Hormone Research in Paediatrics 89.3 (2018): 200-204

DOI: http://doi.org/10.1159/000486336

HORMONE RESEARCH IN PÆDIATRICS

KARGER
www.karger.com

Article title	rhIGF-1 Treatment Increases Bone Mineral Density and Trabecular Bone Structure in Children with PAPP-A2 Deficiency
Article title second language	
Article title third language	
Subtitle	
Short title	rhIGF-1 and Bone in PAPP-A2 Deficiency
Section title	Brief Report

Relation(s) **Example:**	Initials **S.-J.**	Given name Seo-Jin	Surname/Collaboration Park	Affiliation(s) a,b
2304484	F.G.	Federico G.	Hawkins-Carranza	a
2304485	M.T.	María T.	Muñoz-Calvo	b--d
2304483	G.Á.	Gabriel Á.	Martos-Moreno	b--d
2304486	G.	Gonzalo	Allo-Miguel	a
2304487	L.	Luis	Del Río	e
2304488	J.	Jesús	Pozo	b--d
2304489	J.A.	Julie A.	Chowen	b--d,i
2304490	L.A.	Luis A.	Pérez-Jurado	f--h
2304491	J.	Jesús	Argente	b--d,i

Affiliation(s)		City	State	Country
a	Diabetes and Bone Research Group, Institute i+12, Complutense University and Hospital 12 de Octubre	Madrid		Spain
b	Department of Pediatrics and Pediatric Endocrinology, Hospital Infantil Universitario Niño Jesús, Instituto de Investigación La Princesa	Madrid		Spain
c	Department of Pediatrics, Universidad Autónoma de Madrid	Madrid		Spain
d	Centro de Investigación Biomédica en Red de Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III	Madrid		Spain
e	CETIR Centre Medic	Barcelona		Spain
f	Genetics Unit, Universitat Pompeu Fabra	Barcelona		Spain
g	Hospital del Mar Research Institute (IMIM)	Barcelona		Spain
h	Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Instituto de Salud Carlos III	Barcelona		Spain
i	IMDEA Food Institute, CEI UAM + CSIC	Madrid		Spain

Additional information	

Corresponding author	Prof. Dr. Jesús Argente
Full address	Department of Endocrinology, Hospital Infantil Universitario Niño Jesús
	Avda. Menéndez Pelayo, 65
	ES--28009 Madrid (Spain)
E-Mail	E-Mail jesus.argente@uam.es

Citation line	Journal			
	Horm Res Paediatr			
10.1159/000486336	Article-Nr	486336	CCCode	
ISSN	1663-2818			
ISBN				

Received	Received: October 16, 2017
Accepted	Accepted: December 13, 2017
Revised	
Published online	Published online: ■■■

Keywords	Keywords
	IGF-1 rhIGF-1 PAPP-A2 Bone density Bone structure

Keywords Second Language	

Keywords Third Language	

Abbreviations	

Abstract	Abstract

Aim: Our objective was to determine changes in bone mineral density (BMD), trabecular bone score (TBS), and body composition after 2 years of therapy with recombinant human insulin-like growth factor-1 (rhIGF-1) in 2 prepubertal children with a complete lack of circulating PAPP-A2 due to a homozygous mutation in *PAPP-A2* (p.D643fs25*) resulting in a premature stop codon. **Methods:** Body composition, BMD, and bone structure were determined by dual-energy X-ray absorptiometry at baseline and after 1 and 2 years of rhIGF-1 treatment. **Results:** Height increased from 132 to 145.5 cm (patient 1) and from 111.5 to 124.5 cm (patient 2). Bone

mineral content increased from 933.40 to 1,057.97 and 1,152.77 g in patient 1, and from 696.12 to 773.26 and 911.51 g in patient 2, after 1 and 2 years, respectively. Whole-body BMD also increased after 2 years of rhIGF-1 from baseline 0.788 to 0.869 g/cm^2 in patient 1 and from 0.763 to 0.829 g/cm^2 in patient 2. After 2 years of treatment, both children had an improvement in TBS. During therapy, a slight increase in body fat mass was seen, with a concomitant increase in lean mass. No adverse effects were reported. **Conclusion:** Two years of rhIGF-1 improved growth, with a tendency to improve bone mass and bone microstructure and to modulate body composition.

