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Hypophosphatasia: Natural history study of 101 affected children investigated at one research center☆

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ABSTRACT

Hypophosphatasia (HPP) is the inborn-error-of-metabolism that features deficient activity of the tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP). Resultant extracellular accumulation of inorganic pyrophosphate, a TNSALP substrate and potent inhibitor of mineralization, typically leads to tooth loss and sometimes to rickets or osteomalacia. HPP's remarkably broad-ranging severity is largely explained by autosomal dominant versus autosomal recessive transmission from among several hundred usually missense mutations positioned throughout the gene that encodes TNSALP. In 2015, our cross-sectional investigation of 173 affected children validated and expanded the clinical nosology commonly used for pediatric HPP.

Herein, for the 101 patients in that cohort with longitudinal data, we explored the natural history of pediatric HPP by assessing their z-scores for height and then for weight, grip strength, and bone mineral density (BMD) determined by dual energy X-ray absorptiometry (DXA) also after adjusting for patient height. Eighteen patients contributed to "across" puberty evaluation.

According to increasing HPP severity, there were 28 odonto HPP, 28 mild childhood HPP, 37 severe childhood HPP, and 8 infantile HPP patients typically studied from early to mid-childhood. The individual values for each parameter were wide-ranging within, and overlapping between, the four successive patient groups. Final mean/median z-scores, like the published initial values, paralleled the nosology. Longitudinal findings were similar for the boys versus girls and across puberty. Mean/median height z-scores remained constant for all four patient groups. In contrast, mean/median weight z-scores increased with aging, including after height-adjustment, resembling the recent trend for American children. However, excessive weight gain was typically not observed and mean/median values became average for height. Mean/median z-scores calculated routinely for chronologic age did not change for grip strength or for lumbar spine or total hip BMD. However, height-correction of the cohort suggested some worsening of grip strength z-scores and indicated improvement in spine BMD z-scores.

Overall, in affected children and adolescents, HPP represents a clinically stable but chronic disorder.

1. Introduction

Hypophosphatasia (HPP) is the inborn-error-of-metabolism caused by loss-of-function mutation(s) of the TNSALP (ALPL) gene that encodes the "tissue-nonspecific" isoenzyme of alkaline phosphatase (TNSALP) [1]. Because TNSALP is a cell-surface protein, its substrates accumulate extracellularly in HPP, including the potent inhibitor of mineralization, inorganic pyrophosphate (PPi) [2]. The PPi excess usually leads to dental disease and sometimes to rickets or osteomalacia with muscle weakness and sometimes in adults to calcific arthropathies [3,4]. In fact, HPP manifests the most broad-ranging severity of all skeletal diseases as largely explained by autosomal dominant versus autosomal recessive transmission from among several hundred typically missense mutations positioned throughout *TNSALP* [1,3,5]. HPP expressivity spans absence of skeletal mineralization causing stillbirth to difficulties with teeth or arthropathy presenting late in adult life [1,3,4,6].

Abbreviations: ALP, alkaline phosphatase; BMD, bone mineral density; CDC, Centers for Disease Control and Prevention; DXA, dual-energy X-ray absorptiometry; HPP, hypophosphatasia; NIH, National Institutes of Health; PPi, inorganic pyrophosphate; SAS, Statistical Analysis Software; SD, standard deviation; TNSALP, tissue-nonspecific ALP isoenzyme; *TNSALP*, the gene (*ALPL*) that encodes TNSALP.

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To organize this remarkable range of HPP severity, a clinical nosology has evolved since 1957 [7] that emphasizes whether the especially prevalent dental problems [5] are accompanied by skeletal and other complications [1,3,4]. Patient age, if and when non-dental difficulties first manifest, is used to demarcate five principal forms of HPP according to increasing severity: odonto HPP, adult HPP, childhood HPP, infantile HPP, and perinatal HPP [1,3,6]. Nevertheless, the natural histories of only perinatal HPP [8,9] and infantile HPP featuring certain important complications [9] are understood.

To better know HPP in children, we published in 2015 cross-sectional findings accumulated over 25 years from our first encounters with 173 pediatric patients [5]. None was a survivor of perinatal HPP or an HPP "carrier". We validated the extant clinical nosology for pediatric HPP [1,3,6], and then also distinguished severe versus mild childhood forms [5].

Herein, we studied the natural history of HPP in children using this expanded nosology. We focused on several key parameters of HPP severity in the 101 of the 173 patients from whom there was longitudinal data [5].

2. Materials and methods

2.1. Patients

The original cohort of 173 children with HPP had been studied one or more times exclusively as in-patients during September 1983–December 2008 at the Center for Metabolic Bone Disease and Molecular Research, Shriners Hospital for Children; St. Louis, MO, USA (Research Center) [5]. Informed written consent was obtained each time as sanctioned by the Human Studies Committee, subsequently called the Human Research Protection Office, at the Washington University School of Medicine; St. Louis, MO, USA. Referral was required before 18 years-of-age with investigation possible until 21 years-of-age. HPP had been diagnosed based on the following at first admission: i) medical history and/or physical examination consistent with one or more dento-osseous complication(s) of HPP, ii) serum ALP activity below the pediatric reference range established at the Research Center and provided by consulting clinical pathologists for our analytical instruments, iii) plasma pyridoxal 5′-phosphate (PLP) level above the reference range established at the Research Center and published elsewhere (i.e., 154 of the patients since 1985), iv) radiographic changes consistent with HPP if skeletal disease was identified, and v) no evidence for another disorder that could cause hypophosphatasemia, skeletal disease, or premature loss of primary teeth (i.e., before age 5 years) [5]. Therefore, no study subject was a "carrier" of HPP [1,3]. Subsequent analysis revealed one or two *TNSALP* (*ALPL*) mutations in all 105 probands from whom we acquired genomic DNA [5]. After reviewing the referral medical information and first admission clinical and radiographic findings, we had classified each patient into one of four groups: odonto HPP, mild childhood HPP, severe childhood HPP, or infantile HPP [1,3,5]. Depending on their HPP severity, follow-up admissions for study were generally scheduled every one to three years. At the time, no pharmacologic treatment was available for their disorder. At the close of 2008, we locked the database and published in 2015 [5] the detailed methodology and results for our cross-sectional analysis of the initial demographic, clinical, and DXA findings that validated the extant clinical nosology for pediatric HPP [1,3], and further distinguished "mild" versus "severe" childhood forms of the disease. Herein, this expanded classification was used to assess the longitudinal demographic, grip strength, and DXA data from the 101 patients. All 101 were American children. Among them, 18 had evaluations both before puberty (i.e., < age 12 years for girls, and < age 13 years for boys) and after puberty (> age 15 years for both girls and boys) enabling an "across-puberty" investigation using earliest and last admission data to maximize the age-range studied. Future publications will assess the biochemical findings among the 173 patients, including the longitudinal changes of the 101 patients.

2.2. Height and weight

Height and weight z-scores were evaluated using age-appropriate and gender-specific data from the SAS programs and growth charts provided by the Centers For Disease Control and Prevention (CDC) (http://www.cdc.gov/nccdphp/dnpa/growthcarts/resources/sas.htm) from Americans 2–20 years-of-age and downloaded from the CDC web site (http://www.cdc.gov/growthcharts/zscore.htm).

Because height conditions the parameters chosen for our study; i.e., weight, grip strength, and bone mineral density (BMD) determined by dual-energy X-ray absorptiometry (DXA) [5,10], and because patient stature was typically below average (see Results) [5], we first assessed z-scores conventionally for chronologic age, but then additionally refined our data analyses after "correcting" the preteen patients' ages for their heights. We used our gender-specific linear equations published in 2012 [11] to calculate their "height-age", and then applied this value to the parameters of interest. Height-age was defined as the patient's adjusted age matching his/her height measurement extrapolated to the gender-matched 50th centile for height.

$$\text{Girls}: \text{Height-age (years)} = 21.53 + 0.447 \times \text{Height (cm)} - 6.2415 \times \sqrt{\text{Height (cm)}}$$

$$\text{Boys}: \text{Height-age (years)} = 8.23 + 0.3264 \times \text{Height (cm)} - 3.7 \times \sqrt{\text{Height (cm)}}$$

These two equations are applicable only to preteen children, because non-linear growth occurs when >Tanner III [11]. Despite this restriction, most cohort weight, grip strength, and BMD z-scores were eligible for adjustment and evaluation.

2.3. Grip strength

Beginning in 2002 [5], grip strength was measured in 52 of our patients using a calibrated Jamar dynamometer (J. A. Preston Corp., Clifton, NJ, USA) while the child sat with arm adducted, elbow flexed at 90°, and forearm and wrist in neutral position. The mean value of three maximum voluntary contractions was recorded for each hand. The z-scores were calculated from reference data derived using this apparatus by Lee-Valkov et al. [12] for ages 3 to 5 years, and by Mathiowetz et al. [13] for ages 6 to 19 years. For our analysis, we considered the few patients older than age 19 years (all younger than age 21 years) to be 19 years old. The preteen data was "corrected" for height, but not for arm span [10].

2.4. Dual energy X-ray absorptiometry

Beginning in 1990, DXA determined BMD of the L_1–L_4 spine ("spine") and non-dominant total hip ("hip") for the patients 3 and 5 years-of-age or older, respectively. Two Hologic instruments (Waltham, MA, USA) provided the data sequentially [from 1990 to 1997 the QDR-1000™ "pencil-beam" apparatus at Barnes-Jewish Hospital, and from 1997 to 2008 the QDR-4500A™ "fan-beam" apparatus at Shriners Hospital for Children; St. Louis, MO, USA]. Measurements from these instruments are comparable and do not require cross-calibration [14].

