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Authors
Khare, Manaswitha
Gold, June-Anne
Wencel, Marie
et al.

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Manaswitha Khare, June-Anne Gold, Marie Wencel, John Billimek, Abhilasha Surampalli, Bridgette Duarte, Andria Pontello, Pietro Galassetti, Suzanne Cassidy and Virginia E. Kimonis*

Effect of genetic subtypes and growth hormone treatment on bone mineral density in Prader-Willi syndrome

Abstract

Background: Currently, there is limited information on the effects of growth hormone and of the different genetic subtypes on bone mineral density (BMD) in Prader-Willi syndrome (PWS).

Methods: We evaluated BMD in 79 individuals with the common subtypes of PWS (48 with deletion and 27 with UPD) and the effect of growth hormone treatment (n=46) vs. no growth hormone treatment.

Results: Forty-four percent of the individuals studied had whole body, hip, or spine BMD <–1 standard deviation (SD) and 10% had a BMD <–2 SD. BMD Z-scores and total BMD (g/cm^2) of the spine were significantly higher in the growth hormone group. With each year of growth hormone treatment, these values increased by a factor of 0.207 and 0.011 (p=0.006 and 0.032), respectively. Individuals with uniparental disomy revealed higher spine BMD compared with deletion subclass; however, the differences were not significant.

Conclusion: This study emphasizes the importance of evaluating bone mineralization in individuals with PWS and the beneficial effects of prolonged treatment with growth hormone. There was a trend for a higher BMD in individuals with uniparental disomy.

Keywords: BMD; bone mineral density; osteopenia; osteoporosis; Prader-Willi syndrome; RDCRN (Rare Diseases Clinical Research Network); uniparental disomy.

***Corresponding author: Virginia E. Kimonis,** MD, MRCP, Division of Genetics and Metabolism, Department of Pediatrics, University of California Irvine, 101 The City Drive South, ZC4482, Orange, CA 92868, USA, Phone: +1-714-456-5791, Fax: +1-714-456-5330, E-mail: vkimonis@uci.edu

Manaswitha Khare, Marie Wencel and Abhilasha Surampalli: Division of Genetics and Metabolism, Department of Pediatrics, University of California Irvine, Irvine, CA, USA

June-Anne Gold: Division of Genetics and Metabolism, Department of Pediatrics, University of California Irvine, Irvine, CA, USA; and Division of Genetics and Metabolism, Department of Pediatrics, Loma Linda University, Loma Linda, CA, USA

John Billimek: Health Policy Research Institute, University of California, Irvine, CA, USA

Bridgette Duarte, Andria Pontello and Pietro Galassetti: Institute for Clinical and Translational Science, University of California Irvine, Irvine, CA, USA

Suzanne Cassidy: Division of Genetics and Metabolism, Department of Pediatrics, University of California Irvine, Irvine, CA, USA; and Division of Medical Genetics, Department of Pediatrics, University of California San Francisco, San Francisco, CA, USA

Introduction

Prader-Willi syndrome (PWS) is a complex multisystem genetic disorder characterized by infantile hypotonia, developmental delay, hyperphagia that may lead to morbid obesity, short stature, hypogonadism, cognitive difficulties, and characteristic behavioral traits (1–5). PWS results from the lack of paternal expression of the chromosome 15q11–q13 region caused by deletion (~70%), uniparental disomy (UPD) (~25%), imprinting center defects (~2%), or balanced translocations. Hypothalamic insufficiency in individuals with PWS is presumed to result in growth hormone (GH) deficiency (5, 6) in 10% of patients, hypogonadism, disturbed appetite regulation with hyperphagia, and several other hormonal deficiencies. Treatment with GH beginning prior to 2 years of age has been shown to improve body composition, motor function, cognition, height, and lipid profiles (5, 7–9). Individuals with GH deficiency (10) have low bone mineral content (BMC) and bone mineral density (BMD) (11) but a high fat mass (FM) and low lean mass (LM) (12). This pattern is the opposite of that seen in normal obese subjects. Decreased BMD and osteoporosis have been reported in individuals with PWS (13–15), with likely contributing factors being low GH and sex hormone levels, hypotonia, and inactivity (2). Osteoporosis is usually an asymptomatic condition until complications such as fractures occur. The asymptomatic phase of osteoporosis can be recognized by direct measurement of bone mass from the spine or total body using dual-energy X-ray absorptiometry (DEXA) (16).