Abstract Second Language	

Abstract Third Language	

Key Messages	

Body

Introduction

Mutations in the gene for pregnancy-associated plasma protein A-2 *(PAPP-A2)*, a metalloproteinase enzyme [1], produce short stature due to low insulin-like growth factor-1 (IGF-1) availability. Short stature, skeletal abnormalities, and high circulating levels of total IGF-1, IGFBP-3, IGFBP-5, and acid-labile subunit (ALS) characterize this new syndrome. Because PAPP-A2-deficient patients do not exhibit growth hormone (GH) deficiency, they were treated

with recombinant human IGF-1 (rhIGF-1) [2]. We previously reported that these children had improved growth with no adverse effects after 1 year of rhIGF-1 administration [2].

Here, our aim was to assess the effect of 2 years of rhIGF-1 therapy on bone mineral density (BMD) and bone quality, as assessed by trabecular bone score (TBS), as well as body composition in a unique model of 2 children with a complete lack of PAPP-A2 and very low IGF-1 bioavailability.

Subjects and Methods

Two siblings, a prepubertal female (patient 1; chronological age: 10.54 years) and a prepubertal male (patient 2; chronological age: 6 years) with short stature (height SDS --1.10 and --0.96 for age and sex, respectively, but far from their target height in centile 72) were studied. Both patients were born to nonconsanguineous Spanish parents. Length and weight at birth were normal, but postnatally they experienced continuous growth velocity retardation. Phenotype included small chin, modest microcephaly, and long thin digits on hands and feet. Both children had a homozygous frameshift mutation in *PAPP-A2* (p.D643fs25*) [1]. Bone age and chronological age were consistent in patient 1 (Δ = --0.21) and slightly delayed in patient 2 (Δ = 1.5). At diagnosis, the height of the female patient was in the normal range (--1.10 SD), but was 1.6 SDS below her expected height. The height of the male patient was also normal (--0.96 SD), but 1.2 SDS below his expected height. Patient 1 started puberty 3 months after starting rhIGF-1 treatment and thus received GnRH analog in order to delay puberty and to potentiate the effect on height.

Whole-body BMD (WB-BMD), lumbar spine BMD (LS-BMD), hip BMD, and femoral neck BMD (FN-BMD) as well as body composition measurements were performed using dual-energy X-ray absorptiometry (DXA; DXA Discovery Wi, software version 13.3; Hologic, Inc., Waltham, MA, USA) before therapy started and at 1 and 2 years after treatment. Data for BMD are

expressed adjusting for height-for-age *Z* scores [3]. Body composition data obtained by DXA (body fat mass, lean mass, and body fat percentage) were compared from baseline to the end of the study [4]. The coefficient of variation was 0.85 for whole body and 0.70 for lumbar spine.

TBS measurements were obtained from DXA lumbar studies using the TBS iNsight software (MedimapsFrance, v3.0). TBS was calculated from the same DXA acquisition and region of interest as those used for LS-BMD. A higher TBS indicates a healthier bone microarchitecture, whereas a lower value suggests a weaker bone structure. Unfortunately, there is no international consensus regarding what constitutes normal or abnormal TBS in children, but for adults it has been proposed that TBS ≥1,350 is normal, TBS values between 1,200 and 1,350 are consistent with partially degraded bone, and TBS ≤1,200 indicates degraded bone [5].

Results

Height was clearly increased after treatment with rhIGF-1 in both children according to their sex and age and using Spanish tables. For patients 1 and 2, heights were 132 and 111.5 cm at baseline, 139.6 and 118.5 cm after 1 year of treatment, and 145.5 and 124.5 cm at 2 years of rhIGF-1 therapy, respectively. Ultrasound of internal organs (kidney, spleen, and heart) was normal.