We calculated BMD z-scores routinely for chronologic age using the 2005 pediatric BMD reference data of Kelly et al. [15], and subsequently illustrated the data using reference curves that we created (see Results). Then, because HPP can compromise stature [5] and body (bone) size influences DXA "areal" (gm/cm^2) BMD results [11], we corrected the BMD z-scores of our preteen patients for their heights by substituting height-age in the calculation. The BMD z-scores for chronologic age and height-age were determined using a SAS program that we developed (unpublished) for this purpose.

Table 1
Ages (years) at first versus last admissions, and intervals (years) between those admissions.

HPP group	# pts	First admission		Last admission		Interval	
		Mean/median age (SD)	Range (min, max)	Mean/median age (SD)	Range (min, max)	Mean/median age (SD)	Range (min, max)
Odonto	28	4.9/3.6 (3.5)	1.7, 15.5	10.8/10.4 (4.3)	3.7, 20.9	5.9/5.3 (3.3)	1.0, 12.9
Mild Childhood	28	4.3/3.6 (2.4)	1.3, 10.0	10.4/9.6 (4.3)	3.9, 20.0	6.1/5.3 (3.7)	1.0, 16.5
Severe Childhood	37	4.9/3.6 (3.6)	0.8, 14.0	11.9/12.0 (5.8)	1.5, 20.9	7.0/6.3 (4.4)	0.7, 19.4
Infantile	8	2.2/1.6 (1.9)	0.5, 6.2	10.5/11.4 (5.7)	2.2, 17.2	8.2/10.0 (5.1)	1.0, 15.8
Cohort	101	4.5/3.5 (3.2)	0.5, 15.5	11.1/10.8 (5.0)	1.5, 20.9	6.5/5.9 (4.0)	0.7, 19.4

Table 2
Numbers of, and years between, admissions.

HPP group	# pts	# admissions	Admissions		Years between admissions	
			Mean/median (SD)	Range (min, max)	Mean/median interval (SD)	Range (min, max)
Odonto	28	88	3.1/3 (1.3)	2, 5	2.8/2.9 (1.2)	1.0, 6.7
Mild childhood	28	106	3.8/3 (1.6)	2, 7	2.2/2.0 (1.1)	0.8, 6.5
Severe childhood	37	171	4.7/4 (2.7)	2, 14	1.9/1.8 (1.1)	0.3, 8.8
Infantile	8	42	5.1/6 (2.0)	2, 8	2.0/1.9 (1.3)	1.0, 8.6
Cohort	101	407	4.1/4 (2.2)	2, 14	2.2/2.0 (1.2)	0.3, 8.8

2.5. Statistical methods

SAS 9.1.3 (SAS Institute Inc., Cary, NC, USA) was used for all calculations, statistical analyses, and illustrations. When reporting results that reflected the maximum duration of patient investigation (i.e., first to last admissions), a descriptive statistical summary of each parameter (e.g., z-score for height, weight, grip strength, and BMD) was provided in table format. This summary included the mean/median value (SD), range given as minimum and maximum value, and 95% confidence interval of the mean. Because the number of study subjects was limited and the data had large variances, both parametric and non-parametric methods (i.e., paired *t*-test and sign test, respectively) were used to analyze the last versus first patient encounters. Additionally, because most patients had three or more admissions, the two-stage longitudinal analysis (NIH two-step method) could be used. For this analysis, we first performed (step 1) linear regression for the parameter (e.g., height z-score, weight z-score) with age (years) for each patient to calculate the slope (change per year). Then (step 2), the *t*-test assessed the mean slope. The null hypothesis was zero. Proportion evaluations used the Chi-square or Fisher exact test. For the height-corrected grip strength z-scores, we added the mixed model to test for age effects and HPP group z-score differences by including patients with only one measurement. We assessed exclusively two-sided hypotheses. A p-value of <0.05 was considered statistically significant.

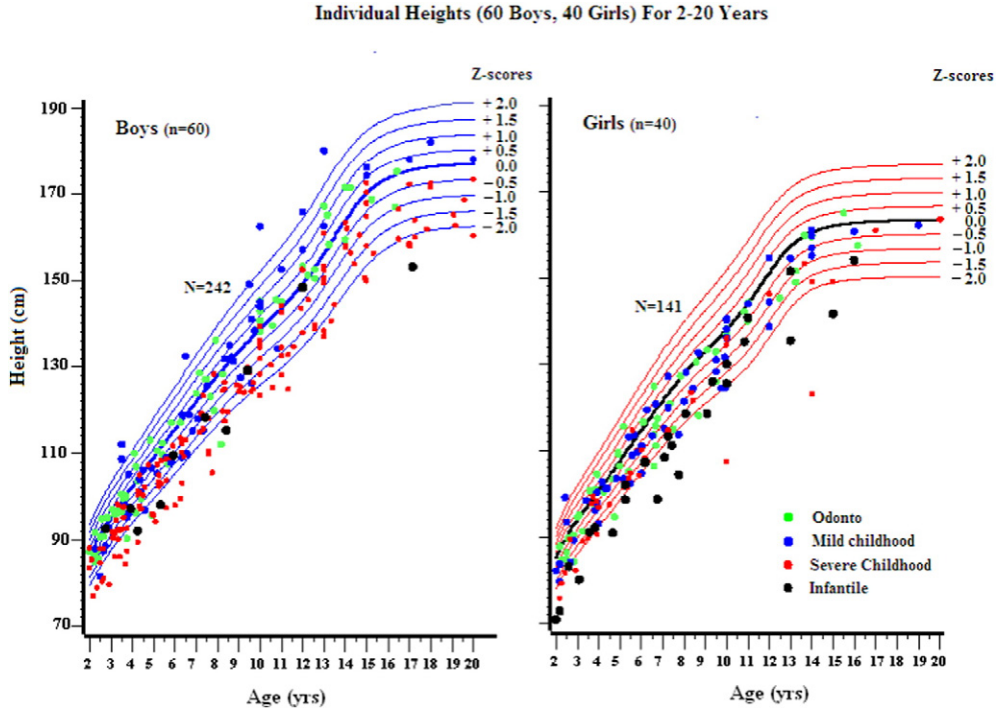

Fig. 1.

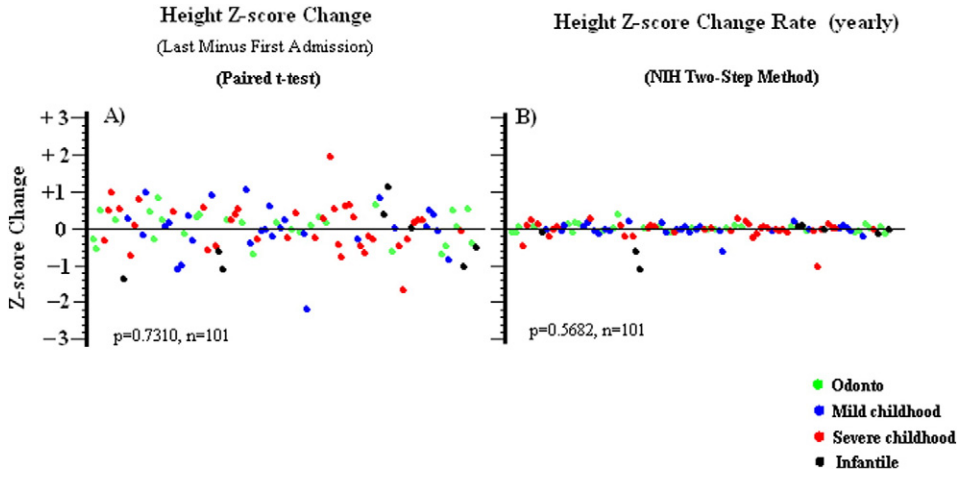

Fig. 2.

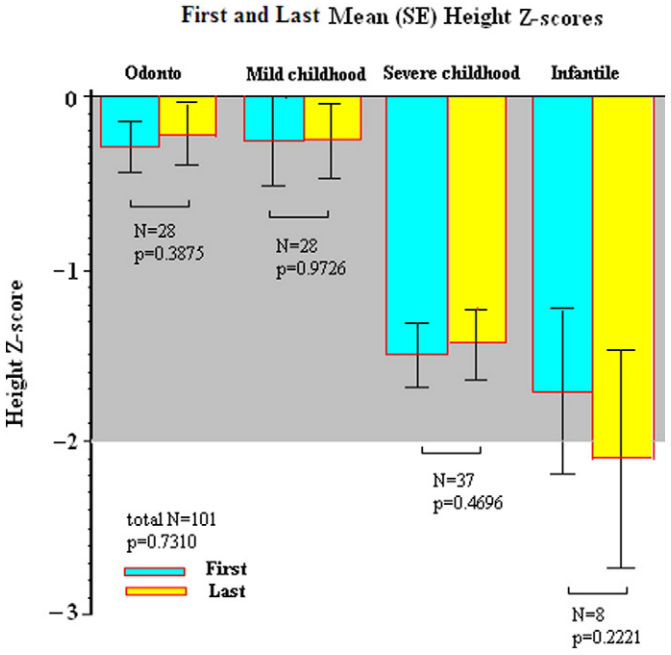

Fig. 3.

3. Results

3.1. Cohort

This study cohort comprised the 101 HPP children with more than one in-patient admission to the Research Center. Four clinical forms of pediatric HPP were represented by 28 odonto HPP, 28 mild childhood HPP, 37 severe childhood HPP, and 8 infantile HPP patients (Table 1).

