

Anthropometric adjustments are helpful in the interpretation of BMD and BMC Z-scores of pediatric patients with Prader-Willi syndrome

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Abstract

Summary Anthropometric adjustments of bone measurements are necessary in Prader-Willi syndrome patients to correctly assess the bone status of these patients. This enables physicians to get a more accurate diagnosis of normal versus abnormal bone, allow for early and effective intervention, and achieve better therapeutic results.

Introduction Bone mineral density (BMD) is decreased in patients with Prader-Willi syndrome (PWS). Because of largely abnormal body height and weight, traditional BMD Z-scores may not provide accurate information in this patient group. The goal of the study was to assess a cohort of individuals with PWS and characterize the development of low bone density based on two adjustment models applied to a dataset of

BMD and bone mineral content (BMC) from dual-energy X-ray absorptiometry (DXA) measurements.

Methods Fifty-four individuals, aged 5–20 years with genetically confirmed PWS, underwent DXA scans of spine and hip. Thirty-one of them also underwent total body scans. Standard Z-scores were calculated for BMD and BMC of spine and total hip based on race, sex, and age for all patients, as well as of whole body and whole-body less head for those patients with total-body scans. Additional Z-scores were generated based on anthropometric adjustments using weight, height, and percentage body fat and a second model using only weight and height in addition to race, sex, and age.

Results As many PWS patients have abnormal anthropometrics, addition of explanatory variables weight, height, and fat resulted in different bone classifications for many patients. Thus, 25–70 % of overweight patients, previously diagnosed as normal, were subsequently diagnosed as below normal, and 40–60 % of patients with below-normal body height changed from below normal to normal depending on bone parameter.

Conclusions This is the first study to include anthropometric adjustments into the interpretation of BMD and BMC in children and adolescents with PWS. This enables physicians to get a more accurate diagnosis of normal versus abnormal BMD and BMC and allows for early and effective intervention.

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Introduction

Prader-Willi syndrome (PWS) is characterized by variable expression of physical, cognitive, and behavioral impairments. Early childhood-onset obesity, hyperphagia, hypotonia,

hypogonadism, and growth hormone deficiency are some of the clinical characteristics. PWS is diagnosed by genetic testing to document the absence of paternally expressed imprinted genes at 15q11.2-q13 due to deletion of this region on the paternally inherited chromosome (65–75 % of individuals), maternal uniparental disomy (20–30 %), or an imprinting center defect (1–3 %) [1].

Diminished bone mineral density (BMD) is common in PWS individuals, especially in adolescence and adulthood, and may contribute to the increased morbidity and poor quality of life in PWS [2].

In a normal population, bone mass generally accumulates until around the age of 30 years, with the maximum accrual time for BMD being in adolescence. In individuals with PWS, puberty is often delayed or incomplete because of a deficiency in sex hormones [3–7]. Incomplete puberty in combination with growth hormone deficiency probably results in less bone mineral mass being accrued during adolescence in individuals with PWS compared to the normal population for a multiplicity of reasons [8]. The low BMD in PWS was thought to be due to increased bone loss, probably linked to sex steroid deficiency [9], physical inactivity, and limited weight bearing [8], as well as the use of psychotropic medications [10]. Dietary restrictions to prevent weight gain may result in limited intake of calcium and vitamin D. On the other hand, prolonged growth hormone treatment has a beneficial effect on BMD with a trend for a higher BMD in individuals with uniparental disomy [11]. When low bone density is diagnosed using dual-energy X-ray absorptiometry (DXA), the primary treatment is to provide vitamin D and calcium supplements. Whereas bisphosphonates are commonly used in adults with osteoporosis, the use of these medications in adolescents and young adults remains controversial [2]. Recently Bakker et al. [12] reported that in a long-term GH study, total body BMD, lumbar spine BMD, and bone mineral apparent density of the lumbar spine all remained stable in prepubertal children with PWS but decreased during adolescence because of incomplete pubertal development. Based on their findings, they suggest treating girls with estrogen replacement from age 11 years and boys with testosterone from age 14 years.