At present, no information is available in the literature on the differences in bone mineralization in genetic subtypes of PWS. Galassetti et al. (17) previously described the beneficial effects of GH treatment on body composition, particularly FM, despite greater caloric intake in 37 individuals with PWS. In that study, BMD of the spine and hip was not analyzed. The aims of the present study, therefore, were to determine the prevalence of osteopenia in individuals with PWS from a larger cohort, compare BMD in the deletion and UPD genetic subtypes of PWS, and study the effects in individuals treated with GH.

Subjects and methods

Subjects

Seventy-nine individuals with PWS were included in this study. We combined 50 individuals from the previous dataset (17) with 29 individuals from the Rare Diseases Clinical Research Network (RDCRN) cohort to analyze BMD of the whole body (WB), hip, and spine in individuals with PWS. Research protocols were approved by the University of California (UC) Irvine Institutional Review Board, and informed assents and consents were obtained from all eligible participants or their legally responsible caregivers. Participants had a genetically and clinically confirmed diagnosis of PWS by methylation, and fluorescent in situ hybridization (FISH)-negative patients were presumed to have uniparental disomy. Not all individuals had UPD studies to determine the 1%–2% of individuals presumed to have an imprinting center defect. Forty-six individuals were receiving GH treatment and 33 never received GH treatment. Body composition and BMD parameters were analyzed in individuals who had DEXA scans performed. The mean duration of GH treatment was 2.5 years (range 0.5–6.5 years). There were 39 males and 40 females, with an age range of 0.2–47 years, weight range of 3.6–138.3 kg, and height range of 53.6–172.5 cm. All studies were carried out using the same densitometer at the Institute of Clinical Translational Science, UC Irvine, Irvine, CA, USA.

DEXA scan

Total and regional body composition was measured by DEXA using a Hologic densitometer (Hologic QDR 4500W; Hologic, Bedford, MA, USA). Scans were performed by pencil-beam mode. Measurement of body composition using DEXA is based on the exponential attenuation due to absorption by body tissues of photons emitted at two energy levels (40 and 70 keV). Subjects were asked to lie on their backs on a padded table, wearing light clothing with metal objects removed for the measurements (18). DEXA provided measures of the following parameters: BMD (g/cm^2) of total body, lumbar spine (L1–L4), femoral neck, and trochanter region; bone mineral content (BMC)-(g); fat and lean tissue weights (g); and total body fat (%). BMD was expressed in absolute terms and as a Z-score in relation to the age- and sex-matched normal population (19). Mild osteopenia was defined as a Z-score lower than –1.0 SD, and severe osteopenia, as a Z-score lower than –2.0 SD.

Data analysis

Statistical analyses were performed with SPSS 15.0 (IBM SPSS; International Business Machines, IBM Corporation, Chicago, IL, USA). All data had a normal distribution, based on a p-value above 0.05 with Levene's test for normal distribution. Therefore, data for all continuous variables were expressed as group means and standard error (SE) of the mean. The categorical variables were compared using χ^2-tests. The effect of genetic subtype and GH treatment was tested in pertinent variables of interest between groups using two-sample t-tests. Additional analysis included multiple linear regression to study the relationship between GH treatment or molecular subclasses and BMD of spine adjusting for age, sex, height, weight, and body mass index (BMI). Effects are presented as β with 95% confidence intervals (CIs). p-Values <0.05 were considered statistically significant.

Results

The demographics of the study population are shown in Table 1. Of the 79 individuals who participated in the study, 39 were males and 40 were females, 48 had a deletion of chromosome 15q11.2–q13, and 27 had UPD; 4 individuals were unclassified and were excluded from the analysis. Forty-six individuals received GH treatment and 33 individuals never received GH treatment.

The proportions of study participants with WB, hip, or spine BMD Z-scores <–1.0 (mild osteopenia) and <–2.0 SD (severe osteopenia) (categories not mutually exclusive) in GH treated and untreated individuals and also in deletion and UPD subclasses are shown in Table 2. A total of eight individuals (10%) had Z-scores below <–2 SD and 35/79 individuals (44.3%) in our study had BMD Z-scores below <–1 SD. A slightly greater proportion of individuals with deletions had BMD Z-scores of <–1 and <–2 SD than the UPD group. None of the individuals with Z-scores <–1 had a history of traumatic or nontraumatic fractures.