3.2. Patient admissions

Patient ages at the first and last admissions spanned 6 months to nearly 21 years, and were broad-ranging in all four groups (Table 1). Similar mean/median ages at the first admission had occurred for odonto HPP (4.9/3.6 years), mild childhood HPP (4.3/3.6 years), and severe childhood HPP (4.9/3.6 years), but were earlier for infantile HPP (2.2/1.6 years) likely explained by their especially severe HPP and quicker diagnosis. At their last admission prior to 2009, the mean/median values were similar across all four groups: odonto HPP (10.8/10.4 years), mild childhood HPP (10.4/9.6 years), severe childhood HPP (11.9/12.0 years), and infantile HPP (10.5/11.4 years). For the cohort, the mean/median age at first investigation was 4.5/3.5 years (range 0.5 to 15.5 years), and therefore represented early childhood. At the last investigation, the age was 11.1/10.8 years, and therefore represented mid-childhood. Among the four patient groups, the mean durations between the first and last admission ranged from 5.9 to 8.2 years, with a mean/median of 6.5/5.9 years for the cohort (Table 1).

Table 3
Preteen height z-score changes.

HPP group	# Pts	Mean/median (SD) (min, max)		Mean/median change (SD)	95% CI of mean change	p-values
		First	Last	Range (min, max)		Paired *t*-/sign (test) (NIH method)
Odonto	28	−0.3/−0.1 (0.8) (−2.7, +0.8)	−0.3/−0.1 (1.0) (−3.0, +1.4)	+0.1/+ 0.2 (0.4) (−0.1, +0.9)	−0.1, +0.2	0.3875/0.1849 (0.1002)
Mild Childhood	28	−0.3/−0.5 (1.4) (−2.6, +3.2)	−0.3/−0.4 (1.1) (−1.9, +3.0)	0.0/0.0 (0.7) (−2.2, +1.1)	−0.3, +0.3	0.9726/0.8506 (0.9568)
Severe Childhood	37	−1.5/−1.2 (1.2) (−5.0, +0.6)	−1.4/−1.3 (1.2) (−5.7, +0.3)	+0.1/+0.2 (0.6) (−1.7, +2.0)	−0.1, +0.3	0.4696/0.7428 (0.7876)
Infantile	8	−1.7/−1.7 (1.6) (−3.2, +0.5)	−2.1/−2.1 (1.6) (−4.2, −0.07)	−0.4/−0.5 (0.8) (−1.3, +1.1)	−1.1, +0.3	0.2221/0.7266 (0.1726)
Cohort	101	−0.8/−0.7 (1.3) (−5.0, +3.2)	−0.8/−0.6 (1.3) (−5.7, +3.0)	+0.0/+0.1 (0.6) (−2.2, +2.0)	−0.1, +0.1	0.7310/0.3197 (0.5682)
Across-Puberty[a]	18	−0.9/−0.6 (1.1) (−3.0, +0.9)	−0.9/−0.8 (1.0) (−2.9, +0.9)	−0.1/−0.2 (0.6) (−1.1, +1.0)	−0.4, +0.2	0.6024[a]/0.8145

[a] Because we chose only two time-points (after vs before puberty), the NIH method was not applied.

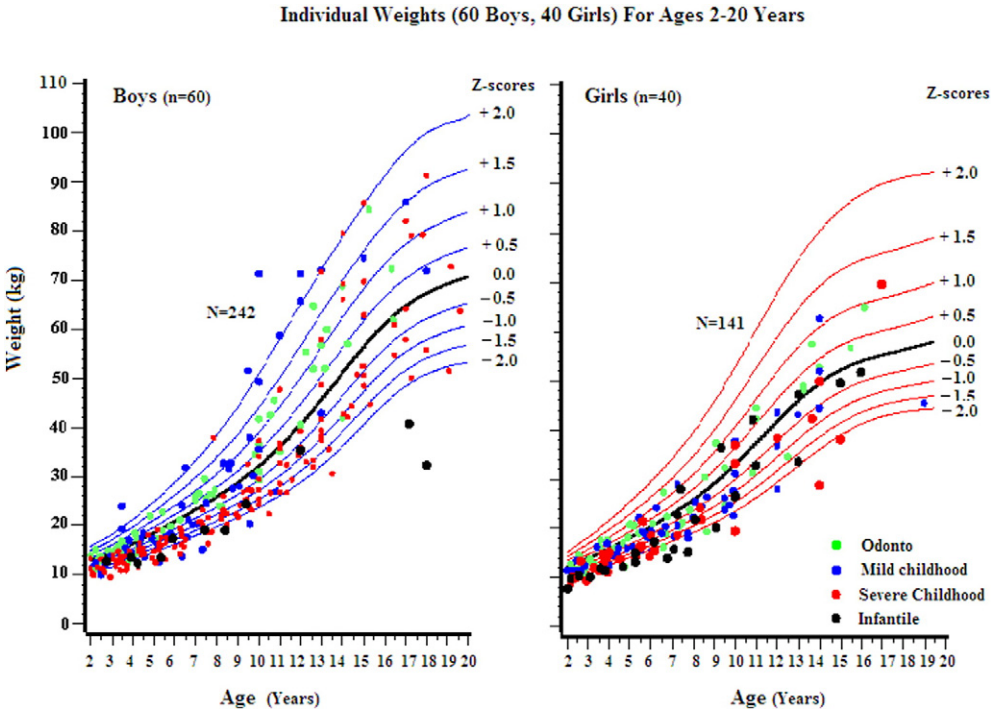

Fig. 4.

Cumulatively, the 101 patients had 407 study admissions (Table 2).

The mean/median number of admissions was, as could be expected, higher as the HPP classification became more severe, with the mean/median being 4.1/4 for the cohort overall (Table 2). The mean/median duration separating admissions was briefer as HPP was designated more severe, and for the total of 407 admissions 2.2/2.0 years for the cohort overall.

3.3. Puberty study

The across-puberty group of 18 subjects comprised 3 odonto HPP, 4 mild childhood HPP, 9 severe childhood HPP, and 2 infantile HPP patients. Their mean/median ages at first and final studies were 6.6/6.4 years (range 1.5 to 12.3 years) compared to 17.9/18.0 years (range 15.3 to 20.0 years), respectively.

3.4. Height changes

Fig. 1 illustrates on the CDC gender-specific growth curves the individual patient heights according to HPP group for the 383 admissions spanning designated ages 2–20 years.

Heights of the boys as well as girls with HPP typically distributed beneath the median line (i.e., z-score = 0) both early on and over time, and overall the values appeared to reflect the HPP nosology.

Lack of any apparent trend for increasing or decreasing height z-scores with aging was supported by additional analysis from randomly plotting on the X-axis the patients' last minus first height z-scores, showing greater change "scatter" (Fig. 2A) compared to rate-of-change determined using all height measurements (Fig. 2B). Although individual patient height z-scores and growth rates ranged widely, the changes over time distributed symmetrically around the zero line for all four HPP groups and for the cohort.

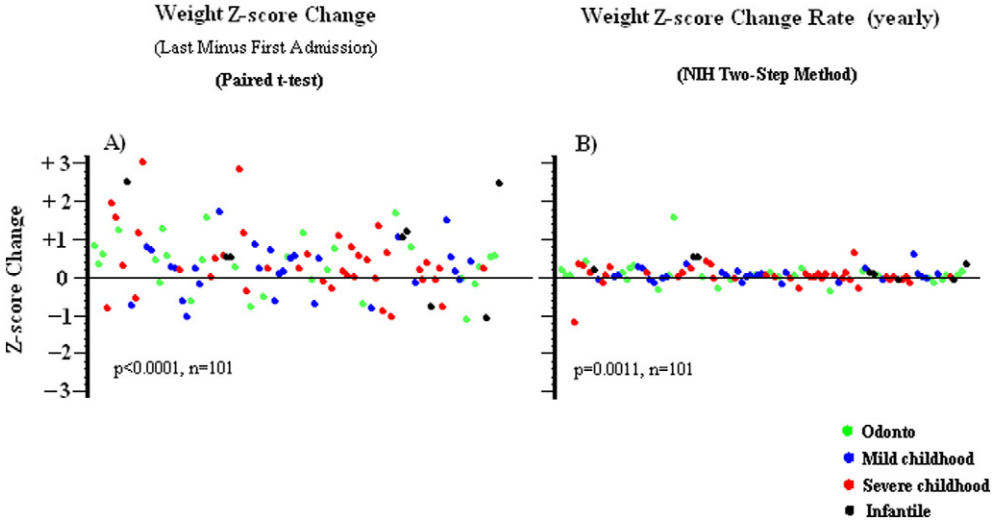

Fig. 5.

Table 4
Weight z-scores per chronologic age at first and last admissions, and changes between those admissions.

HPP group	# Pts	Mean/median (SD) (min, max)		Mean/median change (SD)	95% CI of mean change	p-Values
		First	Last	Range (min, max)		Paired *t*-test/sign test (NIH method)
Odonto	28	−0.2/−0.1 (0.8) (−2.4, +1.3)	+0.2/+0.3 (1.0) (−2.4, +1.9)	+0.4/+0.5 (0.7) (−1.1, +1.7)	+0.1, +0.7	0.0086/0.0872 (0.0885)
Mild childhood	28	−0.5/−0.8 (1.4) (−3.7, +3.3)	−0.2/−0.3 (1.4) (−3.0, +2.3)	+0.3/+0.3 (0.8) (−1.0, +1.8)	−0.02, +0.5	0.0642/0.0872 (0.0146)
Severe childhood	37	−1.4/−1.3 (1.2) (−3.6, +1.5)	−1.0/−0.9 (1.2) (−3.9, +1.6)	+0.4/+0.3 (0.9) (−1.0, +3.1)	+0.1, +0.8	0.0049/0.0051 (0.2892)
Infantile	8	−2.2/−2.4 (0.7) (−2.9, −1.3)	−1.4/−0.7 (1.7) (−4.0, +0.7)	+0.8/+0.8 (1.3) (−1.0, +2.5)	−0.3, +1.9	0.1160/0.2891 (0.0347)
Cohort	101	−0.9/−0.8 (1.3) (−3.7, +3.3)	−0.5/−0.4 (1.3) (−4.0, +2.3)	+0.4/+0.3 (0.9) (−1.1, +3.1)	+0.2, +0.5	<0.0001/<0.0001 (0.0011)

The mean height z-scores for each group were unchanged when the first and last admissions were contrasted, and paralleled the HPP nosology (Fig. 3).