Effects of rhIGF-1 on Bone Mineral Content and BMD (Table 1)

The pretreatment BMD was subnormal in both the female (osteoporosis) and male (osteopenia) subject, according to age- and sex-matched references. In patient 1, bone mineral content (BMC) increased from 933.40 g at baseline to 1,057.97 and 1,152.77 g at 1 and 2 years, respectively, with a total increase of 23.4%. In patient 2, BMC increased from 696.12 g at baseline, to 773.26 and 911.51 g at 1 and 2 years, respectively, with a total increase of 30.8%. At baseline, patient 1 had a WB-BMD of 0.788 g/cm^2, which increased to 0.843 g/cm^2 at 1 year

and 0.869 g/cm^2 at 2 years of rhIGF-1 therapy. Patient 1 had a baseline LS-BMD of 0.582 g/ cm^2 and 0.679 g/ cm^2 after 2 years of rhIGF-1 treatment (a 16.8% increase). Total hip BMD and FN-BMD increased from an initial 0.644 and 0.578 g/cm^2 to 0.688 and 0.582 g/cm^2, respectively, with an increase of 6.8%. Despite this, the adjusted LS-BMD *Z* score (--0.3) and total hip *Z* score (--1.5) were in the low normal range, but her annual increase was acceptable according to national values for age and sex (+0.094 g/cm^2) [6].

The initial WB-BMD in patient 2 was 0.763 g/cm^2, 0.784 g/cm^2 at 1 year, and 0.829 g/cm^2 at 2 years of rhIGF therapy. Patient 2 had a baseline LS-BMD of 0.488 g/cm^2 and 0.532 g/cm^2 after 2 years. Total hip BMD and FN-BMD were initially 0.596 and 0.572 g/cm^2 and after 2 years of rhIGF-1 treatment 0.708 and 0.646 g/cm^2, respectively, with a positive change of 8.5% during this period. The annual increase was similar to that described for Spanish children for age and sex (+0.042 g/cm^2) [6]. The height-adjusted LS-BMD *Z* score (--0.4) and total hip score (0.3) were in the normal range.

Effects of rhIGF-1 on TBS

TBS values were compared to normative data from a group of 4,126 healthy Spanish children of both sexes (2,600 girls and 1,520 boys between 1 and 19 years) according to age and sex [Del Rio et al., unpubl. data].

The initial TBS value for patient 1 was in the lower range: 1,223 (normal range: 1,285 ± 0.10). In patient 2, it was acceptable: 1,291 (normal range: 1,269 ± 0.10). After 2 years of treatment, patient 2 showed an increase to 1,312, which is above the normal range adjusted for age and sex (1,228 ± 0.11). Patient 1 had a substantial decline in TBS after the first year of treatment (1,147), but after 2 years it increased to 1,337, which is in the normal range for age and sex (1,355 ± 0.08).

Effects of rhIGF-1 on Body Composition

The percentage of total body fat mass was reduced, by --4.5 and --4.7% in patient 1 and 2, respectively, during the first year of rhIGF-1 therapy. During the second year of treatment, a non significant increase in the percentage of total body mass was found in patient 1 (+2.7%) and in patient 2 (+1.3%), with the percentage of total body fat mass being below the expected value for age and sex in both. The small positive effects of rhIGF-1 on fat mass during the second year could reflect the severe nature of their IGF-1 deficiency [7]. There was a concomitant increase in lean mass from 15,471.8 g at baseline to 19,490.5 and 22,165.6 g after 1 and 2 years of rhIGF-1 treatment in patient 1 and from 11,468.3 g at baseline to 13,892.2 and 16,019.3 g in patient 2. The increases in lean mass in patient 1 (43%) and in patient 2 (40%) during the treatment period are acceptable according to age and sex reference published database [8].

No adverse effects were seen during rhIGF-1 therapy in either patient. There were no episodes of symptomatic hypoglycemia or hyperglycaemia reported during the 2 years of the study and no local reactions at the site of subcutaneous injections were seen.

Discussion

This is the first study confirming an improvement in BMD, body composition, and microstructure in patients with short stature due to mutations in *PAPP-A2* after 2 years of treatment with rhIGF-1. The therapeutic option of rhIGF-1 seems reasonable, as this syndrome is associated with postnatal growth failure and low free IGF-1 bioavailability necessary for bone remodeling during development [9]. Low levels of free IGF-1 are detrimental to bone, as it is fundamental for optimizing peak bone mass. Therefore, it is essential to consider therapeutic interventions to optimize bone mass accrual and bone density during these development years.

Our 2-year study demonstrates that rhIGF-1 treatment is capable of improving WB-BMD, BMC, and LS-BMD towards the normal range and results in an acceptable annual BMD

increase. This trend toward increasing BMD of the whole skeleton is similar to previous observations of treatment with rhIGF-1 in other growth-retarded conditions [10].