The BMD Z-scores were also analyzed in different age groups by dividing the individuals into three subgroups of 0–5 years, 5–15 years, and >15 years. There were 23 individuals ages 0–5 years, 38 individuals ages 5–15 years, and 18 individuals >15 years. The spine BMD Z-score was higher in the GH-treated group >15 years (p=0.021). There were no differences in the 0–5 years and 5–15 years subgroups. Similarly, there were no differences in spine Z-scores in the deletion and UPD subgroups (Figure 1).

Differences in body composition parameters

Comparison of the body composition parameters in the GH treatment vs. no GH treatment groups and in the

Table 1 Demographic characteristics of individuals with PWS in the study.

Characteristic	GH treatment vs. no GH treatment (total n=79)			Molecular subclass (total n=79)			
	GH (n=46)	No GH (n=33)	p-Value[a]	Deletion (n=48)	UPD (n=27)	Unclassified (n=4)[b]	p-Value[a]
Age, years							
Mean	9.14	13.89	0.02	9.94	13.34	10.27	0.14
Gender							
Males	22 (48%)	17 (51%)	0.29	25 (52%)	13 (48%)	1 (25%)	0.57
Females	24 (52%)	16 (48%)	0.20	23 (48%)	14 (52%)	3 (75%)	0.56
Molecular subclass							
Deletion (n=48)	26 (56%)	22 (67%)	0.56	–	–	–	–
UPD (n=27)	17 (37%)	10 (30%)	0.18	–	–	–	–
Unknown (n=4)	3 (6%)	1 (3%)	0.31	–	–	–	–
GH treatment							
Yes (n=46)	–	–	–	26 (56%)	17 (37%)	3 (6%)	0.59
No (n=33)	–	–	–	22 (67%)	10 (30%)	1 (3%)	0.48

[a]χ^2-test for categorical variables and unpaired Student's t-tests for continuous variables. [b]Unclassified subgroup was excluded from the comparison.

molecular subclasses was carried out using unpaired Student's t-tests (Tables 3 and 4). As expected, individuals who were treated with GH had a significantly higher height centile and lower BMI when compared with individuals not treated with GH. The spine BMD Z-score was higher in the GH-treated group; however, the differences between the two groups did not reach statistical significance (p=0.06, 95% CI −0.02, 1.2). Comparison of body composition parameters across molecular subclasses revealed a significantly lower WB fat% and a significantly higher WB BMD in the UPD subclass compared with the deletion subclass [p=0.05 (95% CI 0.002, 9.680) and p=0.037 (95% CI −0.2, −0.01), respectively].

Table 2 Prevalence of low BMD based on <−1 and <−2 SD cut-offs for GH treatment and molecular subclass categories.

BMD Z-scores (WB, hip or spine)	GH treatment, n (%)			Molecular subclasses, n (%)		
	Yes	No	p-Value[a]	Deletion	UPD	p-Value[a]
<−1 (mild osteopenia)	22 (47.8)	13 (39.4)	0.554	22 (45.8)	12 (44.4)	0.650
<−2 (severe osteopenia)	4 (8.7)	4 (12.1)	0.248	5 (10.4)	3 (11.1)	0.484

[a]χ^2-tests.