Steady patient growth featuring unchanging height z-scores was confirmed for the cohort using both the paired *t*-test and the sign-test to compare the last versus first measurements ($p = 0.7310/0.3197$, respectively), and also using the NIH method when there had been three or more study admissions ($p = 0.5682$) (Table 3). A few patients showed substantial spontaneous increases or decreases in height z-scores (last versus first assessments ranging from −2.2 to +2.0).

The mean/median height z-scores for all four HPP groups began and remained within the lower half of the normal range except the lower −2.1 final value for the infantile HPP group (Fig. 3). The last as well as the first [5] mean/median height z-scores paralleled the HPP nosology, with the more severely affected patients being shorter (Table 3).

Similarly, for the 18 patients in the across-puberty study, the paired *t*-test/sign test revealed no significant change in their height z-scores ($p = 0.6024/0.8145$) (Table 3). Individual patient changes during this timeframe ranged from −1.1 to +1.0.

3.5. Weight changes

In contrast to no change in mean/median height z-scores over time for all four HPP groups, the distribution of the total of 383 individual weights for all patients ages 2–20 years plotted on CDC gender-specific growth curves suggested accelerated weight gain for all four HPP groups, and for both genders but especially the boys (Fig. 4).

Because height conditions weight, we first assessed the weight z-scores for chronologic age, but then proceeded to adjust the scores using height-age. Body mass index (BMI) was not utilized because it would excessively reflect height effects.

3.5.1. Weight z-scores calculated for chronologic age

Weight for chronologic age was typically below average at first admission. A scatter plot of the changes in weight z-scores for the last versus first admissions, displayed randomly along the X-axis for the 101 patients, supported a trend for accelerated weight gain with aging for the HPP groups and cohort (Fig. 5). Although the individual patient weight z-score changes calculated per chronologic age ranged widely (−1.1 to +3.1), the generally positive values (above the zero line) indicated accelerated weight gain for most patients in all four HPP groups [paired *t*-test/signed test ($p < 0.0001/<0.0001$; NIH two-step method ($p = 0.0011$)]. Accelerated weight gain was confirmed for both genders ($p < 0.0001$ for boys, $p = 0.0140$ for girls), but did not differ ($p = 0.4903$) between the boys versus girls.

The mean/median weight z-scores per chronologic age increased ($p_s < 0.05$) for all four HPP groups, with an especially significant ($p < 0.0001$) increase of +0.4/+0.3 for the cohort (Table 4).

The mean weights per chronologic age for all four groups were initially below average, but only the infantile HPP group typically began below the reference range, having a mean/median z-score of −2.2/−2.4 (Table 4). Nevertheless, the infantile HPP group seemed to have the greatest z-score increase (mean/median +0.8/+0.8) as verified ($p = 0.0347$) using the NIH method (Table 4). For the other HPP groups, the weight z-score increases were more modest at +0.4/+0.5 for odonto HPP ($p = 0.0086/0.0872$), +0.3/+0.3 for mild childhood HPP ($p = 0.0642/0.0872$), and +0.4/+0.3 for severe childhood HPP ($p = 0.0049/0.0051$). For the cohort, the mean/median increase in weight z-score (last vs first admission) was +0.4/+0.3 ($p < 0.0001$) assessed using the paired *t*-test/sign test.

Although the mean/median weight z-scores calculated per chronologic age had increased at last visit for each group, the values continued to parallel the HPP nosology (Fig. 6).

The final mean/median weight z-scores per chronologic age for the odonto HPP and mild childhood HPP groups reached essentially average healthy values; i.e., +0.2/+0.3 ($p = 0.2821/0.1849$) and −0.2/−0.3 ($p = 0.3936/0.3449$), respectively. Although improved, the values per chronologic age remained clearly below average for the severe

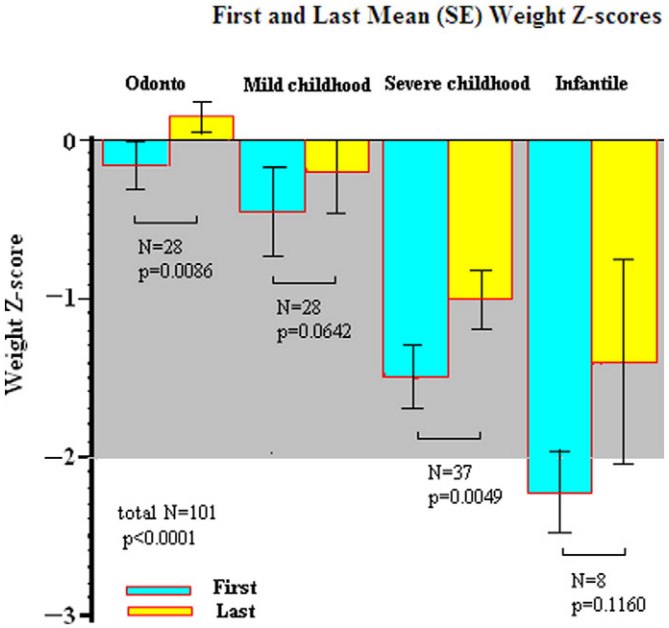

Fig. 6.

Table 5
Preteen patients: weight z-scores per chronologic age at first and last admissions, and changes between admissions.

Group	# pts	Mean/median (SD) (min, max)		Mean/median change (SD)	95% CI of mean change	p-Values
		First	Last	Range (min, max)		Paired *t*-test/sign test
Odonto	26	−0.2/−0.1 (0.8) (−2.4, +0.9)	+0.1/+0.2 (0.9) (−2.4, +1.3)	+0.3/+0.3 (0.7) (−1.1, +0.5)	−0.0, +0.6	0.0527/0.0755
Mild Childhood	27	−0.5/−0.8 (1.4) (−3.7, +3.3)	−0.3/−0.3 (1.3) (−3.0, +2.3)	+0.3/+0.3 (0.7) (−1.0, +1.8)	−0.01, +0.5	0.0553/0.092
Severe Childhood	33	−1.5/−1.6 (1.1) (−3.6, +0.8)	−1.1/−1.0 (1.0) (−3.5, +1.2)	+0.4/+0.3 (0.8) (−1.0, +2.9)	+0.1, +0.7	0.0052/0.0351
Infantile	8	−2.2/−2.4 (0.7) (−2.9, −1.3)	−1.5/−1.0 (1.5) (−4.0, +0.7)	+0.8/+0.6 (1.0) (−1.0, +2.5)	−0.1, +1.6	0.0733/0.0703
Cohort	94	−0.9/− 0.9 (1.3) (−3.7, +3.3)	−0.6/−0.6 (1.2) (−4.0, +2.3)	+0.4/+0.3 (0.8) (−1.1, +2.9)	+0.2, +0.5	<0.0001/<0.0001

Table 6
Preteen height-corrected weight z-score changes.

HPP group	# pts	Mean/median (SD) (min, max)		Mean/median change (SD)	95% CI of mean change	p-Values
		First	Last	Range (min, max)		Paired *t*-test/sign test
Odonto	24	−0.1/−0.0 (0.7) (−1.3, +1.2)	+0.2/+0.2 (0.7) (−1.1, +1.3)	+0.3/+0.4 (0.6) (−0.9, +1.4)	+0.04, +0.6	0.0253/0.0066
Mild Childhood	26	−0.3/−0.3 (0.8) (−2.6, +1.3)	−0.0/−0.2 (0.8) (−1.6, +1.6)	+0.3/+0.3 (0.7) (−0.6, +1.7)	+0.1, + 0.5	0.0084/0.0290
Severe Childhood	28	−0.7/−0.5 (0.7) (−2.0, +0.8)	−0.1/−0.2 (0.9) (−1.4, +1.5)	+0.6/+0.4 (0.7) (−0.3, +2.8)	+0.4, + 0.9	<0.0001/0.0002
Infantile	6	−0.9/−1.0 (0.5) (−1.6, −0.2)	−0.1/−0.4 (0.9) (−0.8, +1.5)	+0.9/+0.5 (1.1) (−0.2, + 2.4)	−0.3, +2.0	0.1052/0.2188
Cohort	84	−0.4/−0.4 (0.7) (−2.6, +1.3)	+0.0/−0.1 (0.8) (−1.6, +1.6)	+0.4/+0.4 (0.7) (−0.9, +2.8)	+0.3, +0.6	<0.0001/<0.0001

childhood HPP group at −1.0/−0.9 (p < 0.0001/0.0001) and −1.4/−0.7 (p = 0.0516/0.0703) for the infantile HPP group. For the cohort, the final mean/median weight z-scores per chronologic age were within the normal range (±2 SD mean) for healthy American children, but remained below average at −0.5/−0.4 (p = 0.0004/0.0072).

Similar results were obtained from study of the preteen patients and showed the accelerated weight gain began early on, thus excluding any effect of puberty (Table 5).

Accelerated weight gain continued throughout the study as the 18 patients investigated across-puberty showed a mean/median weight z-score increase per chronologic age of +0.5/+0.6 (p = 0.0314/0.0963).