Traditional, normative comparisons in DXA assessment use age-, sex- and ethnicity-matched normals to calculate Z-

scores, which represent the number of standard deviations difference from the normal mean. As DXA measurements are projection measurements, the BMD parameter, expressed in grams per square centimeter, is influenced by the size of the bone. A smaller person with smaller bones will automatically have a smaller BMD value. This bone size influence is particularly important in pediatrics, where bone growth can happen in spurts or where a disease can delay bone development. The comparison to normals based on age assumes an average growth pattern of the body. Taking into account body size and weight allows for individual growth patterns and assesses BMD and bone mineral content (BMC) relative to the actual size of the patient. An additional correction of body fat might be valuable in this cohort of PWS patients, as many of the children are obese, and a major percentage of the soft tissue is fat and not muscle mass. Muscle mass is considered to influence bone mass, as larger muscles can create larger forces, which, in turn, require stronger, i.e., larger bones [13].

The goal of this study was to assess the changes in DXA parameters in a pediatric group of PWS patients between the traditional approach of calculating Z-scores based on age, sex, and ethnicity and the anthropometrically corrected models by also adjusting for weight and height or for weight, height, and percentage body fat.

Patient population and methods

The cohort of PWS patients originates from the Shaare Zedek Medical Center in Jerusalem and contains a total of 54 individuals, aged 5–20 years, with genetically confirmed PWS. Of these, 23 are boys and 31 are girls. Height was measured using a wall-mounted stadiometer, and patients were weighed in light clothing. Table 1 provides details about these patients, including age, weight, height, and diagnosed genetic defect. Thirteen of the 23 male participants and 23 of the 31 female participants were or had been treated with recombinant human growth hormone. Supplemental vitamin D at a dose range of 600 to 1000 IU daily was prescribed to each patient, but compliance was highly variable. For the purpose of this study, we categorized results of serum 25-vitamin D levels according to the following criteria: ‘normal, vitamin D sufficiency’

Table 1 Characteristics of patient PWS patient cohort

	Number	Age [y]	Height		Weight		Genetic defect ^b		
			[cm]	[Z-score] ^a	[kg]	[Z-score] ^a	DEL	UPD	IMP
Male	23	5.2–19.5	105–175	-1.0 ± 1.4 (-4.3–2.2)	16.0–104.0	1.1 ± 1.7 (-2.3–>3)	14	8	1
Female	31	5.0–18.6	103–161	-1.4 ± 1.4 (-5.8–1.8)	18.2–146.6	0.9 ± 1.3 (-1.5–>3)	20	11	0

DEL deletion, UPD uniparental disomy, IMP imprinting center defect

^a Z-score based on WHO growth charts (15); mean ± SD (range)

>30 ng/ml, ‘vitamin D insufficiency’ 20–29 ng/ml, ‘vitamin D deficiency’ 10–19 ng/ml, and ‘severe deficiency’ <10 ng/ml. Results of vitamin D levels were available for 22 males, of whom 4 had normal levels, 13 had vitamin D insufficiency, 4 were deficient, and 1 had severe deficiency. Levels were available for 30 females, wherein vitamin D sufficiency, insufficiency, deficiency, and severe deficiency were found in 6, 12, 9, and 3 females, respectively.

The DXA measurements were obtained from a single scanner, which is a Hologic Discovery. All patients underwent a spine and hip scan, and 31 of the 54 patients also underwent a whole-body scan. The Z-scores for BMD and BMC were calculated based on three different models of normative populations: traditional Z-score based on age, sex, and ethnicity; weight-height-corrected Z-score adding weight and height into the traditional model; and weight-height-fat-corrected Z-score adding DXA-based percentage body fat into the weight-height model for those patients who also had a whole-body scan. The normative models are based on the Bone Mineral Density in Childhood Study (BMDCS), which contains over 10,000 observations for each measurement parameter [14]. We initially classified all patients based on deviations from normal height and weight based on the WHO growth charts [15] to facilitate interpretation of height and weight influence on the BMD and BMC Z-scores. Patients with a height standard deviation score (SDS) below -2 were classified as short, and patients with a weight SDS above $+2$ were defined as overweight.

