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Clinical Research Article

Bone Health in Adults With Prader–Willi Syndrome: Clinical Recommendations Based on a Multicenter Cohort Study

Denise H. van Abswoude,[1,2,3,4,*] Karlijn Pellikaan,[1,2,3,4,*] Anna G. W. Rosenberg,[1,2,3,4] Kirsten Davidse,[1,2,3,4] Muriel Coupaye,[5,6] Charlotte Høybye,[6,7,8,9] Tania P. Markovic,[6,10,11] Graziano Grugni,[6,7,12] Antonino Crinò,[6,13] Assumpta Caixàs,[6,14,15] Christine Poitou,[5,6,7] Helena Mosbah,[5] Tessa Weir,[16,17] Leo A. van Vlimmeren,[18] Joost P. H. J. Rutges,[19] Luuk W. L. De Klerk,[20] M. Carola Zillikens,[1,7,21,22] Aart J. van der Lely,[1] and Laura C. G. de Graaff[1,2,3,4,6,7]

[1]Department of Internal Medicine, Division of Endocrinology, Erasmus Medical Center, University Medical Center Rotterdam, 3015 GD Rotterdam, The Netherlands
[2]Center for Adults with Rare Genetic Syndromes, Department of Internal Medicine, Division of Endocrinology, Erasmus Medical Center, University Medical Center Rotterdam, 3015 GD Rotterdam, The Netherlands
[3]Dutch Center of Reference for Prader-Willi Syndrome, 3015 GD Rotterdam, The Netherlands
[4]Academic Center for Growth Disorders, Erasmus Medical Center, University Medical Center Rotterdam, 3015 GD Rotterdam, The Netherlands
[5]Assistance Publique-Hôpitaux de Paris, Rare Diseases Center of reference 'Prader-Willi Syndrome and obesity with eating disorders' (PRADORT), Nutrition Department, Institute of Cardiometabolism and Nutrition, ICAN, Pitié-Salpêtrière Hospital, Sorbonne Université, INSERM, Nutriomics, F75013 Paris, France
[6]International Network for Research, Management & Education on adults with Prader-Willi Syndrome (INfoRMEd-PWS)
[7]ENDO-ERN (European Reference Network)
[8]Department of Molecular Medicine and Surgery, Karolinska Institute and Karolinska University Hospital, Stockholm, Sweden
[9]Department of Endocrinology, Karolinska Institute and Karolinska University Hospital, Stockholm, Sweden
[10]Metabolism & Obesity Services, Royal Prince Alfred Hospital, Camperdown, Australia
[11]Boden Initiative, Charles Perkins Centre, University of Sydney, Sydney Australia
[12]Divison of Auxology, Istituto Auxologico Italiano, IRCCS, Piancavallo (VB), Italy
[13]Reference Center for Prader-Willi syndrome, Bambino Gesù Hospital, Research Institute, Palidoro (Rome), Italy
[14]Department of Endocrinology and Nutrition, Hospital Universitari Parc Taulí, Institut d'Investigació i Innovació Parc Taulí (I3PT), Universitat Autònoma de Barcelona, Sabadell, Spain
[15]Department of Medicine, Universitat Autònoma de Barcelona, Sabadell, Spain
[16]Department of Endocrinology, Nepean-Blue Mountains Hospital, Sydney, NSW, Australia
[17]Northern Clinical School, Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia
[18]Department of Rehabilitation and Pediatric Physical Therapy, Radboud University Medical Centrum, 6525 GA Nijmegen, The Netherlands
[19]Department of Orthopedic surgery, Erasmus Medical Center, University Medical Center Rotterdam, 3015 GD Rotterdam, The Netherlands
[20]Department of Orthopedic surgery, Sint Maartensclinic, 6500 GM Nijmegen, The Netherlands
[21]Academic Center for Rare Bone Disorders, Erasmus Medical Center, University Medical Center Rotterdam, 3015 GD Rotterdam, The Netherlands
[22]European Reference Network for rare bone diseases (ERN BOND)

Correspondence: Laura de Graaff, MD, PhD, Dept. of Internal Medicine, Erasmus MC, University Medical Center, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. Email: l.degraaff@erasmusmc.nl.
*These authors contributed equally to this study.