3.5.2. Weight z-scores adjusted for height-age

Among the 101 patients, 84 (52 boys, 32 girls) had at least two preteen weight assessments: 24 odonto HPP, 26 mild childhood HPP, 28

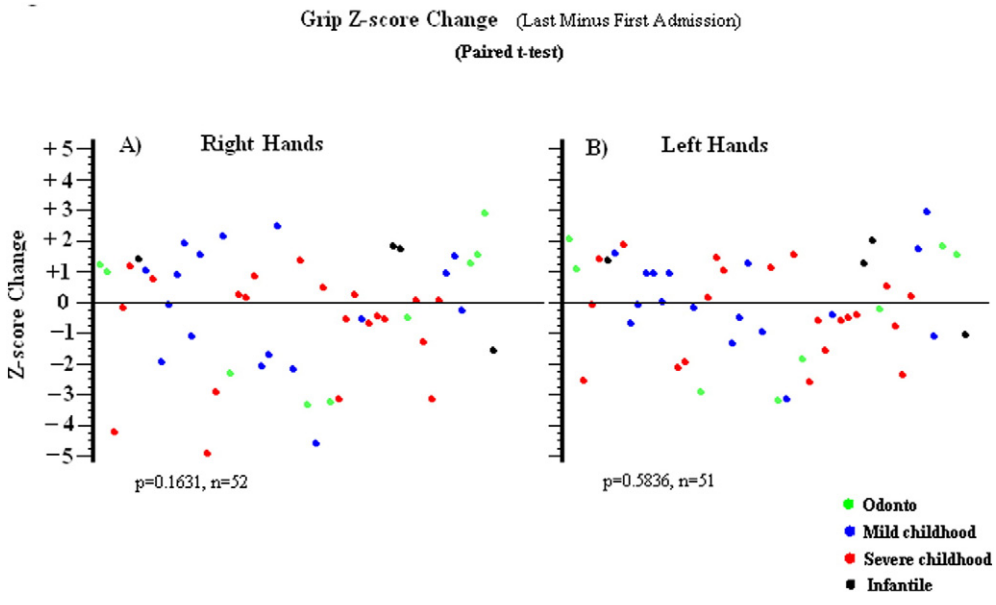

Fig. 7.

Table 7
Grip strength per chronologic age change.

	HPP Group	# pts	Mean/Median (SD) (min, max)		Mean/Median Change (SD)	95% CI of mean change	P-values
			First	Last	Range (min, max)		Paired *t*-test/ Sign test (NIH Method)
Right Hand	Odonto	9	−1.3/−1.6 (2.0) (−4.3, +1.8)	−1.4/−1.6 (1.5) (−3.4, +1.5)	−0.1/+1.0 (2.2) (−3.3, +2.9)	−1.9, +1.6	0.8601/1.000 (0.6173)
	Mild Childhood	18	−0.6/−0.9 (1.6) (−4.3, +1.5)	−1.0/−1.8 (1.6) (−4.4, −1.0)	−0.4/−0.2 (2.2) (−5.2, +2.5)	−1.5, +0.7	0.4858/0.8145 (0.5901)
	Severe Childhood	21	−0.9/−0.6 (1.9) (−4.3, +2.6)	−1.6/−1.8 (1.6) (−4.1, +1.6)	−0.8/−0.2 (1.8) (−4.9, +1.4)	−1.6, +0.1	0.0638/1.000 (0.0657)
	Infantile	4	−2.3/−2.7 (1.0) (−3.0, −0.7)	−1.4/−1.1 (0.6) (−2.3, −1.0)	+0.9/+1.6 (1.6) (−1.6, +1.9)	−1.7, +3.5	0.3591/0.6250 (0.1173)
	Cohort	52	−1.0/−1.0 (1.8) (−4.3, +2.6)	−1.4/−1.3 (1.7) (−4.4, +2.6)	−0.4/0.0 (1.0) (−5.2, +2.9)	−1.0, +0.2	0.1631/1.000 (0.5815)
Left Hand	Odonto	8	−0.8/−1.2 (1.7) (−3.2 + 1.5)	−1.1/0.8 (1.3) (−3.5, +0.9)	−0.2/+0.5 (2.2) (−3.2, +2.1)	−2.0, +1.6	0.8169/1.000 (0.6140)
	Mild Childhood	18	−0.8/− 0.3 (1.5) (−4.3, +1.7)	−0.9/−0.8 (1.6) (−3.8, +2.6)	−0.1/−0.1 (1.9) (−5.1, +3.0)	−1.1, +0.8	0.7415/0.8145 (0.5101)
	Severe Childhood	21	−0.7/−0.5 (1.8) (−4.2, +3.4)	−1.0/−1.3 (1.2) (−2.6, +1.8)	−0.3/−0.4 (1.4) (−2.6, +1.9)	−1.0, +0.4	0.3564/0.6636 (0.4406)
	Infantile	4	−2.4/−2.8 (0.8) (−2.9, −1.1)	−1.5/−1.4 (0.6) (−2.2, −0.9)	+0.9/+1.4 (1.4) (−1.1, +2.0)	−1.2, +3.1	0.2668/0.6250 (0.0955)
	Cohort	51	−0.9/−0.7 (1.6) (−4.3, +3.4)	−1.0/−1.0 (1.3) (−3.8, +2.6)	−0.1/−0.1 (1.7) (−5.1, +3.0)	−0.6, +0.3	0.5836/0.7798 (0.9731)

severe childhood HPP, and 6 infantile HPP patients (Table 6). This permitted an evaluation after height correction of the weight z-score changes.

As expected with height-age adjustment and the briefer timeframe for study of the preteen patients, the increases in mean/median weight z-scores seemed not as large (Table 6). Once again, the greatest increase (+0.9/+0.5) involved the infantile HPP group, but the lack of statistical significance ($p = 0.1052/0.2188$) may be due to the few patients ($n = 6$). Otherwise, the weight z-score increases, now height-corrected, were especially apparent over time at +0.3/+0.4 for odonto HPP ($p = 0.0253/0.0066$), +0.3/+0.3 for mild childhood HPP ($p = 0.0084/0.0290$), and +0.6/+0.4 for severe childhood HPP ($p < 0.0001/0.0002$). For the cohort, the increase was +0.4/+0.4 ($p < 0.0001$). Notably, and in contrast to the chronologic age analysis, the height-corrected final values for all four patient groups were essentially average for healthy children (Table 6). No significant differences for weight change were noted among the four HPP groups for chronologic age ($p = 0.3717$), after correcting for height ($p > 0.05$), or for the boys versus girls ($p = 0.4903$).

3.6. Grip strength

Grip strength data were available for at least two admissions from approximately one-half the cohort of 101 patients; right hand ($n = 52$) and left hand ($n = 51$). Only two patients were left hand dominant. Herein, we do not display the individual patient values, including according to group.

Table 8
Preteen height-corrected grip strength change.

	HPP group	# pts	Mean/median (SD) (min, max)		Mean changes (SD)	95% CI of mean change	p-Values
			First	Last	Range (min, max)		Paired *t*-test (sign test)
Right hand	Odonto	7	+0.3/+0.4(2.1) (−2.2, +3.5)	−0.6/−1.0(1.4) (−2.0, +2.3)	−0.9/−1.6 (2.5) (−4.0, +1.9)	−3.2, +1.4	0.3661 (1.000)
	Mild childhood	13	−0.4/−0.2(1.7) (−2.8, +3.1)	−1.6/−1.7(1.7) (−4.5, +2.3)	−1.2/−0.7 (2.2) (−4.6, +2.2)	−2.6, +0.1	0.0738 (0.5811)
	Severe childhood	13	+0.6/+0.8(2.0) (−2.9, +3.5)	−1.1/−1.3(2.0) (−3.0, +2.2)	−1.7/−1.9 (2.8) (−5.5, +3.2)	−3.4, +0.0	0.0513 (0.2668)
	Infantile	3	−2.0/−2.8(1.9) (−3.4, +0.2)	−1.9/−1.1(1.9) (−4.0, −0.5)	+0.1/−0.7 (1.4) (−0.7, +1.7)	−3.3, +3.5	0.9017 (1.000)
	Cohort[a]	36	−0.0/+0.0 (2.0) (−3.4, +3.5)	−1.2/−1.1(1.8) (−4.4, +2.3)	−1.2/−0.7 (2.4) (−5.5, +3.2)	−2.0, −0.4	0.0046 (0.1325)
Left hand	Odonto	7	+0.3/+0.5 (2.1) (−2.1, +3.6)	−0.6/−0.9 (1.1) (−2.0, +1.6)	−0.6/−0.4(2.5) (−4.6, +2.1)	−3.2, +2.0	0.5653 (1.000)
	Mild childhood	13	−0.6/−0.3(1.4) (−2.6, +1.3)	−1.5/−1.6 (1.3) (−3.8, +0.4)	−0.9/−0.9 (1.9) (−4.0, +3.0)	−2.1, +0.2	0.1002 (0.5811)
	Severe childhood	13	+0.3/+0.8 (1.4) (−2.9, +2.1)	−0.4/−0.9 (1.8) (−2.4, +3.4)	−0.7 −1.4(2.3) (−3.6, +4.0)	−2.1, +0.7	0.3255 (0.5811)
	Infantile	3	−2.2/−2.9 (1.3) (−3.0, −0.7)	−1.1/−0.7 (0.9) (−2.2, −0.4)	+1.1/0.8(1.0) (+0.3, +2.2)	−1.3, +3.5	0.1855 (0.2500)
	Cohort[a]	36	−0.3/−0.6 (1.7) (−3.0, +3.6)	−0.9/−1.3 (1.5) (−3.8, +3.4)	−0.6/−0.4 (2.1) (−4.6, +4.0)	−1.3, +0.1	0.0991 (0.7359)

[a] The mixed model with an unstructured covariance component indicated a significant negative age effect for the height-corrected grip strength z-score for the entire cohort estimated as −0.4 (−0.3) per year for right (left) hand ($Ps < 0.0001$), but no group difference ($p = 0.3847$ for right hand, and $p = 0.0681$ for left hand).