Results

Scatter plots of percentage body fat, height, and weight by age are presented in Fig. 1 as well as Supplemental Fig. 1-2 (Online Resource). The cloud of normals is based on the BMDCS, and the points outside the ± 2 standard deviation

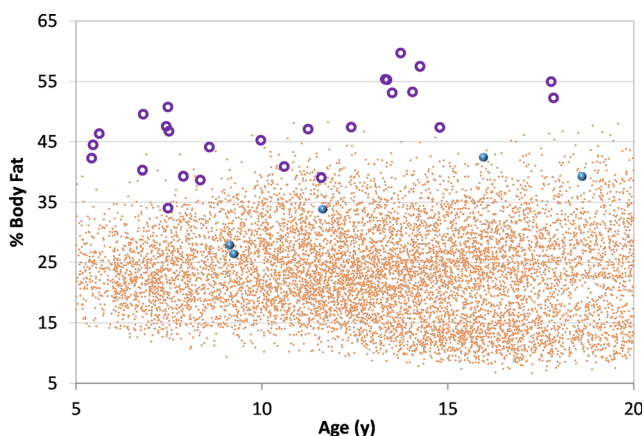


Fig. 1 PWS patient’s age and percentage body fat in blue closed circles and purple open circles mapped against a normal cloud. Purple markers represent Z-scores >2 for age-matched body fat (color figure online)

range for height and weight are marked based on the WHO growth charts. The cohort average age-matched Z-score for height is -1.25 , and 13 of the 54 patients show a Z-score below normal. For weight, the average age-matched Z-score is $+1.68$, and 18 of the 54 patients are above the normal range. As there were a number of extreme outliers for weight Z-score, up to a value of $+14$, weight Z-scores above 3.0 were cut to 3.0 for statistical purposes. For percentage body fat, there are no CDC reference tables available, but compared to the BMDCS normals, 26 of the 31 patients have values above the normal range.

Average Z-scores based on the traditional model, weight/height correction and weight/height/fat correction are shown in Table 2 for spine, total hip, whole body, and whole-body less head. Separate averages are provided for patients of normal height and those with below-normal height as well as those with normal weight and above-normal weight. Z-scores are shifted compared to the standard model by decreasing those for overweight patients and increasing those for under-height patients. Overweight patients would be expected to have larger bones to support their increased body weight; thus, comparison with larger bones decreases the Z-score. Alternatively, patients with smaller body size, indicated by reduced body height, are expected to have smaller bones and, thus, a comparatively higher Z-score.

To allow a more intuitive interpretation for these shifts, it is useful to create graphs of anthropometrically adjusted Z-scores versus traditional Z-scores. Supplemental Fig. 3 (Online Resource) provides the basic illustration of the four quadrants, indicating the reclassification groups in quadrants 2 and 4, where patients that were previously considered in the normal range are now classified below normal (quadrant 4) or previously in the below normal range and now normal (quadrant 2). Figures 2 and 3 illustrate the classifications based on whole-body less head BMD, which is a parameter often preferred in pediatric bone density assessment. For graphical purposes, one patient’s Z-score below -5 was rounded to -5.0 . A large fraction of the overweight patients (8/11) gets reclassified from normal to below normal based on the weight/height (WH) and the weight/height/fat (WHF) models for BMD. The reclassifications for all bone parameters and both anthropometric models are provided in Table 3. It is apparent that most reclassifications for BMD happen for overweight patients from normal to subnormal. For BMC, some patients previously classified as subnormal get reclassified as normal, most often for patients with short stature.

Discussion

This study represents the first analysis of DXA data, which utilizes our previously described method [14] for adjusting the raw data using anthropometric parameters.

Table 2 Average Z-score of the whole cohort and relevant subgroups obtained by the three models for the various bone parameters: standard model, weight/height (WH), and weight/height/fat (WHF) model