Abstract

Context: Prader–Willi syndrome (PWS) is a rare complex genetic syndrome, characterized by delayed psychomotor development, hypotonia, and hyperphagia. Hormone deficiencies such as hypogonadism, hypothyroidism, and growth hormone deficiency are common. The combination of hypotonia, low physical activity, and hypogonadism might lead to a decrease in bone mass and increase in fracture risk. Moreover, one would expect an increased risk of scoliosis due to hypotonia and low physical activity.

Objective: To study the prevalence and risk factors for skeletal problems (reduced bone mineral density, fractures, and scoliosis) in adults with PWS.

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Methods: We retrospectively collected patient characteristics, medical history, medication, biochemical measurements, dual-energy X-ray absorptiometry scans, and spinal X-rays and reviewed the current literature.

Results: We included 354 adults with PWS (median age 31 years; 43% males), of whom 51 (14%) had osteoporosis (T-score below −2.5) and 143 (54%) had osteopenia (T-score −1 to −2.5). The most prevalent modifiable risk factors for osteoporosis were hypogonadism, insufficient dairy intake, sedentary lifestyle, and corticosteroid use. Male sex was associated with osteoporosis ($P = .005$). Growth hormone treatment was not associated with osteoporosis. A history of vertebral fractures was present in 10 (3%) and nonvertebral fractures in 59 (17%). Scoliosis was present in 263 (80%), but no modifiable risk factors were identified.

Conclusion: Besides scoliosis, osteoporosis is common in adults with PWS. Based on the literature and the risk factors for osteoporosis found in our cohort, we provide practical clinical recommendations to avoid skeletal complications in these vulnerable patients.

Key Words: Prader–Willi syndrome, osteoporosis, bone density, human growth hormone, hormone replacement therapy, scoliosis

Abbreviations: 25(OH) vitamin D, 25-hydroxyvitamin D; BMD, bone mineral density; BMI, body mass index; DXA, dual-energy X-ray absorptiometry; GH, growth hormone; GHt, growth hormone treatment; ICD, imprinting center defect; IQR, interquartile range; mUPD, maternal uniparental disomy; OPG, osteoprotegerin; P1NP, propeptide of type I procollagen; PTH, parathyroid hormone; PWS, Prader–Willi syndrome; RANKL, Receptor activator of nuclear factor-κB Ligand; SHRT, sex hormone replacement therapy.

Prader–Willi syndrome (PWS) is a rare, complex genetic syndrome with an estimated prevalence of 1:10.000 to 30.000 (1). It arises from a loss of expression of paternally expressed genes in the PWS region on chromosome 15q11.2-13, most often caused by a de novo paternal deletion (65-75%), a maternal uniparental disomy (mUPD, 20-30%), an imprinting center defect (ICD, 1-3%), or a paternal chromosomal translocation (0.1%) (2, 3). Clinical features of PWS include infantile hypotonia, obesity due to hyperphagia (an insatiable appetite), sleep disorders, disturbed temperature regulation, disturbed pain perception, challenging behavior, and intellectual disability (4–6). Furthermore, hypothalamic dysfunction in PWS can lead to multiple pituitary hormone deficiencies (1, 4–7).

In patients with PWS, 29% to 44% have a history of bone fractures, which might be related to the high recorded prevalence of osteoporosis of up to 21% (8–12). Several risk factors contribute to this high prevalence. Firstly, there is a high prevalence of hypogonadism in adults with PWS (up to 100% in both males and females) (13–16), leading to increased bone turnover (17, 18). Secondly, adults with PWS are considered (functionally) growth hormone (GH) deficient, and GH deficiency has been linked to osteoporosis (19–24). Other risk factors for osteoporosis that are prevalent in adults with PWS are reduced physical activity (25–28) and low levels of fat-soluble vitamin D (29). A prevalent risk factors for fractures without a low bone mineral density (BMD) is type 2 diabetes mellitus (30, 31), which is present in 11% to 24% of adults with PWS compared with 5% to 7% in the general population (11, 32). The combination of hypotonia, hypogonadism, and decreased physical activity can lead to decreased bone mass and an increased fracture risk, as has previously been reported in Down syndrome (33).