In a recent study, Cabrera-Salcedo et al. [11] reported a moderate increase in total BMD in a patient with a missense mutation in *PAPP-A2* after 1 year of treatment. The differential response to rhIGF-1 treatment, including a lower growth velocity than that of our patients [2], could be explained by the differences in the affectation of the IGF-1 system due to the different genetic mutations. Indeed, our patients have a total lack of PAPP-A2 compared to a mutated form of this protease in the patient reported by Cabrera-Salcedo et al. [11]. Although the descriptions of this patient and his brother and sister were published together with the two Spanish subjects, our patients have been under treatment for a longer period due to their earlier diagnosis [1, 12], and it will be of interest to see how the other patient responds to longer treatment.

Although initially there was a slight decrease in TBS in patient 1, with that of patient 2 being acceptable 1 year after rhIGF-1 treatment, afterwards there was an increase in both children that resulted in a TBS score in the normal range after 2 years of therapy. The small decrease in TBS in patient 1 at 1 year could possibly be due to rhIGF-1 initially increasing bone remodeling. Our study suggests that TBS and BMD may need more than 2 years of therapy to improve significantly, as reported for treatment in other chronic conditions [5]. Preliminary data show an improvement in fracture prediction in adults when TBS is used in combination with FRAX [13], but the utility of this technique has not been evaluated in children. Longer studies in large series of children with healthy and chronic diseases are necessary to analyze the relationship between TBS and anthropometric clinical variables. Unfortunately, results of TBS cannot be compared with the study by Cabrera-Salcedo et al. [11] as this analysis was not performed.

After the first year of rhIGF-1 treatment, a small decrease in the percentage of body fat mass (<5%) was registered, but in the second year there was a nonsignificant increase (<3%) in

both children. This is similar to a recent study, in which an early decrease in the percentage of body fat, followed by a longer-term increase, was reported in 21 children with GH receptor deficiency treated with rhIGF-1 for 3 years [14]. In patients with GH insensitivity syndrome, a small reduction in 3 patients and a 7% rise in the percentage of body fat in 1 patient were found as early as 3 months after treatment with IGF-1 [15].

Lean mass also increased in both patients, confirming the anabolic effects of IGF-1. The observed increases were normal compared to age-matched controls and similar to those described by others. The significant increase in lean body mass, but no change in BMI, is similar to that reported in GH-deficient patients treated with GH [8]. DXA was used to measure body composition, as this technology is a sensitive tool with good precision for assessment of longitudinal changes [16].

When we compare the BMD of these patients with PAPP-A2 deficiency to that of our patients with primary ALS deficiency due to recessive *IGFALS* mutations associated with low IGF-1 levels, differences can be observed. Even without therapy (neither hGH nor rhIGF-1), no affectation of whole-body BMC or LS-BMD was observed in our patients, with the exception of 1 patient who exhibited a very moderately decreased lumbar spine BMC, but not whole-body BMC, as found by DXA analysis [17]. In contrast, a modest decrease in the BMC of the lumbar spine was found in the first reported patient with primary ALS deficiency due to a homozygous *IGFALS* mutation [18] as well as in 2 male siblings born to consanguineous parents [19]. Thus, we can speculate that the availability of IGF-1 is important for BMD and that, although our 2 patients have very high total IGF-1 levels, IGF-1 availability is very low due to the complete lack of PAPP-A2 deficiency [1].

In summary, our study indicates that rhIGF-1 increased growth in 2 children lacking PAPP-A2 and hence with free/bioactive IGF-1 deficiency, with a tendency to improve bone mass, quality of bone, and body composition. Nonetheless, a follow-up of these patients will be required to demonstrate whether they can normalize BMD and TBS as well as to determine their

final height. In addition, further research is necessary to evaluate the clinical significance of BMD and TBS changes during growth as a useful tool for the management of these children with this new syndrome.

Acknowledgments

We would like to thank the patients and their family for their generosity and cooperation. The authors are funded by Fondos de Investigación Sanitaria and FEDER (Grants PI1302195 and PI1600485 to J.A.), Ministerio de Ciencia e Innovación (BFU2014-51836-C2-2-R to J.A.C.), Centro de Investigación Biomédica en Red Fisiopatología de Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III (J.A.), and Fundación Endocrinología y Nutrición.