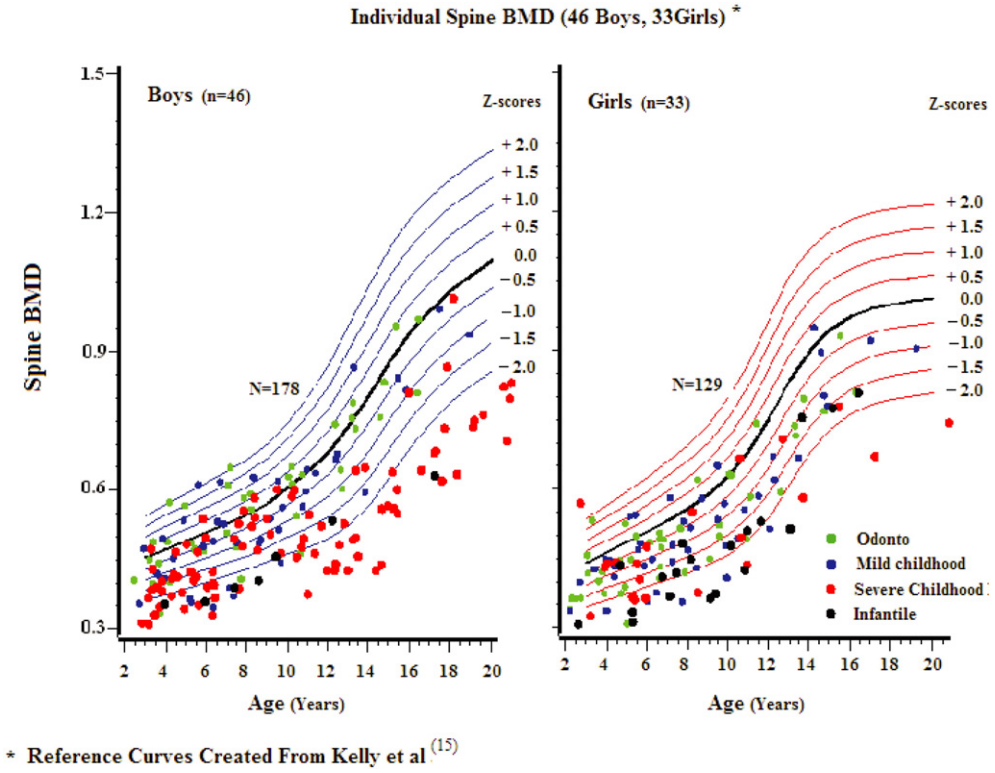

Fig. 8.

Changes in the individual grip strength z-scores calculated for chronologic age, contrasting the last versus first admission, had wide-ranging values. However, the changes were evenly distributed around the zero line when displayed randomly along the X-axis for the right as well as left hand for each of the four HPP groups (Fig. 7).

Despite the accelerating weight gains for the patients (see before), mean grip strength z-scores calculated for chronologic age did not change with aging for any of the four HPP groups, or for the cohort for the right hand, [paired *t*-test/sign test (NIH Method)] p = 0.1631/1.000 (0.5815), or for the left hand p = 0.5836/0.7798 (0.9731) (Table 7).

After height-correction (i.e., preteen data), no significant change was detected with aging in the right or left-hand last minus first mean/median grip strength z-scores for any patient group (ps > 0.05). However, for the cohort these z-scores assessed by the paired *t*-test decreased −1.2 for the right hand (p = 0.0046) and perhaps decreased −0.6 for the left hand (p = 0.0991) (Table 8). In concordance, the mixed model analysis for height-corrected grip strength, using an unstructured covariance component that accommodated single admissions, indicated for the cohort worsening grip strength in both hands (p < 0.0001) (Table 8).

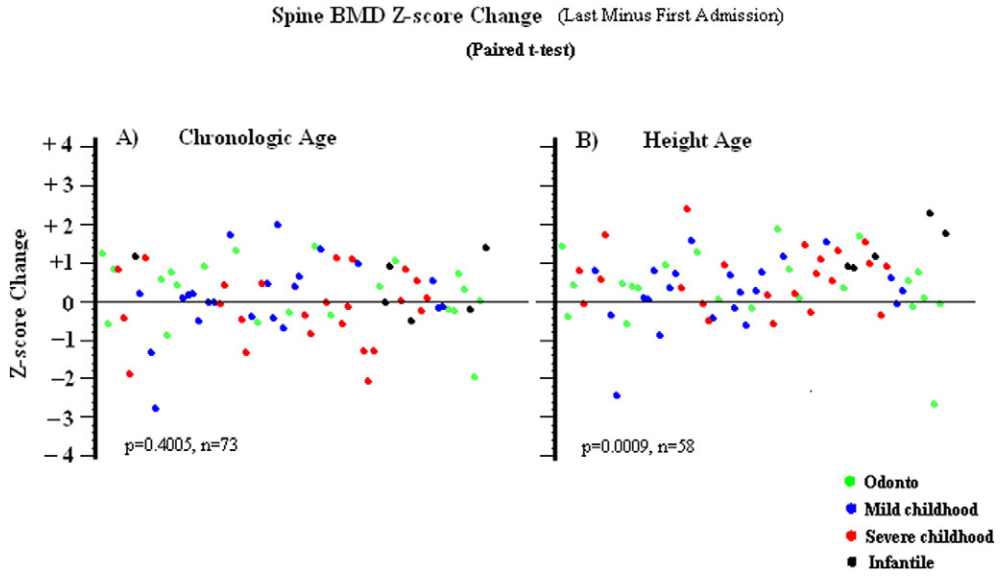

Fig. 9.

Table 9
Chronologic age spine BMD z-score changes.

HPP group	# pts	Mean/median z-score (SD) (min, max)		Mean/median change (SD)	95% CI of mean change	p-Values
		First	Last	Range (min, max)		Paired *t*-test/sign test (NIH method)
Odonto	21	−0.7/−0.8 (1.2) (−3.2, +2.0)	−0.5/−0.3 (0.9) (−1.9, +0.8)	+0.3/+0.4 (0.8) (−1.9, +1.4)	−0.1, +0.6	0.1812/0.3835 (0.0386)
Mild childhood	22	−0.7/−0.8 (1.1) (−2.6, +1.7)	−0.6/−0.7 (1.1) (−2.3, +2.1)	+0.1/+0.1 (1.0) (−2.8, +2.0)	−0.3, +0.6	0.5877/0.5235 (0.1710)
Severe childhood	24	−1.8/−1.9 (1.0) (−3.3, −0.2)	−1.9/−1.8 (1.1) (−3.4, +0.2)	−0.2/−0.1 (0.9) (−2.0, +2.3)	−0.5, +0.4	0.3719/0.5413 (0.4305)
Infantile	6	−2.2/−2.6 (0.9) (−3.2, −0.8)	−1.8/−1.6 (0.7) (−3.0, −1.0)	+0.5/+0.5 (0.8) (−0.5, +1.4)	−0.4, +1.3	0.2152/1.0000 (0.4787)
Cohort	73	−1.2/−1.2 (1.2) (−3.3, +2.0)	−1.1/−1.0 (1.2) (−3.4, +2.1)	+0.1/+0.1 (1.0) (−2.8, +2.1)	−0.1, +0.3	0.4005/0.6400 (0.1777)

Table 10
Preteen height-corrected spine BMD z-score change.

HPP group	# pts	Mean/median z-score (SD) (min, max)		Mean/median change (SD)	95% CI of mean change	p-Values
		First	Last	Range (min, max)		Paired *t*-/sign (test) (NIH method)
Odonto	17	−0.8/−0.6 (1.3) (−3.2, +2.3)	−0.3/−0.4 (1.0) (−1.9, +1.7)	+0.5/+0.5 (0.9) (−2.1, +1.9)	+0.0, +1.0	0.0493/0.0490 (0.0163)
Mild childhood	20	−0.6/−0.8 (1.1) (−2.4, +1.7)	−0.6/−1.0 (1.1) (−1.7, +2.3)	+0.1/+0.1 (1.0) (−2.6, +1.6)	−0.4, +0.5	0.7809/0.8238 (0.5368)
Severe childhood	16	−1.5/−1.5 (1.0) (−3.2, −0.1)	−0.8/−0.7 (1.1) (−2.8, +0.7)	+0.8/+0.6 (1.0) (−0.4, +3.0)	+0.3, +1.3	0.0039/0.2101 (0.0264)
Infantile	5	−2.3/−2.4 (0.7) (−3.0, −1.2)	−1.1/−1.4 (0.8) (−1.8, +0.2)	+1.2/+1.0 (1.0) (−0.2, +2.3)	−0.01, +2.4	0.0510/0.3710 (0.2650)
Cohort	58	−1.1/−1.0 (1.2) (−3.2, +2.3)	−0.6/−0.8 (1.0) (−2.8, +2.3)	+0.5/+0.4 (1.0) (−2.6, +3.0)	+0.2, +0.7	0.0009/0.0119 (0.0044)

3.7. DXA bone mineral density

Because reference data for DXA BMD were limited to ages 3–20 years for the spine and to ages 5–20 years for the hip, 73 and 60 of our HPP patients, respectively, could be studied longitudinally using chronologic age. Among them, 58 and 41 patients had multiple preteen spine and hip DXA studies, respectively, enabling also height-corrected assessments.

3.7.1. Spine BMD

Spine BMD for the boys and girls was wide-ranging. On our reference curves, no trend up or down with aging was apparent for any HPP group (Fig. 8).