Another frequent bone-related health problem in both children and adults with PWS is scoliosis. The reported prevalence of scoliosis ranges between 38% and 86% (8, 10, 34–40). Scoliosis is likely related to hypotonia of (paravertebral) muscles, low physical activity, and obesity (35, 38, 41). Additionally, late menarche and low estrogen levels might be linked to scoliosis in females with PWS (42–45), although results are inconclusive (40).

Therefore, we studied the prevalence of osteoporosis, osteopenia, fractures, and scoliosis and their risk factors in a large cohort of adults with PWS. In addition, we performed a literature review. Based on both clinical and literature data, we provide clinical recommendations for prevention and treatment of skeletal problems in adults with PWS.

Materials and Methods

This study is a multicenter, retrospective cohort study. Ethical approval and/or individual informed consent was obtained by the participating centers according to local rules and regulations. We included patients with genetically confirmed PWS, aged 18 years or older with available dual-energy X-ray absorptiometry (DXA) scans who had been treated at one of the participating PWS reference centers. A total of 354 patients were included from six countries: Australia (n = 51), The Netherlands (n = 78), France (n = 64), Italy (n = 130), Sweden (n = 4), and Spain (n = 27).

Data on osteoporosis, risk factors for osteoporosis, growth hormone treatment (GHt), sex hormone replacement therapy (SHRT), scoliosis, previous fractures, medication, and genotype were collected from medical records. We studied demographic (eg, ethnicity, sex), life style–related (eg, physical inactivity, smoking, alcohol intake, body mass index [BMI], and vitamin D and calcium intake), and comorbidity-related risk factors (eg, previous fractures, type 2 diabetes mellitus, hypogonadism, hyperparathyroidism, hyperthyroidism, chronic corticosteroid use, and malabsorption) (22, 46–49).

A BMI between 18.5 and 25 kg/m^2 was considered lean, 25 to 30 kg/m^2 overweight, and more than 30 kg/m^2 obesity, according to the 1997 World Health Organization criteria (50). Exercise of less than 30 minutes per day was considered insufficient for adults with PWS.

Scoliosis was diagnosed when a gibbus deformity was observed during physical examination and/or if a Cobb angle of ≥10 degrees was present on X-ray, according to the Scoliosis Research Society criteria (51). If a patient had more than one spinal curvature, the largest Cobb angle was used. If a patient had received surgery for scoliosis, the Cobb angle before surgery was used.

The most recent 25-hydroxyvitamin D (25(OH) vitamin D) levels were collected in patients who did not receive vitamin D supplementation. Vitamin D deficiency was defined as a 25(OH) vitamin D level <50 nmol/L (52), and severe vitamin D deficiency was defined as a 25(OH) vitamin D level of <20 nmol/L.

Bone mineral density was measured using DXA scans. Different DXA machines were used (Hologic DEXA systems® or GE Healthcare Lunar), depending on availability in participating centers. In the absence of a spine phantom, we calculated the standardized BMD (sBMD) in order to compare

the results from the different machines. sBMD in g/cm^2 was calculated using the following formulas (53, 54):

$$\text{sBMDspine Lunar} = 0.9683 \times (\text{BMDspine-1.100}) + 1.0436$$

$$\text{sBMDspine Hologic} = 1.0550 \times (\text{BMDspine-0.972}) + 1.0436$$

$$\text{sBMDfemur neck Lunar} = 0.939 \times \text{BMDfemur} - 0.023$$

$$\text{sBMDfemur neck Hologic} = 1.087 \times \text{BMDfemur} + 0.019$$

Osteopenia was defined as a T-score between −1 and −2.5 SD and osteoporosis was defined as a T-score below or equal to −2.5 SD, according to the World Health Organization criteria (55–58). T-scores are calculated based on a reference population, according to sex, ethnicity, skeletal site, and the bone densitometer used. When only Z-scores were available and not T-scores, osteopenia and osteoporosis were considered missing.

When information on the day and month of biochemical and/or imaging data were missing while the year was known, we assigned the date of July 1 to calculate the age and other time intervals.