Statement of Ethics

All of the studies involving the Spanish patients with mutations in the *PAPPA2* gene were approved by the Institutional Ethics Review Board at the Hospital Infantil Universitario Niño Jesús. Written informed consent was obtained from the legal guardians.

Disclosure Statement

The authors declare no conflict of interest.

References

1 Dauber A, Muñoz-Calvo MT, Barrios V, Domené HM, Kloverpris S, Serra-Juhé C et al. Mutations in pregnancy-associated plasma protein A2 cause short stature due to low IGF-I availability. EMBO Mol Med. 2016 Apr;8(4):363–74.

2 Muñoz-Calvo MT, Barrios V, Pozo J, Chowen JA, Martos-Moreno GA, Hawkins F et al. Treatment With Recombinant Human Insulin-Like Growth Factor-1 Improves Growth in Patients With PAPP-A2 Deficiency. J Clin Endocrinol Metab. 2016 Nov;101(11):3879–83.

3 Zemel BS, Leonard MB, Kelly A, Lappe JM, Gilsanz V, Oberfield S et al. Height adjustment in assessing dual energy x-ray absorptiometry measurements of bone mass and density in children. J Clin Endocrinol Metab. 2010 Mar;95(3):1265–73.

4 Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey. Body composition data for individual 8 years of age and older: U.S. Population, 1999–2004. Available from: https://www.cdc.gov/nchs/data/series/sr_11/sr11_250.pdf.

5 Silva BC, Leslie WD, Resch H, Lamy O, Lesnyak O, Binkley N et al. Trabecular bone score: a noninvasive analytical method based upon the DXA image. J Bone Miner Res. 2014 Mar;29(3):518–30.

6 Moreno Perea M, González Hachero J, Sanchez Calero J, Morón Romero M, Vázquez Gámez MA, Pérez Cano R. Contenido mineral óseo en niños normales. An Esp Pediatr. 1994;41:31–5.

7 Mauras N, Haymon MW. Are the metabolic effects of GH and IGF-I separable? Growth Horm IGF Res. 2005 Feb;15(1):19–22.

8 Weber DR, Moore RH, Leonard MB, Zemel BS. Fat and lean BMI reference curves in children and adolescents and their utility in identifying excess adiposity compared with BMI and percentage body fat. Am J Clin Nutr. 2013 Jul;98(1):49–56.

9 Argente J, Chowen JA, Pérez-Jurado LA, Frystyk J, Oxvig C. One level up: abnormal proteolytic regulation of IGF activity plays a role in human pathophysiology. EMBO Mol Med. 2017 Oct;9(10):1338–45.

10 Martinez V, Vasconez O, Martinez AL, Moreno Z, Davila N, Rosenbloom AL et al. Body changes in adolescent patients with growth hormone receptor deficiency receiving recombinant human insulin-like growth factor I and luteinizing hormone-releasing hormone analogue: preliminary results. Acta Paediatr Suppl. 1994 Apr;399:133–6.

11 Cabrera-Salcedo C, Mizuno T, Tyzinski L, Andrew M, Vinks AA, Frystyk J et al. Pharmacokinetics of IGF-1 in PAPP-A2-Deficient Patients, Growth Response, and

Effects on Glucose and Bone Density. J Clin Endocrinol Metab. 2017 Dec;102(12):4568–77.

12 Muñoz-Calvo MT, Barrios V, Pozo J, Martos-Motreno GÁ, Hawkins FG, Domene H et al. New syndrome of short stature, mild microcephaly, skeletal abnormalities and high circulating IGF1, IGFBP3 and ALS associated with a homozygous mutation in the gene for Pregnancy-Associated Plasma Protein A2 (PAPP-A2, pappalysin2). 97th Annual Meeting of the Endocrine Society; 2015 March 5–8; San Diego (CA) (OR03-1).

13 Krueger D, Fidler E, Libber J, Aubry-Rozier B, Hans D, Binkley N. Spine trabecular bone score subsequent to bone mineral density improves fracture discrimination in women. J Clin Densitom. 2014 Jan–Mar;17(1):60–5.