The changes (last minus first admissions) in spine BMD z-scores for chronologic age distributed evenly around the zero line when displayed randomly along the X-axis; i.e., 39 above versus 34 below ($p = 0.5584$ by Chi-square test) (Fig. 9A).

Spine mean/median BMD z-scores per chronologic age did not change significantly between the first and last determinations for any of the four groups, or for the cohort ($p = 0.4005/0.6400$), using the paired *t*-test or sign test (Table 9). However, the NIH longitudinal analysis method indicated a significant spontaneous improvement ($p = 0.0386$) for the odonto HPP group.

Similarly, no significant changes occurred for the spine BMD z-scores calculated per chronologic age before puberty using the preteen patient values ($ps > 0.05$, data not shown), or for the 15 patients for whom there was across-puberty DXA data (mean z-score change −0.1, 95% CI −0.5 to +0.2, $p = 0.4694$).

In contrast, for the 58 preteen HPP patients whose spine BMD z-scores could be corrected for height, the last minus first values distributed primarily above the zero line when plotted randomly along the X-axis; 39 differences greater than, and 19 differences less than, zero (Chi-square $p = 0.0086$) (Fig. 9B). Their mean/median height-corrected spine BMD z-score increase (+0.5/+0.4) evaluated by the paired *t*-test/sign test was statistically significant ($p = 0.0009/0.0119$) (Table 10).

Height correction revealed statistically significant spine BMD z-score increases for severe childhood HPP +0.8/+0.6 [$p = 0.0039/0.2101$

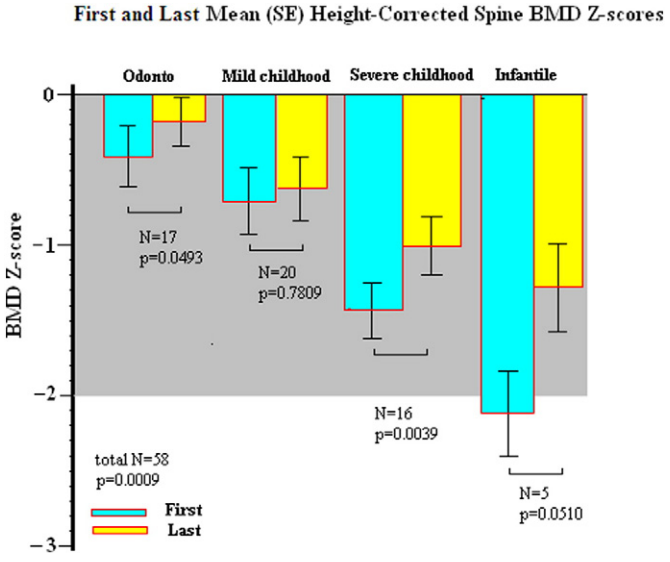

Fig. 10.

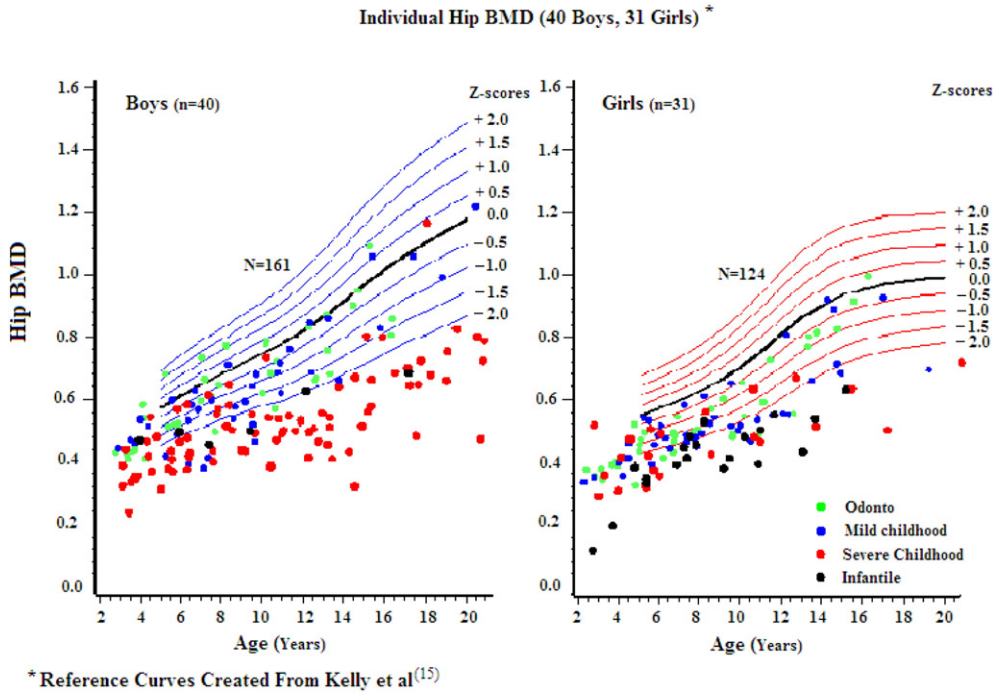

Fig. 11.

(0.0264)], borderline significance for odonto HPP +0.5/+0.5 [p = 0.0493/0.0490 (0.0163)] and perhaps infantile HPP +1.2/+1.0 [p = 0.0510/0.3710 (0.2650)], but no change for mild childhood HPP +0.1/+0.1 [p = 0.7809/0.8238 (0.5368)] (Table 10). For the cohort, the height-corrected spine BMD z-score increase was +0.5/+0.4 (p = 0.0009/0.0119), but the final value remained below average (p < 0.0001). These final mean/median spine z-score values for the four HPP groups were within the lower half of the normal range, and continued to parallel the HPP nosology [5] (Fig. 10).

For the odonto HPP, mild childhood HPP, severe childhood HPP, and infantile HPP groups and the cohort overall, the p-values for the final mean/median height-corrected spine z-scores compared to an average value of zero were 0.2552/0.3323, 0.0270/0.0041, 0.0069/0.0758, 0.0328/0.3750, and <0.0001/0.0009, respectively (data not shown), indicating values significantly below average except for odonto HPP (Fig. 10).

3.7.2. Hip BMD

Hip BMD z-scores for the individual boys and girls was nearly always below the reference average value, and generally paralleled the HPP nosology (Fig. 11).

When displayed randomly along the X-axis, the change (last minus first admission) for individual patient hip BMD z-scores calculated per chronologic age distributed evenly around the reference line of zero indicating no trend with patient aging (Fig. 12A), but after height-correction the paired *t*-test showed a significant (p = 0.0380) decrease (Fig. 12B).

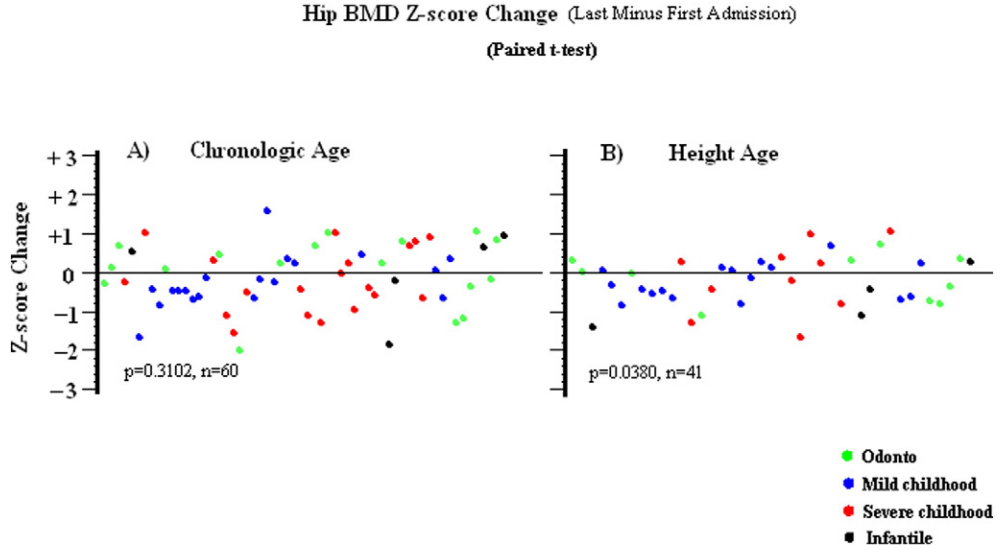

Fig. 12.

Table 11
Chronologic age hip BMD z-score changes.

HPP group	# pts	Mean/median Z-score (SD) (min, max)		Mean/median change (SD)	95% CI of mean change	p-Values
		First	Last	Range (min, max)		Paired *t*-test/sign test (NIH method)
Odonto	17	−1.1/−1.3 (1.0) (−2.5, +1.7)	−1.0/−0.8 (1.1) (−2.8, +0.9)	+0.1/+0.2 (0.9) (−2.0, +1.1)	−0.4, +0.5	0.7437/0.3323 (0.2937)
Mild childhood	19	−1.4/−1.5 (0.9) (−2.7, +0.3)	−1.6/−1.6 (1.0) (−3.3, −0.1)	−0.2/−0.4 (0.7) (−1.7, +1.6)	−0.5, +0.1	0.1697/0.1671 (0.4228)
Severe childhood	19	−2.7/−2.8 (1.2) (−5.1, −0.5)	−2.9/−2.9 (1.1) (−4.3, −0.2)	−0.2/−0.4 (0.8) (−1.5, +1.0)	−0.6, +0.2	0.3344/0.3593 (0.8877)
Infantile	5	−2.6/−2.9 (1.0) (−3.6, −1.4)	−2.6/−2.6 (0.5) (−3.2, −2.0)	+0.0/+0.6 (1.1) (−1.8, +1.0)	−1.4, +1.4	0.9501/1.000 (0.5907)
Cohort	60	−1.8/−1.8 (1.2) (−5.1, +1.7)	−1.9/−2.0 (1.2) (−4.3, +0.9)	−0.1/−0.2 (0.8) (−2.0, +1.6)	−0.3, +0.1	0.3102/0.5190 (0.7162)

Table 12
Preteen height-corrected hip BMD z-score changes.