Literature Review

In collaboration with the Medical Library of the Erasmus University Medical Center, a literature search was performed in March 2021 and last updated on 21 June 2022. D.v.A. and K.P. reviewed the medical literature on osteoporosis, fractures, scoliosis, and bone-related factors in adults with PWS in several databases (Embase, Medline All, Web of Science Core Collection, Cochrane database, and Google Scholar). Search terms included "Prader-Willi Syndrome," "osteoporosis," "osteopenia," "fracture," "scoliosis," "DEXA," "DXA," "bone health," and "bone mineral density". The full search strategy is available elsewhere (Table S1 (59)). Additionally, the references of relevant articles were screened. We included articles reporting on osteoporosis, scoliosis, or bone-related factors in adults with genetically confirmed PWS (≥16 years old). Nonoriginal research articles, conference abstracts, articles describing fewer than 10 patients, nonhuman research, non-English articles, and articles without full-text availability were excluded. Articles about both children and adults were only included if a subgroup analysis for the age group of 16 years old or older was available. When articles reported on the same population, both articles were combined.

Data Analysis

Data were analyzed using IBM SPSS version 25.0. Continuous variables were displayed as median (interquartile range [IQR]), dichotomous variables as number and percentage of patients, n (%). To investigate the relationship between the determinants and osteoporosis or scoliosis, a chi-squared test was used for dichotomous variables, a Mann–Whitney U test for continuous variables when we compared 2 groups, and a Kruskal–Wallis H test for continuous variables to compare 3 or more groups. Ordinal and logistic regression models were used to correct for GHt, age, height, weight (and thereby indirectly for BMI), and/or sex. BMI was considered a possible confounder as high BMI is associated with an increased BMD (60–62). Correction for GHt was performed because GHt improves body composition (63–65) and could therefore influence BMD. $P < .05$ was considered to be statistically significant.

Table 1. Baseline characteristics of 354 adults with PWS

	Total n = 354
Age at baseline in years, median (IQR)[a]	31 (25-40)
Age at first DXA (T-scores), median (IQR)	24 (21-33), n = 332
Male sex	152 (43)
Height in m, median (IQR)	1.56 (1.49-1.64)
Weight in kg, median (IQR)	81.3 (67.2-98.1)
BMI in kg/m^2, median (IQR)	33.3 (26.8-41.4)
Obesity	219 (62)
Ever received GHt	223 (64), n = 351
Genetic subtype	
Deletion	217 (61)
Deletion type 1	24
Deletion type 2	43
Deletion, unspecified	141
Atypical deletion	9
mUPD	105 (30)
ICD	7 (2)
Other[b]	25 (7)
Country	
Australia	51 (14)
France	64 (18)
Italy	130 (37)
Sweden	4 (1)
Spain	27 (8)
The Netherlands	78 (22)
Ethnicity	
White/Caucasian	313 (88)
Black/African American	5 (1)
Hispanic	2 (1)
Asian	6 (2)
Arabic	6 (2)
African American	5 (1)
Hispanic	2 (1)
Eurasian	1 (0)
Unknown	21 (6)
Osteoporosis	
Currently diagnosed	51 (14)
Ever diagnosed	75 (21), n = 340
Current osteopenia[c]	143 (54), n = 263
History of vertebral fracture(s)	10 (3), n = 336
History of nonvertebral fracture(s)	59 (17), n = 326
Scoliosis	263 (80), n = 329
Largest cobb angle in degrees, median (IQR)	23.0 (13.0-41.5)

Data are presented as n (%), unless otherwise specified.
Abbreviations: BMI, body mass index; DXA, dual-energy X-ray absorptiometry; GHt, growth hormone therapy; ICD, imprinting center defect; IQR, interquartile range; mUPD, maternal uniparental disomy.
[a]Current age or age of death for deceased patient.
[b]Other genetic subtypes included nonspecified mUPD or ICD, nonspecified methylation positive, and rare genetic subtypes such as translocations.
[c]In patients not currently diagnosed with osteoporosis.