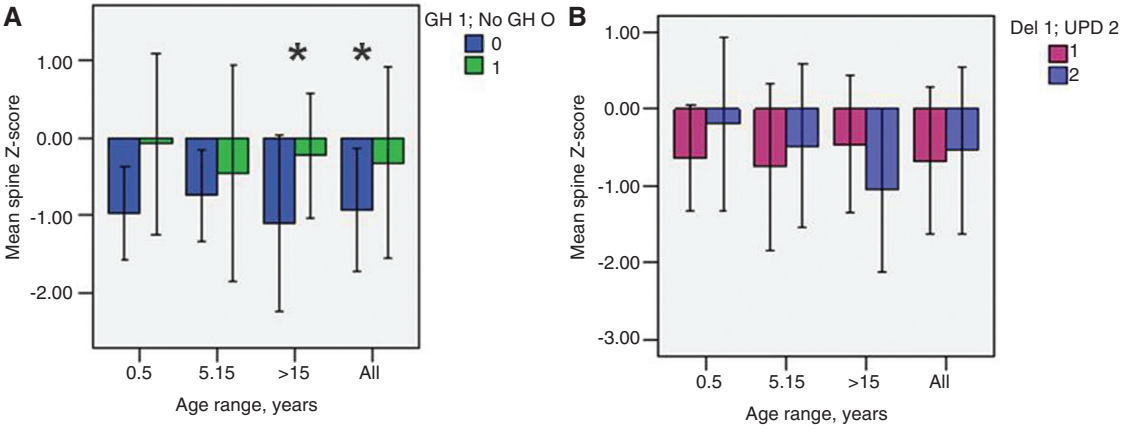

Figure 1 Analysis of BMD Z-scores in different age groups. There were 23 individuals ages 0–5 years (15 GH, 8 no GH, 14 Del, 7 UPD, 2 unknown), 38 individuals ages 5–15 years (24 GH, 14 no GH, 25 Del, 12 UPD, 1 unknown), and 18 individuals in the >15 year (7 GH, 11 no GH, 9 Del, 8 UPD, 1 unknown) group. The spine BMD Z score was higher in growth hormone treated group in >15 years and all age sub-groups (p=0.021 and 0.042 respectively). There were no differences noted in the spine Z-scores in deletion/UPD subgroups. *p value<0.05. Del, deletion; UPD, uniparental disomy; GH, on growth hormone; no GH, never treated with growth hormone.

Table 3 Comparison of individuals with and without GH treatment (unpaired Student's t-tests).

Variable	GH, mean (SE) (n=46)	No GH, mean (SE) (n=33)	95% CI	p-Value
Height centile	37.891 (4.44)	19.545 (4.37)	5.5, 31.1	0.006[a]
Weight centile	71.261 (3.65)	75.909 (5.21)	−16.9,7.6	0.454
BMI, kg/m^2	22.625 (1.09)	28.974 (1.73)	−10.2, −2.4	0.002[a]
BMI centile	84.404 (2.65)	91.848 (3.03)	−15.4, 0.6	0.069
WB fat, g	10,244.78 (1904.07)	28,061.53 (4049.06)	−9735, 5039.2	0.527
WB LM, g	22,768.91 (2088.07)	30,275.28 (3696.38)	−15,427.4, 414.6	0.063
WB fat, %	39.041 (1.45)	41.795 (1.82)	−7.3, 1.86	0.238
WB BMC, g	1238.17 (241.81)	1183.20 (164.11)	−707.2, 817.2	0.886
WB BMD, g/cm^2	0.77 (0.03)	0.849 (0.06)	−0.2, 0.04	0.207
BMD hip, g/cm^2	0.66 (0.03)	0.67 (0.04)	−0.1, 0.08	0.776
Hip Z-score	−0.578 (0.30)	−1.227 (0.41)	−0.4, 1.7	0.210
BMD spine, g/cm^2	0.658 (0.03)	0.661 (0.05)	−0.1, 0.1	0.964
Spine Z-score	−0.322 (0.19)	−0.933 (0.19)	−0.02, 1.2	0.060

[a]Statistically significant.

We also analyzed the data on diet in this patient cohort. The average calorie intake in the GH treatment group was 43.40 kcal/kg/day and in the untreated group was 35.03 kcal/kg/day. The average calorie intake in the deletion subgroup was 40.16 kcal/kg/day and in the UPD subgroup was 41.04 kcal/kg/day. However, these differences were not statistically significant. A total of 17.7% of individuals in our study [14/79; 9 males and 5 females; 10 deletion; 7 males and 3 females; and 4 UPD; (2 males and 2 females) received sex hormone treatment for hypogonadism at some point in their life]. Among these individuals, six were receiving GH and eight never received GH. These data could not be correlated with BMD because of the small sample size.

Linear regression analysis after adjustment for confounders

To eliminate the effects of potential confounders such as age, gender, height, and weight on BMD measurements, we performed linear regression analysis comparing spine BMD Z-scores and total spine BMD (g/cm^2) across GH treatment groups, molecular subclasses, and duration of GH treatment after adjusting for these covariates (Tables 5 and 6). After adjusting for covariates, both spine BMD Z-scores and total spine BMD (g/cm^2) were significantly higher in the GH treatment group. We found that for each year of GH treatment, the spine BMD Z-scores increased by a factor of 0.207 (p=0.006, 95% CI 0.06, 0.35) and total spine BMD

Table 4 Comparison between individuals with deletion or uniparental disomy (unpaired Student's t-tests).