Group	Model	Spine		Total hip		Whole body		Whole-body less head	
		BMD	BMC	BMD	BMC	BMD	BMC	BMD	BMC
Whole cohort	Standard	0.20	-1.08	-0.66	-1.65	-0.65	-0.77	-0.83	-0.91
	WH	-0.54	-1.03	-1.37	-1.36	-0.98	-1.06	-1.34	-1.30
	WHF	0.04	-0.29	-0.50	-0.52	-0.75	-0.80	-1.06	-1.02
Height >-2 (normal height)	Standard	0.36	-0.84	-0.47	-1.32	-0.68	-0.63	-0.87	-0.80
	WH	-0.53	-1.15	-1.29	-1.42	-1.11	-1.18	-1.54	-1.49
	WHF	-0.05	-0.42	-0.56	-0.65	-0.92	-0.96	-1.28	-1.25
Height <-2 (short)	Standard	-0.31	-1.84	-1.25	-2.67	-0.55	-1.21	-0.72	-1.26
	WH	-0.57	-0.66	-1.64	-1.18	-0.57	-0.69	-0.71	-0.69
	WHF	0.30	0.12	-0.31	-0.12	-0.24	-0.30	-0.35	-0.30
Weight <+2 (normal weight)	Standard	-0.10	-1.32	-1.09	-2.32	-0.64	-0.84	-0.88	-1.05
	WH	-0.08	-0.54	-1.24	-1.29	-0.56	-0.59	-0.87	-0.81
	WHF	0.52	0.36	-0.14	-0.13	0.00	0.04	-0.27	-0.18
Weight >+2 (overweight)	Standard	0.84	-0.55	0.27	-0.17	-0.67	-0.60	-0.72	-0.62
	WH	-1.52	-2.10	-1.66	-1.51	-1.90	-2.09	-2.36	-2.37
	WHF	-1.00	-1.69	-1.28	-1.37	-2.39	-2.63	-2.78	-2.86

Whereas traditional DXA comparisons are based on age, sex, and ethnicity, this approach comes mostly from the assessment of osteoporosis in adults. Although age might be a reasonable input parameter, mostly because osteoporosis is an age-related disease, such an approach in children is less warranted. As stated before, bone size directly influences the DXA parameters, and if bone size is not developing according to average established growth patterns, the measured DXA parameters cannot be interpreted without reference to body size.

Although de Lind van Wijngaarden et al. [16] reported bone mineral density in PWS children after correcting separately for height and for BMI SDS, they did not evaluate body composition in their cohort. Furthermore, their study population was limited to prepubertal children. Other reports of bone density in PWS did not modify results of DXA data with respect to height, weight, or fat content [8, 9, 11, 12, 17, 18].

The deviation of expected body size in this group of PWS patients is demonstrated by the considerable number of patients who are overweight or below expected height

Fig. 2 Classification of *weight/height* BMD Z-score for whole-body less head

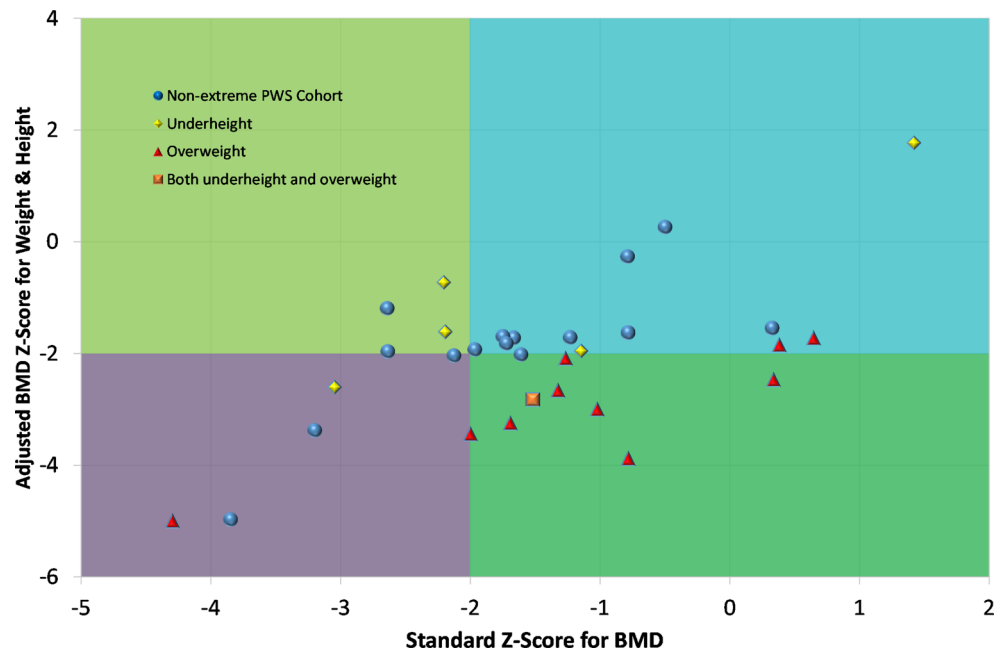


Fig. 3 Classification of *weight/height/fat* BMD Z-score for whole-body less head