Results

Baseline Characteristics

We included 354 adults (152 males, 202 females) with PWS. The median age was 31 years (IQR 25-40 years) and 43%

Table 2. Characteristics and risk factors of Patients with PWS with normal BMD, osteopenia and osteoporosis

	Number of observations	Normal BMD (n = 120)	Number of observations	Osteopenia (n = 143)	Number of observations	Osteoporosis (n = 51)	*P*-value	Adjusted *P*-value[j]
Age in years, median (IQR)[a]	120	31.4 (24.8-38.5)	143	31.4 (26.3-39.8)	51	44.8 (32.4-52.2)	**<.001**	**<.001**
Male sex	120	41 (31)	143	60 (46)	51	31 (61)	**.005**	**<.001**
Height in m, median (IQR)	120	1.56 (1.48-1.65)	143	1.56 (1.49-1.63)	51	1.54 (1.44-1.61)	.34	**.045**
Weight in kg, median (IQR)	120	87.4 (68.0-102.6)	143	80.6 (66.7-95.1)	51	74.0 (63.1-92.4)	**.010**	**<.001**
BMI in kg/m^2, median (IQR)	120	34.9 (27.2-42.9)	143	32.9 (27.0-40.6)	51	30.3 (26.5-38.9)	.12	.58
Genotype	120		143		51			
Deletion		73 (61)		87 (61)		36 (71)	.13[b]	.86[b]
mUPD		38 (32)		43 (29)		8 (16)		
ICD		2 (2)		3 (2)		1 (2)		
Other		7 (6)		11 (8)		6 (12)		
Scoliosis	111	82 (74)	135	115 (85)	44	38 (86)	**.049**	.061
Cobb angle, median (IQR)	48	19.5 (10.4-44.8)	63	24.0 (15.0-43.0)	18	25.0 (16.5-39.0)	.66	.75
Fractures								
Vertebral	117	0	137	4 (3)	42	6 (14)	**<.001**	**.025**
Nonvertebral	116	15 (13)	133	24 (18)	41	16 (39)	**.001**	**.010**
Bisphosphonate treatment	120	0 (0)	142	5 (4)	47	19 (40)	**<.001**	**<.001**
Alcohol usage	112	6 (5)	135	10 (7)	47	5 (10)	.49	.68
Units/week median (IQR)	6	2.5 (1.0-6.5)	10	1.5 (1.0-3.3)	5	3.0 (0.5-4.0)	.76	.72
Smoking	112	9 (8)	133	12 (9)	48	6 (13)	.67	.69
Cigarettes/week median (IQR)	9	50 (15-85)	12	57 (26-70)	6	70 (70-98)	.14	.20
Ever	120	78 (65)	140	93 (66)	51	23 (45)	**.020**	.88
During childhood[b]	109	67 (62)	117	70 (60)	38	10 (26)	**<.001**	.45
During adulthood[c]	91	49 (54)	95	48 (51)	42	14 (33)	.080	.73
Current	119	40 (34)	136	40 (29)	47	11 (23)	.42	.65
Hypogonadism males	41	37 (90)	59	57 (97)	30	28 (93)	.42	.13
Ever received SHRT	40	30 (75)	60	41 (68)	30	22 (73)	.75	.96
Untreated hypogonadism	37	7 (19)	57	17 (30)	28	6 (21)	.44	.61
Hypogonadism females	78	66 (85)	82	71 (87)	20	16 (80)	.76	.45
Ever received SHRT	75	55 (73)	79	56 (71)	19	15 (79)	.77	.43
Untreated hypogonadism	66	13 (20)	71	16 (23)	16	2 (13)	.66	.70
Hyperthyroidism	120	1 (0.8)	143	1 (0.7)	51	2 (4)	.071	.088
Hyperparathyroidism	120	0	143	1 (0.7)	50	2 (4)	NA[i]	NA[i]
Diabetes mellitus	120		143		48			
Type 1		0		0		0	NA[i]	NA[i]
Type 2		27 (23)		37 (26)		10 (21)	.69	.96

(*continued*)

