren and Wikland[10] (2005) >2 y	-1.2	0.7	36	-2.0	0.8	34	20.5%	0.80 [0.45–1.15]	
Van Dijk et al[13] (2007)	-1.4	1.0	37	-2.6	0.6	25	19.2%	1.20 [0.80–1.60]	
Van Pareren et al[12] (2003)	-1.0	0.8	54	-2.3	0.7	15	18.8%	1.30 [0.89–1.71]	
Total (95% CI)			270			155	100%	0.85 [0.52–1.17]	
Heterogeneity: $\tau 2=0.10$; $\chi 2=15.58$, $df=4$($P=0.004$); $\rho=74\%$									
Test for overall effect: $z=5.11$ ($P<0.00001$)									



Maiorana A, Cianfarani S. *Pediatrics.* 2009;124(3);e519–e531.
Carel JC, et al. *J Clin Endocrinol Metab.* 2003;88(4):1587–1593.
Dahlgren J, Wikland KA. *Pediatr Res.* 2005;57(2):216–222.
van Dijk M, et al. *J Clin Endocrinol Metab.* 2007;92(1):160–165.
van Pareren Y, et al. *J Clin Endocrinol Metab.* 2003;88(8):3584–3590.

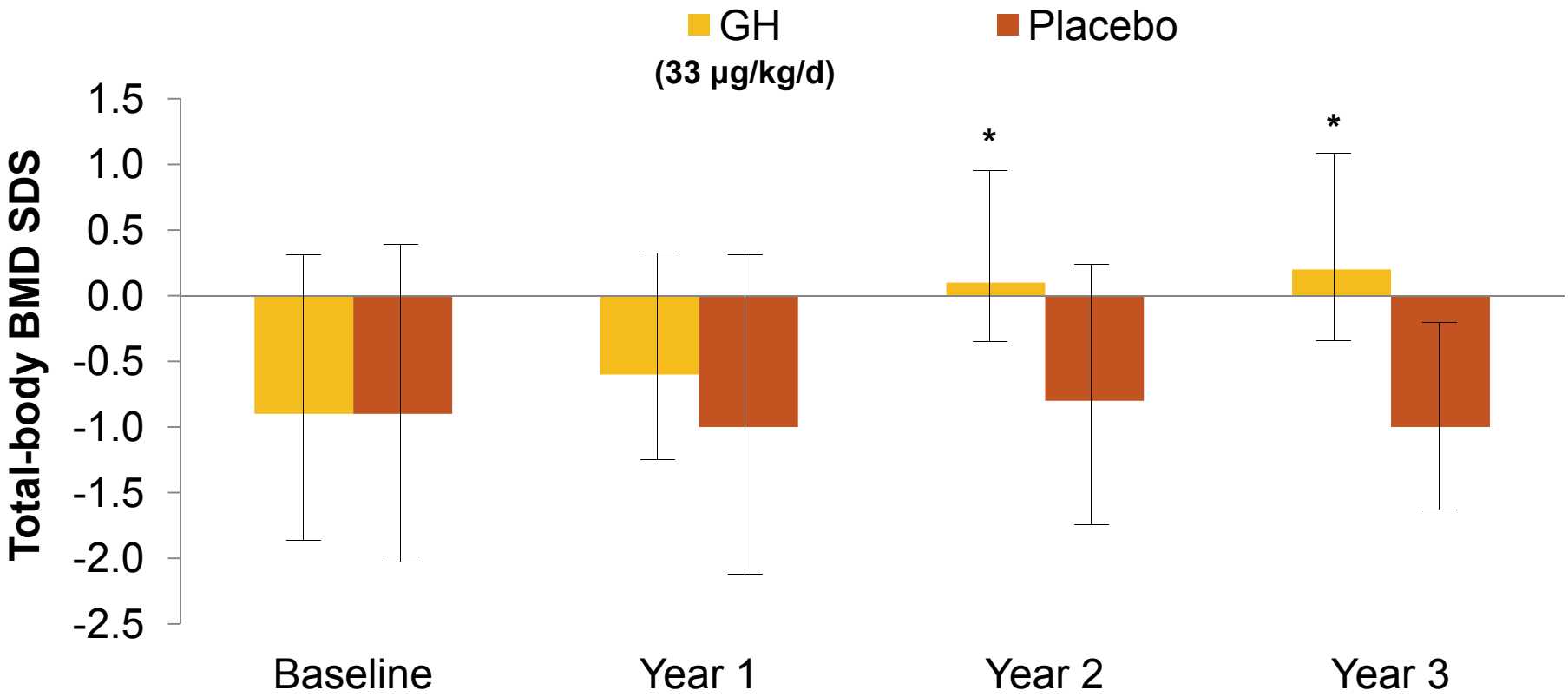
SGA Children Without Spontaneous Catch-up Growth Benefit From GH Treatment



*P<0.05 Group I <4 years vs Group I ≥4 years
†P<0.05 Group I <4 years vs Group II <4 and ≥4 years
‡P<0.05 Group I ≥4 years vs Group II <4 and ≥4 years
§P<0.05 Group I ≥4 years vs Group II ≥4 years

Argente J, et al. *J Clin Endocrinol Metab*. 2007;92(8):3095–3101.