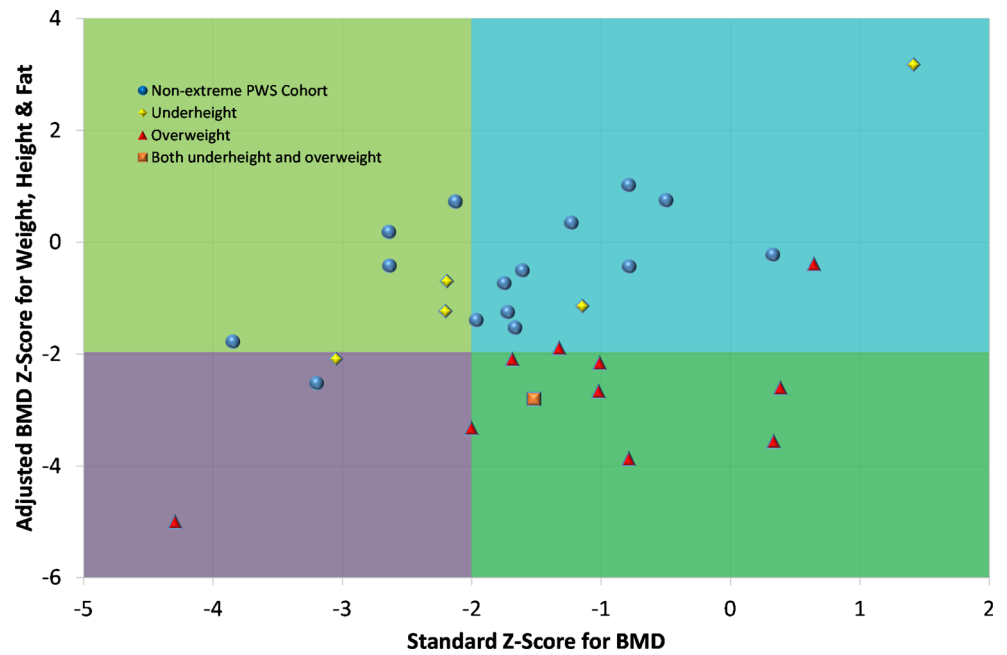


Table 3 Reclassification of patients depending on height and weight group based on the WH and WHF models for BMD and BMC

Parameter	Site	Group	WH Model				WHF Model			
			Normal→ Subnormal		Subnormal → Normal		Normal→ Subnormal		Subnormal→ Normal	
BMD	Spine	Normal H&W	2/25	8%	1/25	4%	0/14	0%	0/14	0%
		Short	2/11	18%	1/11	9%	1/6	17%	0/6	0%
		Overweight	6/17	35%	0/17	0%	4/12	33%	0/15	0%
	Total Hip	Normal H&W	2/27	7%	0/27	0%	0/14	0%	1/14	7%
		Short	1/13	8%	0/13	0%	0/7	0%	0/7	0%
		Overweight	4/17	24%	0/17	0%	3/12	25%	0/15	0%
	Whole Body	Normal H&W	0/14	0%	2/14	14%	0/14	0%	4/14	29%
		Short	1/7	14%	1/7	14%	1/7	14%	1/7	14%
		Overweight	6/11	55%	0/11	0%	5/11	45%	0/11	0%
	Whole Body Less Head	Normal H&W	1/14	7%	2/14	14%	0/14	0%	4/14	29%
		Short	1/7	14%	2/7	29%	1/7	14%	2/7	29%
		Overweight	8/11	73%	0/11	0%	8/11	73%	0/11	0%
BMC	Spine	Normal H&W	0/25	0%	4/25	16%	0/14	0%	2/14	14%
		Short	3/11	27%	4/11	36%	0/6	0%	2/6	33%
		Overweight	7/17	41%	0/17	0%	5/12	42%	0/15	0%
	Total Hip	Normal H&W	1/27	4%	4/27	15%	0/14	0%	6/14	43%
		Short	2/13	15%	5/13	38%	0/7	0%	3/7	43%
		Overweight	2/17	12%	0/17	0%	1/12	8%	0/15	0%
	Whole Body	Normal H&W	1/14	7%	2/14	14%	0/14	0%	4/14	29%
		Short	1/7	14%	3/7	43%	1/7	14%	3/7	43%
		Overweight	6/11	55%	0/11	0%	8/11	73%	0/11	0%
	Whole Body Less Head	Normal H&W	1/14	7%	3/14	21%	0/14	0%	5/14	36%
		Short	1/7	14%	4/7	57%	1/7	14%	4/7	57%
		Overweight	8/11	73%	0/11	0%	8/11	73%	0/11	0%