Table 2. Continued

	Number of observations	Normal BMD (n = 120)	Number of observations	Osteopenia (n = 143)	Number of observations	Osteoporosis (n = 51)	*P*-value	Adjusted *P*-value[j]
Not specified		1 (0.8)		2 (1)		0	NA[i]	NA[i]
IGT		10 (8)		6 (4)		1 (2)	NA[i]	NA[i]
Current corticosteroid use	119	16 (13)	140	11 (8)	47	3 (6)	.22	.14
Exercise <30 minutes/day	109	38 (35)	131	55 (42)	40	16 (40)	.52	.19
Dairy intake <3 units/day	82	69 (84)	105	95 (91)	37	29 (78)	.15	.74
Calcium supplements	116	10 (9)	136	35 (26)	44	24 (55)	**<.001**	**<.001**
Vit D supplements	116	83 (72)	138	112 (81)	46	40 (87)	.055	.25
Vit D levels in nmol/L without supplements, median (IQR)	30	71.4 (58.4-85.5)	25	61.9 (40.4-86.4)	5	77.4 (50.5-129.1)	.39	.93
Vit D deficiency[d]	30	5 (17)	25	8 (32)	5	1 (20)	.40	.18
Severe vit D deficiency[e]	30	1 (3)	25	2 (8)	5	0	NA[i]	NA[i]
Malabsorption								
Gastrointestinal surgery[f]	116	9 (8)	138	8 (6)	48	7 (15)	.15	.23
Gastrointestinal comorbidities[g]	117	4 (3)	137	8 (6)	47	6 (13)	.74	.16

Data are presented as n (%), unless otherwise specified. *P* values are calculated using a chi-squared test for dichotomous variables and a Kruskal–Wallis H test for continuous variables. The adjusted *P* value was calculated using an ordinal regression analysis. Bold *P* values represent statistically significant differences. Forty patients were excluded from this analysis, as they were not diagnosed with osteoporosis but it was unknown whether they had osteopenia or a normal BMD.

As not all variables were available for all included patients, we display the number of observations, representing the number of patients for whom that variable was known.

Abbreviations: BMI, body mass index; BMD, bone mineral density; del, deletion; GHt, growth hormone treatment; IGT, impaired glucose tolerance; IQR, interquartile range; mUPD, maternal uniparental disomy; NA, not applicable; SHRT, sex hormone replacement therapy; vit, vitamin.

[a]Current age or age of death for deceased patients.

[b]During childhood includes all patients who received GHt at some point during childhood, independent of whether the patient received GHt during adulthood compared with patients who never received GHt.

[c]During adulthood includes all patients who received GHt at some point during adulthood, independent of GHt during childhood compared with patients who never received GHt.

[d]Vitamin D deficiency was defined as a vitamin D level <50 nmol/L without the use of vitamin D supplements.

[e]Severe vitamin D deficiency was defined as a vitamin D level <20 nmol/L without the use of vitamin D supplements.

[f]In the normal BMD group, operations included sleeve gastrectomy and/or gastric bypass (n = 4), cholecystectomy (n = 3), appendectomy (n = 1), and bioenteric intragastric balloon (n = 1). In the osteopenia group, operations included sleeve gastrectomy, gastric bypasss or biliopancreatic diversion (n = 6), and cholecystectomy (n = 3). In the osteoporosis group, operations performed were biliopancreatic diversion (n = 4), and cholecystectomy (n = 2), which was combined with ileal resection for ileus in 1 patient (n = 1).

[g]In the normal BMD group, gastrointestinal comorbidities included malabsorption after previous sleeve gastrectomy (n = 4), dysbiosis (n = 1), acute alithiasic cholecystitis (n = 1). In patients with osteopenia, the most common causes of malabsorption were postoperative (n = 3), inflammatory bowel disease (n = 2), and hepatic disease (n = 2). In the patients with osteoporosis, 3 patients had malabsorption due to biliopancreatic diversion.

[h]*P* value calculated for deletion vs mUPD only, other genotypes were excluded from this analysis.

[i]*P* value not calculated because of small numbers.

[j]*P* values were adjusted for age, sex, height, and weight except for hypogonadism. For hypogonadism the *P* value was adjusted for age, height, and weight only.