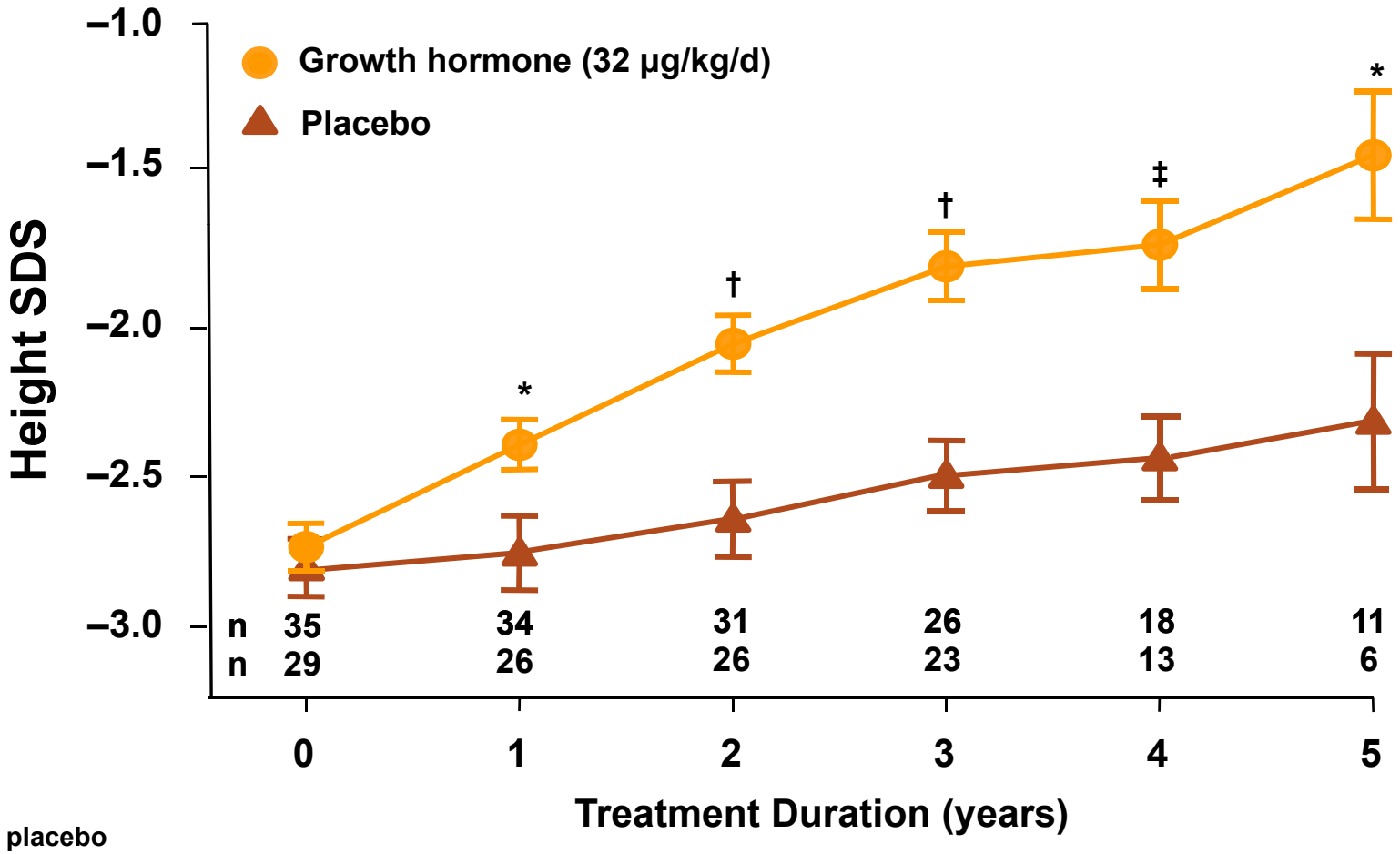
GH Therapy Normalized BMD in Children Born Small for Gestational Age



*P<0.001 vs placebo

Arends NJ, et al. *Clin Endocrinol (Oxf)*. 2003;59(6):779–787.