A person concurrently short and overweight was counted in both short and overweight categories. There were three such patients for spine and total hip and one person for whole body and whole-body less head. Cells with values above 20 % are shaded gray

(Supplemental Figs. 1 and 2, Online Resource). In addition, the overweight patients are predominantly ‘overfat’ (47 %), compared to only 19 % of ‘overfat’ patients in the normal weight and height group or 23 % in the short group. As additional body weight through fat has a different influence on bone development compared to additional body weight through muscle [13], the WHF model to include fat is of particular interest in PWS patients.

The average Z-scores for the various bone parameters, given also by subgroups (Table 2), illustrate the influence of body size. Looking at the standard values, patients with lower body height have mostly lower Z-scores for BMD and BMC than those with normal body height. The same observation applies by comparing patients with normal body weight and those with above-normal body weight, as the latter have mostly higher Z-scores. Using the current model, which also corrects for height and weight, the average difference between the normal height and short groups shrinks from -0.57 to $+0.38$. Specifically, the standard Z-scores of the short group are in the average 0.57 lower than those of the normal height group. After WH correction, the difference is in the opposite direction, as the short group now has an average Z-score, which is 0.38 higher than that of the normal height group. This means that these patients probably have, in the average, sufficiently strong bones to support their daily activities. This is further supported by the fact that the WHF model further increases their Z-score, as a lower percentage of their body weight is fat and more is muscle.

Looking at the overweight patients, a different picture emerges. Whereas the standard Z-scores show an average value 0.75 higher in the overweight patients compared to the normal weight patients, the WH correction puts this back into perspective by making the average difference -1.19 , meaning that the overweight patients have a considerably lower Z-score than what should be expected based on their body weight. As most of these patients are also overfat, the WHF model further decreases the Z-scores of the overweight patients to an average of -2.03 .

Our models for BMD and BMC were not created on the basis of BMI, and therefore, we did not use BMI as a model parameter. Utilizing height and weight as independent parameters, the Z-scores are expected to be rather similar to results of BMI data, because both independent parameters, height and weight, are included. In any case, a high BMI would be due to a large weight/height ratio. Using weight and height separately gives us better information, as we analyze both parameters independently.

Whereas the average Z-scores provide insight into the correction pattern, the clinical use is in the decision of normal versus abnormally low bone density. For pediatric applications, this threshold is based on a Z-score value of -2.0 [19]. Patients who remain in the same category before or after anthropometric corrections are of little concern in the present

context. However, patients who change from normal to abnormal or vice versa warrant some interest (Table 3). This reclassification may have an impact on treatment decisions, although no such decisions should be made on bone parameter Z-scores alone.

Looking at the reclassifications based on BMD parameters (Table 3), we have highlighted the cells that show more than 20 % of the patients of that particular group as reclassified. Most of the normal to subnormal reclassification happens with overweight patients, both for the WH and for the WHF model. In the reverse reclassification, where a patient is considered subnormal based on the standard Z-score but normal based on the anthropometrically corrected Z-score, the WHF model appears to have more influence, as it includes the fat parameter, and it is particularly visible in the two whole-body measurements.