Variable	Deletion, mean (SE) (n=48)	UPD, mean (SE) (n=27)	95% CI	p-Value
Height centile	32.167 (4.11)	26.815 (5.71)	−8.5, 19.2	0.444
Weight centile	75.167 (4.03)	67.778 (5.04)	−5.7, 20.5	0.265
BMI, kg/m^2	26.524 (1.50)	22.952 (1.16)	−0.8, 7.9	0.108
BMI centile	90.149 (2.52)	82.563 (3.66)	−1.0, 16.2	0.083
WB fat, g	10,432.32 (2213.81)	13,589.88 (2953.11)	−10,593.8, 4278.6	0.399
WB LM, g	23,929.71 (2629.28)	28,121.32 (2468.19)	−12,241.6, 3858.3	0.302
WB fat,%	41.639 (1.51)	36.793 (1.65)	0.002, 9.68	0.050[a]
WB BMC, g	962.80 (110.32)	1212.62 (117.00)	−601.5, 101.8	0.160
WB BMD, g/cm^2	0.745 (0.04)	0.873 (0.03)	−0.2, −0.01	0.037[a]
BMD hip, g/cm^2	0.655 (0.03)	0.668 (0.03)	−0.1, 0.08	0.785
Hip Z-score	−1.130 (0.33)	−0.702 (0.45)	−1.6, 0.7	0.450
BMD spine, g/cm^2	0.634 (0.04)	0.681 (0.04)	−0.1, 0.06	0.392
Spine Z-score	−0.672 (0.17)	−0.539 (0.23)	−0.7, 0.4	0.633

[a]Statistically significant.

Table 5 Comparison of spine BMD Z-scores.

	GH vs. no GH				Deletion vs. UPD				Duration of GH		
	β estimate	95% CI	p-Value		β estimate	95% CI	p-Value		β estimate	95% CI	p-Value
(Constant)	−0.701	−3.00, 1.59	0.544	(Constant)	−0.525	−2.69, 1.64	0.628	(Constant)	−0.115	−2.54, 2.31	0.924
GH vs. no GH	0.777	0.03, 1.51	0.041	Deletion vs. UPD	0.218	−0.38, 0.81	0.467	Duration of GH	0.207	0.06, 0.35	0.006
Height, cm	−0.007	−0.03, 0.02	0.603	Height, cm	−0.007	−0.03, 0.02	0.688	Height, cm	−0.012	−0.04, 0.02	0.394
Weight, kg	0.012	−0.01, 0.03	0.345	Weight, kg	0.010	−0.01, 0.03	0.354	Weight, kg	0.015	−0.01, 0.04	0.236

Table 6 Comparison of total spine BMD (g/cm^2).

	GH vs. no GH				Deletion vs. UPD				Duration of GH		
	β estimate	95% CI	p-Value		β estimate	95% CI	p-Value		β estimate	95% CI	p-Value
(Constant)	−0.053	−0.23, 0.12	0.553	(Constant)	−0.093	−0.27, 0.08	0.294	(Constant)	−0.071	−0.26, 0.12	0.462
GH vs. no GH	0.064	0.01, 0.11	0.014	Deletion vs. UPD	0.036	−0.005, 0.07	0.084	Duration of GH	0.011	0.001, 0.02	0.032
Age, years	0.008	0.005, 0.01	0.000	Age, years	0.006	0.003, 0.009	0.000	Age, years	0.007	0.004, 0.01	0.000
Gender	0.055	1.02, 0.09	0.006	Gender	0.043	0.004, 0.08	0.029	Gender	0.062	0.02, 0.10	0.002
Height, cm	0.003	0.001, 0.005	0.004	Height, cm	0.004	0.002, 0.005	0.000	Height, cm	0.003	0.001, 0.005	0.002
Weight, kg	0.003	0.001, 0.004	0.002	Weight, kg	0.002	0.001, 0.004	0.002	Weight, kg	0.002	0.001, 0.004	0.006

increased by a factor of 0.011 (p=0.032, 95% CI 0.001, 0.02). The UPD subclass revealed a trend for a higher spine BMD Z-scores and total spine BMD (g/cm^2) compared with the deletion subclass; however, the differences were not statistically significant after adjusting for covariates.

Discussion

GH deficiency seen in approximately 10% of individuals with PWS might place these patients at risk for metabolic diseases in adult life, including premature osteopenia and osteoporosis (2, 15). Previous studies have reported variable results of the benefits of GH on BMD in PWS. Some studies claimed that there were no differences in spine BMD Z-scores after treatment with GH (20–22), whereas other studies reported significant increases in BMD after GH therapy (7, 23).

The major determinants of BMD are age, sex, pubertal stage, genetic-ethnic factors, hormonal status, diet, physical activity, height, and weight, and therefore, problems with the interpretation of results can arise when comparing groups that differ in these parameters (24, 25). The importance of this relationship when assessing BMD in disorders with growth alterations has not been completely understood. Interpretation of BMD in individuals with PWS will differ significantly if the values were corrected for height rather than age because of the short stature in those not treated with GH.