Height Is Greater in GH-treated Idiopathic Short Stature Patients vs Controls

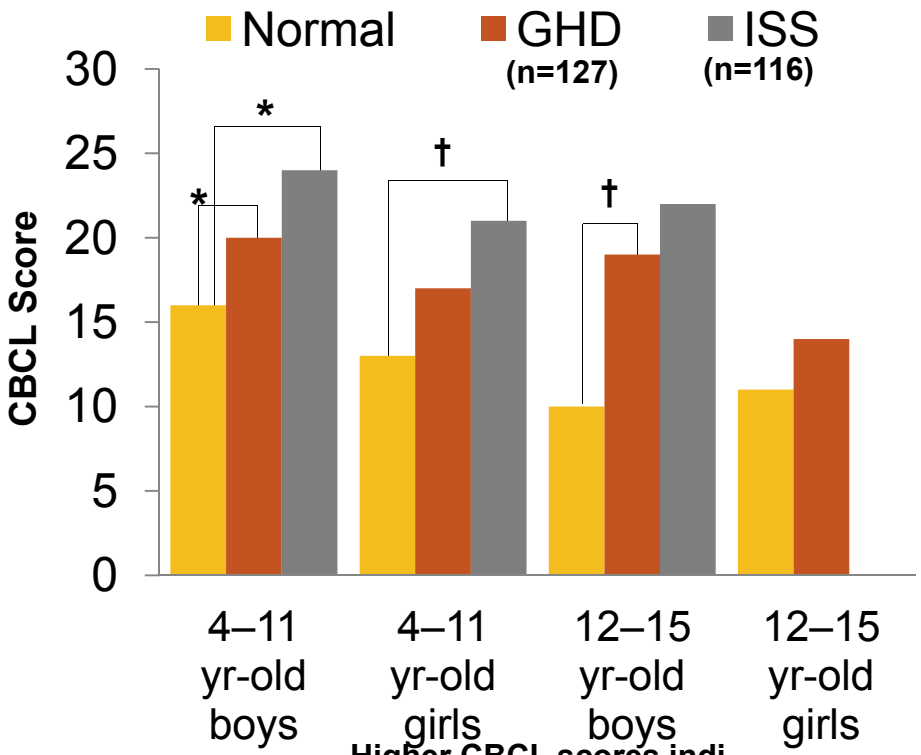


*P<0.05 vs placebo
†P<0.001 vs placebo
‡P<0.01 vs placebo

Leschek EW, et al. *J Clin Endocrinol Metab*. 2004;89(7):3140–3148.

Efficacy of GH Therapy on the Psychosocial Profile of ISS Children

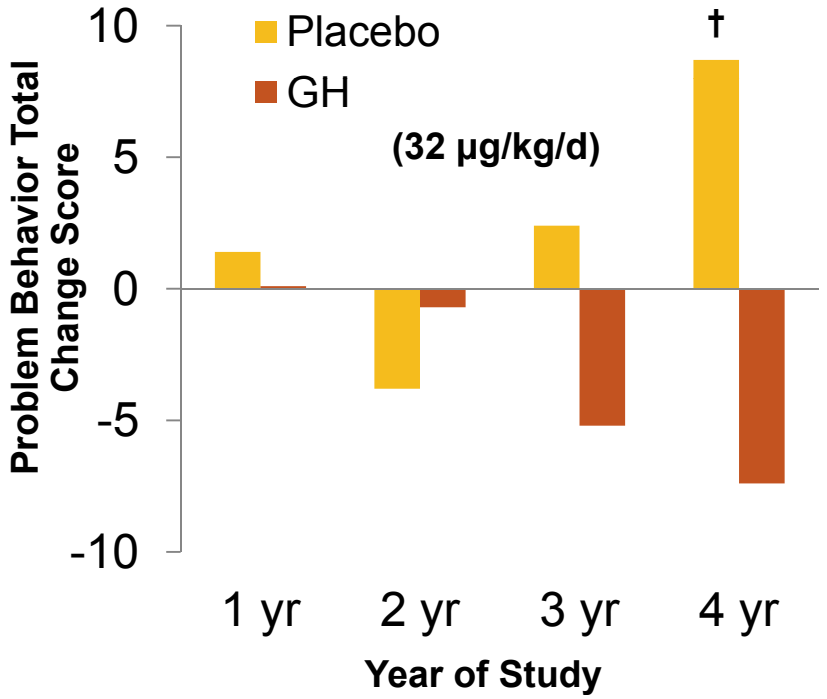
Child Behavioral Checklist (CBCL) Score by Age[1]



Higher CBCL scores indicate inferior functioning.

*P<0.001 vs control
†P<0.05 vs control

Total Change in CBCL Score After 4 Years of GH Therapy[2]



Sample sizes for years 1, 2, 3, and 4: Placebo=9, 19, 9, 3; GH=17, 23, 12, 9, respectively.

1. Tanaka T, et al. *Clin Pediatr Endocrinol*. 2009;18(1):15–22.
2. Ross JL, et al. *J Clin Endocrinol Metab.* 2004;89(10):4873–4878.

Childhood GHD: Summary

- 1 in 3,500 children in the US are diagnosed with GHD
  - Only 20% have organic GHD; readily identifiable cause absent in the majority of cases
- Approximately 90,000 infants are born SGA in the US annually
  - GH treatment in SGA include increased final adult height and bone mineral density
  - GH therapy can be a cost-effective treatment for SGA
- Approximately 400,000 children in the US have ISS
  - GH therapy increases height and may improve behavioral profile of children with ISS
  - However, no consensus exists on the use of GH in ISS