14 Guevara-Aguirre J, Rosenbloom AL, Guevara-Aguirre M, Saavedra J, Procel P. Recommended IGF-I dosage causes greater fat accumulation and osseous maturation than lower dosage and may compromise long-term growth effects. J Clin Endocrinol Metab. 2013 Feb;98(2):839–45.

15 Shaw NJ, Fraser NC, Rose S, Crabtree NJ, Boivin CM. Bone density and body composition in children with growth hormone insensitivity syndrome receiving recombinant IGF-I. Clin Endocrinol (Oxf). 2003 Oct;59(4):487–91.

16 Crabtree NJ, Arabi A, Bachrach LK, Fewtrell M, El-Hajj Fuleihan G, Kecskemethy HH et al; International Society for Clinical Densitometry. Dual-energy X-ray absorptiometry interpretation and reporting in children and adolescents: the revised 2013 ISCD Pediatric Official Positions. J Clin Densitom. 2014 Apr–Jun;17(2):225–42.

17 Heath KE, Argente J, Barrios V, Pozo J, Díaz-González F, Martos-Moreno GÁ et al. Primary acid-labile subunit deficiency due to recessive IGFALS mutations results in postnatal growth deficit associated with low circulating insulin growth factor (IGF)-I, IGF binding protein-3 levels, and hyperinsulinemia. J Clin Endocrinol Metab. 2008 May;93(5):1616–24.

18 Domené HM, Bengolea SV, Jasper HG, Boisclair YR. Acid-labile subunit deficiency: phenotypic similarities and differences between human and mouse. J Endocrinol Invest. 2005;28(5 Suppl):43–6.

19 van Duyvevoorde HA, Twickler TB, van Doorn J, Gerver WJ, Noordam C, Karperien M et al. A novel mutation of the acid-labile subunit (ALS) in two male siblings is associated with persistent short stature, microcephaly and osteoporosis. 46th Annual Meeting of the European Society for Paediatric Endocrinology (ESPE), Helsinki, 2007. Horm Res 68(Suppl 1):108.

Appendix after References (Editorial Comments)

Legend(s)

Table(s)

Footnote(s)

Table 1. Baseline values and the response of patient 1 and patient 2 to rhIGF–1 treatment at 1 and 2 years

Parameter	Baseline	Year 1	Year 2
Patient 1			
Age, years	10.54	11.54	12.5
Height, cm	132 (–1.25)	139.6 (–0.86)	145.5 (–0.81)
BMI	14.1 (–1.51)	14.8 (–1.44)	15.6 (–1.3)
Lumbar spine			
BMD, g/cm^2	0.582	0.601	0.679
Z score[1]	–0.1	–0.4	–0.3
TBS	1,223	1,147	1,337
Whole-body mineral density			
Total BMC, g	933.40	1,057.97	1,152.77
Total BMD, g/cm^2	0.788	0.843	0.869
Body composition			
Fat mass, g	7,611.1	7,663.6	9,928.3
Lean mass, g	15,471.8	19,490.5	22,165.6
Lean and BMC, g	16,405.1	20,548.5	23,318.0
Total mass, g	24,016.3	28,212.0	33,246.7
Total body fat, %	31.7	27.2	29.9
Patient 2			
Age, years	6.1	7.1	8.2
Height, cm	111.5 (–0.74)	118.5 (–0.34)	124.5 (0.31)
BMI	13.38 (–1.81)	13.64 (–1.69)	14.39 (–1.24)
Lumbar spine			
BMD, g/cm^2	0.488	0.476	0.532
Z score[1]	–0.1	–0.7	–0.2
TBS	1,291	1,278	1,312
Whole-body mineral density			
Total BMC, g	696.12	773.26	911.51
Total BMD, g/cm^2	0.763	0.784	0.829
Body composition			
Fat mass, g	4,630.5	4,332.2	5,401.3
Lean mass, g	11,468.3	13,829.2	16,019.3
Lean and BMC, g	12,164.5	14,602.5	16,930.8
Total mass, g	16,794.9	18,934.7	22,332.1
Total body fat, %	27.6	22.9	24.2

Values in parentheses indicate SDS. BMI, body mass index; BMD, bone mineral density; BMC, bone mineral content. [1] *Z* score: age and height adjusted (3).