The magnitude of reclassifications for BMC is not quite as consistent as that for BMD. There are still considerable numbers of patients reclassified from normal to subnormal, but numerous patients are now reversely changing from subnormal to normal. This less predictable pattern is probably due to the fact that BMC is fully influenced by the bone size, whereas BMD is, at least to two thirds, a density parameter. In this cohort of patients who are largely different in height and weight from a normal population, the bone size will be more variable and will influence BMC more than BMD. It is, thus, preferable to use BMD in PWS patients for the assessment of their bone status.

We have tested two adjustments for the BMD and BMC Z-scores: one based on height and weight and the other based on height, weight, and body fat. In theory, the more independent parameters are used for adjustment, the more accurately the resulting Z-score is supposed to reflect the actual patient situation. In our particular case, an additional measurement is needed, which is a whole-body scan, to allow including fat into the model. Although this will require additional time and resources beyond just those needed to measure spine and hip, the whole-body less head evaluation is one of the measurement sites recommended by the International Society for Clinical Densitometry (ISCD) [19]. Thus, the necessary fat parameter to use the WHF model would be available.

Patients with short stature often receive growth hormone treatment, and in our cohort, 36 of the 54 subjects received such treatment. The question arises if growth hormone treatment results in bone density values that are different compared to those individuals who did not receive such treatment. We performed ANOVA tests for all models of whole-body less head BMD Z-scores, and we could not find any significant relationship with growth hormone treatment. Similarly, pubertal status did not appear to have any significant influence on these same Z-scores.

Current ISCD recommendations [20] suggest correction of DXA bone parameters for children with short stature or growth delay. In the current dataset, 24 % of the subjects show

height below normal based on WHO growth charts. To assess the influence of height-only correction, we compared height-corrected, weight/height-corrected and weight/height/fat-corrected BMD of whole-body less head with the traditional model. The R^2 value of the comparison for the height-corrected model, as is recommended by the ISCD, is 0.61, whereas the other two comparisons result in R^2 values of 0.32 and 0.11, respectively. This indicates that the height-corrected values are considerably more similar to the traditional values than the weight/height and weight/height/fat-corrected values.

Does the fat correction beyond correction for height and weight really add substance to the Z-score calculation for this extreme dataset? Based on our data, over half of the overweight patients are also overfat. As we can see from Table 3, adding fat to the models for BMD does not change the reclassification percentages much from just using the WH model. These percentages are actually made up of largely the same patients, meaning that a patient reclassified by the WHF model is also reclassified by the WH model. We can, thus, conclude that calculating Z-scores based on weight and height is adequate for obtaining anthropometrically corrected Z-scores in PWS patients.

We have included spine, total hip, whole body, and whole-body less head in this analysis. We are fully aware that the ISCD recommendations [20] prefer spine and whole-body less head for pediatric assessment, although ‘other sites may be useful depending on the clinical need.’ Our inclusion of other sites does not mean that we think they should be used at this point, but future research might provide different insights into patients with PWS.

This study is not without limitations. The sample size included all PWS individuals of the appropriate age range followed in our national multidisciplinary PWS clinic. However, whole-body scans could not be acquired in all patients, as these scans require a greater degree of cooperation than was possible in the younger patients. Because of the variable cognitive impairment and behavior disorders in PWS, full cooperation was only possible in 31 of the 54 participants.

Throughout the data collection period of this study, we did not observe any fractures in this patient cohort. It was, therefore, not possible to relate the bone density Z-scores with fracture occurrence and decide which model more appropriately identifies fracture risk. A larger cohort will be necessary to connect DXA Z-scores with fracture occurrence.

In conclusion, we have shown, for the first time, that anthropometrically corrected Z-scores for BMD and BMC in children and adolescents with PWS reclassify large percentages of patients either from normal to subnormal or from subnormal to normal compared to standard Z-scores. This is largely due to the fact that a major percentage of PWS patients is either below normal height or above normal weight, and height and weight

have a major influence on bone assessment parameters. We suggest that the more refined anthropometrically adjusted Z-scores may provide a more accurate reflection of the patient’s bone status and, thus, allow to tailor a more personalized treatment for those individuals at high risk for fractures, while providing a more conservative follow-up and preventive measures for those at lower risk.

Compliance with ethical standards

Conflicts of interest None.

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