Previous studies have shown subtle intellectual and behavioral differences (26, 27) among genetic subtypes of PWS. In this large cross-sectional study, we identified some potential differences in BMD across the deletion and UPD subclasses of PWS, although these differences did not reach statistical significance. Therefore, future larger studies comparing BMD between genetic subtypes will determine if this trend reaches statistical significance.

Many previous studies evaluating the effect of GH treatment on BMD in children with PWS reported varied opinions and conclusions (7, 20–23). A study by Myers et al. (23) in a cohort of 54 patients revealed that in the GH-treated PWS group, the total body BMD increased from baseline at 12 months and increased further at 24 months. Carrel et al. (7) studied 46 children with PWS previously treated for 4 years with GH therapy and reported that the mean total body BMD increased from 0.94±0.09 g/cm^2 to 1.03±0.09 g/cm^2 during 12–24 months of GH treatment and the improvement in BMD was sustained during an additional 24 months (48 months total) regardless of the dose of GH.

In contrast, Hoybye (22) reported that in a cohort of 19 young adults with PWS, BMD of the femoral neck or in the lumbar spine did not change significantly during 12 months of GH treatment. This cohort, however, included individuals 17–37 years old (mean age 25 years), who were past the pubertal age, unlike the majority of our study participants, who are children. A randomized controlled GH trial of 24 months was conducted by de Lind van Wijngaarden et al. (21) in 46 prepubertal children. Their findings revealed that total body and lumbar spine BMD, as well as lumbar spine bone mineral apparent density standard deviation score (BMADSDS), was normal in prepubertal children with PWS compared with healthy controls and that BMADSDS did not significantly change during GH treatment (21). A prospective study by Colmenares et al. (20) evaluated the effects of GH treatment on bone mineralization in a cohort of 36 children (1–15 years of age) with PWS who were given hGH for 36 months. Their study revealed stable mean area BMD Z-score during duration GH therapy.

Galassetti et al. (17) assessed body composition variables in 37 individuals with PWS and demonstrated that older GH-treated children (Tanner stage 3–4) displayed improved body composition (BMI, total and percentage FM, truncal fat) ($p<0.05$) and younger children (Tanner stage 1–2) displayed only minor differences in body composition.

We now report the BMD data of the spine and hip from this previous cohort. Expanding on this previous study, we found that 10% of individuals had BMD Z-score <–2 SD (severe osteopenia) and 44.3% had BMD Z-score <–1 SD (mild osteopenia). After adjustment for confounders of age, gender, height, and weight, individuals in the UPD subclass revealed a trend of higher total BMD and BMD Z-scores of the spine compared with the deletion subclass; however, differences were not significant. Spine BMD Z-scores and total spine BMD (g/cm^2) were significantly higher in the GH treatment group and these values showed an increase with each corresponding year of GH treatment. One of the limitations of our study is that this is a cross-sectional study, and longitudinal follow-up of individuals with low BMD treated with GH is crucial to evaluate the sustained benefits of GH therapy on BMD. The other limitation is the relatively small number of individuals in each group after stratification into subgroups. Longitudinal studies with considerable longer follow-up will determine whether complete restoration of bone mass can be achieved by GH treatment.

The majority of children with PWS in our study have not yet entered their pubertal growth spurt. Bone deficits may be magnified during the pubertal years, with a failure to reach optimal peak bone mass in adulthood leading to a risk of osteoporosis and increased fractures. It is therefore essential to monitor long-term bone health in children with PWS, optimize GH treatment, and intervene with

appropriate therapies such as hormone replacement (sex hormone and thyroid hormones if deficiency is found), strength and resistance exercise, bisphosphonates, and calcium and vitamin D supplements as necessary.

Conclusions

In our study, 44.3% of individuals with PWS had mild osteopenia and 10% had severe osteopenia. The finding that GH has a cumulative beneficial effect on bone mineralization of the spine is a compelling rationale for early diagnosis and early and sustained GH treatment. We recommend that BMD be evaluated at regular intervals in individuals with PWS. Osteopenia was found in greater proportion of individuals in the deletion subclass compared with the UPD subclass. It will also be important to evaluate if deletion and UPD subclasses have inherent differences in response to GH treatment pertaining to BMD improvement in future larger studies.

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