HPP Group	# pts	Mean/median Z-score (SD) (min, max)		Mean/median change (SD)	95% CI of mean change	p-Values
		First	Last	Range (min, max)		Paired *t*-test/Sign test (NIH Method)
Odonto	10	−1.1/−1.1 (1.2) (−2.5, +1.5)	−1.2/−1.3 (1.0) (−2.7, +0.4)	−0.1/0.0 (0.6) (−1.1, +0.7)	−0.5, +0.3	0.5590/1.000 (0.6147)
Mild Childhood	17	−1.4/−1.6 (0.8) (−3.1, +0.1)	−1.6/−1.7 (0.9) (−2.9, +0.2)	−0.2/−0.3 (0.5) (−0.8, +0.7)	−0.4, +0.0	0.0646/0.6291 (0.0815)
Severe Childhood	10	−2.4/−2.2 (1.3) (−4.9, −0.1)	−2.2/−2.5 (1.3) (−4.2, +0.2)	+0.2/+0.0 (1.2) (−1.7, +2.6)	−0.8, +0.5	0.6474/1.000 (0.9378)
Infantile	4	−1.6/−1.6 (0.6) (−2.4, −0.9)	−2.3/−2.1 (0.6) (−3.1, −1.8)	−0.7/−0.8 (0.7) (−1.4, +0.3)	−1.8, +0.5	0.1725/0.6250 (0.2161)
Cohort	41	−1.6/−1.6 (1.1) (−4.9, +1.5)	−1.7/−1.9 (1.1) (−4.2, +0.4)	−0.1/−0.1 (0.8) (−1.7, +2.6)	−0.4, −0.01	0.0380/0.5327 (0.1385)

Hip BMD z-scores per chronologic age did not change with aging by the paired *t*-test, sign test, or the NIH method for the cohort or for any of the four HPP groups (Table 11).

Although the paired *t*-test alone was significant for the cohort, their small height-corrected hip BMD z-score decrease with aging was not documented for any of the preteen HPP groups (Table 12).

Notably, the BMD z-scores, either per chronologic age or height-corrected, were significantly lower at the hip compared to the spine at both the first [5] ($p < 0.0001$ by paired *t*-test) and last determinations (Tables 9 & 10 versus Tables 11 & 12).

4. Discussion

To understand the natural history of HPP during childhood and adolescence, we assessed height, weight, grip strength, and DXA BMD data from the 101 such patients studied longitudinally during the initial 25 years of our Research Center. These parameters were chosen to provide objective measures of HPP severity. In 2015, we had reported a cross-sectional evaluation from the first encounters with the entire cohort of 173 patients [5]. Perinatal HPP was not represented, but our retrospective studies of perinatal HPP reported in 2013 [8] and perinatal and infantile HPP reported in 2016 [9] had helped to delineate these most severe forms of pediatric HPP [6,9,17]. Our publication in 2015 [5] validated and expanded the clinical classification for pediatric HPP [1,3] to include odonto HPP, mild childhood HPP, severe childhood HPP, infantile HPP, and perinatal HPP by documenting increasingly aberrant values as it signified worse disease [5]. Parameters of patient body size (height, weight) and DXA BMD z-scores discriminated best among the four studied HPP groups. Thus, for our natural history investigation of pediatric HPP herein, we used this expanded clinical nosology [5].

For these 101 American children representing four pediatric types of HPP, the period of observation was extensive but averaged 6.5 years typically spanning early to mid-childhood and usually consisting of four admissions each separated by 2.2 years. Among the cohort, 18 patients were studied across puberty.

Concordant with our published cross-sectional evaluation of data from the first encounters [5], the individual patient data acquired later for this longitudinal study remained broad-ranging within and overlapping between the patient groups.

Compared to healthy American boys and girls, mean/median height z-scores started below average for all four HPP groups, and did not change significantly as the patients aged. Individual patient height z-scores from the initial to final assessments typically remained in the lower half of the normal range, except the infantile HPP group having a final mean/median value that was just below the normal range. Thus, although below-average height is typical for these four pediatric forms of HPP, only survivors of infantile HPP seem to feature short stature as defined by a height z-score < -2 (i.e., < -2 SD mean). The height z-scores did not change significantly for the boys or girls, or across puberty. The mean/median values at final admission further validated our expanded HPP nosology [5]. Some spontaneous improvement or worsening in height was equally likely, and we will explore for severe childhood HPP if *TNSALP* mutation dosage is a factor perhaps reflected in the HPP biochemical findings.

Like the findings for height, mean/median weight z-scores determined routinely for chronologic age began below average but within the normal range except for the low value for the infantile HPP group. However, when the patient weights were height-adjusted, the values for the four HPP groups all began in the normal range, and subsequently increased significantly placing higher within the normal range but did not become elevated. Instead, the height-adjusted patient weights

became proportionate to the patient heights. Both the boys and girls with HPP showed this trend. This accelerated weight gain resembled what was occurring generally during this timeframe for American children [16]. However, for those severely affected patients who were clearly "skinny" – a finding especially striking at first admission perhaps reflecting increased energy expenditure to walk [5] – our dieticians had counseled and assisted for weight gain. All four HPP patient groups at final visit had mean/median height-corrected weight z-scores near average compared to healthy children. They had not become overweight.

Muscle weakness sometimes features prominently in pediatric HPP [17,18]. In 2015, we had reported for our patients that their initial mean/median grip strength z-scores calculated for chronologic age, although in the normal range, were typically below average and paralleled the HPP nosology [5]. When we corrected for height [5], the values seemed importantly conditioned by body size. For the 52 patients studied longitudinally herein, the mean/median grip strength z-scores after height correction were indeed substantially better, with a below-average value having been documented only for the relatively numerous mild childhood HPP group [5]. Values per chronologic age or height-corrected did not change over time for any HPP group, and typically remained in the lower half of the normal range for all groups. However, for the cohort of 101 patients, the grip strength values were significantly below average and decreasing when analyzed using the mixed model with an unstructured covariance component.

Finally, we studied longitudinally areal (gm/cm^2) BMD using DXA. At the Research Center, a historical control group (spanning two years) of 16 notably affected children had shown no spontaneous radiographic change [18]. In 2007, Girschik et al. [19] had reported for six boys with severe childhood HPP a 4-year follow-up study of BMD showing less distal wrist and femur metaphyseal osteosclerosis by peripheral qCT, but stable DXA values. In the L_1–L_4 spine of our patients, the mean/median z-score values determined routinely per chronologic age did not change significantly with aging, except for a small improvement using the NIH statistical method in the odonto HPP group. No change was detected across puberty. With height correction, spine BMD z-scores showed a significant increase for the cohort, and puberty could be excluded to explain this improvement. The final height-corrected mean/median spine BMD z-scores, although below average, were in the normal range for all four HPP groups and continued to reflect the HPP nosology. Possibly, the improved BMD was from their accelerated gain in weight. For hip BMD, the mean/median z-scores calculated for chronologic age or height-corrected did not change for any HPP group, although for the entire cohort the NIH method suggested a decrease. As we had reported for our first DXA assessments of the patients [5], final hip BMD mean/median z-score values were consistently lower than the lumbar spine values, perhaps explained by lower extremity weakness.

Thus, young American children with odonto HPP, mild childhood HPP, severe childhood HPP, and those who survive infantile HPP typically grow steadily, including across puberty, but with below-average heights that reflect the HPP clinical nosology. Nevertheless, there is unexplained patient-to-patient variation, and precisely predicting adult stature during early childhood seems implausible. Although severely affected pediatric HPP patients are often "skinny" in early childhood, they can show accelerated weight gain and achieve weights appropriate for their heights. Muscle weakness assessed as grip strength per chronologic age did not change, including across puberty, but height-correction suggested some progressive upper extremity weakness. Spine BMD z-scores after height correction typically improved and became normal. However, hip BMD z-scores did not improve, possibly due to persisting weakness in the lower extremities. We have continued after 2008 to study these and new HPP patients into adult life to understand pediatric HPP outcomes.

Findings reported herein support our clinical impressions from evaluating >200 children with HPP that, at their ages, the natural history of this disorder is typically one of a chronic but stable condition. Although there is patient-to-patient variation, children with HPP typically progress through childhood without substantial clinical deterioration or remission. Knowing the natural history of the key demographic, clinical, and DXA parameters studied here should help evaluate therapeutic responses. In 2012, we published favorable one-year experience concerning bone-targeted TNSALP-replacement therapy (asfotase alfa) for life-threatening perinatal and infantile HPP [8,9,17]. In 2016, we reported success using this biologic for debilitating HPP in children [18]. In 2015, asfotase alfa was approved as the first medical treatment for HPP in Japan and for pediatric-onset HPP in Canada, the European Union, and the United States [1], and then elsewhere [17,18]. Accordingly, our natural history information should help understand this and future therapies for pediatric HPP [1,3].

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Conflicts of interest

MPW received consulting fees and research grant support from Enobia Pharma, Montreal, Canada, and research grant support, travel, and honoraria from Alexion Pharmaceuticals Inc., New Haven, CT, USA. DW had consulting fees from Enobia Pharma, Montreal, Canada, and has stock from Amgen Inc., Thousand Oaks, CA, USA. FZ reports no conflict of interest.

Authors' contributions

All authors helped write and approved the submitted manuscript. MPW conceptualized the patient investigations and drafted and finalized the manuscript. DW helped study the patients and plan and organize the data acquisition. FZ analyzed and illustrated the data.

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