Table 3. Comparison of adults with PWS with and without fractures

	Number of observations	No fracture	Number of observations	Vertebral fracture	*P* value	Number of observations	Nonvertebral fracture	*P* value
Age, median (IQR)[a]	326	31.3 (25.2-40.0)	10	54.5 (45.2-56.3)	**<.001**	59	36.3 (30.5-45.3)	**.001**
Male sex	326	134 (41)	10	7 (70)	.068	59	34 (58)	**.005**
Height in m, median (IQR)	326	1.56 (1.49-1.64)	10	1.56 (1.50-1.65)	.92	59	1.59 (1.49-1.68)	.13
Weight in kg, median (IQR)	326	82.0 (67.1-98.5)	10	71.4 (55.3-80.4)	.069	59	82.1 (72.2-104.1)	.14
BMI in kg/m^2, median (IQR)	326	33.4 (26.8-41.6)	10	28.4 (24.4-31.4)	.056	59	34.3 (26.9-40.5)	.48
Current osteoporosis	153	36 (24)	6	6 (100)	**<.001**[b]	31	16 (52)	**<.001**[c]
Current osteopenia	250	133 (53)	4	4 (100)	.062	39	24 (62)	.27
Scoliosis Cobb angle, median (IQR)	313 144	251 (80) 22.5 (13.0-41.0)	8 1	5 (63) 51.0	.22 .23	53 20	42 (79) 23.5 (13.5-37.75)	.77 .95
GHt								
Ever	326	217 (67)	10	2 (20)	**.002**[d]	58	35 (60)	.36
During childhood	278	169 (61)	10	2 (20)	**.010**[e]	50	27 (54)	.33
During adulthood	237	128 (54)	8	0 (0)	**.003**[f]	41	18 (44)	.22
Hypogonadism males	133	123 (93)	6	6 (100)	.49	33	32 (97)	.26
Ever received SHRT	131	93 (71)	7	5 (71)	.98	33	24 (73)	.59
Hypogonadism females	188	162 (86)	3	2 (67)	.34	24	22 (92)	.40
Ever received SHRT	184	133 (72)	2	2 (100)	.38	24	18 (75)	.77

Data are presented as n (%), unless otherwise specified. *P* values are calculated using a chi-squared test for dichotomous variables and a Mann–Whitney U test for continuous variables. *P* values are calculated for patients with vertebral fractures vs no fractures and for patients with nonvertebral fractures vs no fractures. Bold *P* values represent statistically significant differences.
Abbreviations: BMI, body mass index; GHt, growth hormone treatment; IQR, interquartile range; SHRT, sex hormone replacement therapy.
[a]Current age or age of death for deceased patients.
[b]$P = .996$ after adjusting for age, sex, weight, and GHt (ever received) for patients with osteoporosis compared to normal BMD.
[c]$P = .003$ after adjusting for age, sex, weight, and GHt (ever received) for patients with osteoporosis compared with normal BMD.
[d]$P = .117$ after adjusting for age, sex, height, and weight.
[e]$P = .867$ after adjusting for age, sex, height, and weight.
[f]$P = .995$ after adjusting for age, sex, height, and weight.

were male. Median BMI was 33 kg/m^2(IQR 27-41 kg/m^2); 62% had obesity. Paternal deletion was the most common genotype (61%), followed by mUPD (30%). ICD (2%) was less common. One percent of subjects were methylation positive, but the underlying genetic defect was unknown. In the remaining 6%, the genotype was either mUPD or ICD (not specified) or a rare genetic defect. Sixty-four percent (223 of 351) had ever received GHt. The median (IQR) duration of GHt during childhood was 6.0 (3.3-9.5) years. Baseline characteristics are displayed in Table 1.

Osteoporosis

Fifty-one of 354 patients (14%) had osteoporosis based on a T-score below or equal to −2.5 SD at the time of data collection ("current osteoporosis"); 143 of 263 (54%) had current osteopenia based on a T-score between −1 and −2.5 SD. Seventy-five patients (21%) had ever been diagnosed with osteoporosis, either at the time of data-collection or at some point in their medical history. The median T-scores and sBMD values of the most recent DXA scans are shown elsewhere (Table S2 (59)). The median age of patients currently diagnosed with osteoporosis was 45 years (IQR 32-52 years) compared with 31 years (IQR 25-39 years) for patients with a normal BMD and 31 (26-40) in osteopenia ($P < .001$ after adjusting for sex, height, and weight) (Table 2). There was a male predominance in the osteoporosis group, but not in the normal BMD group (61% vs 31% $P < .001$); males had a significantly lower BMI than females (31 [IQR 27-38] kg/m^2 vs 35 [IQR 27-42] kg/m^2, $P = .013$). After adjusting for age, height, and weight, sex remained significantly associated with current osteoporosis ($P < .001$). Both height and weight were significantly associated with osteopenia or osteoporosis (adjusted $P = .045$ and $P < .001$ respectively). We corrected for BMI indirectly by correcting for height and weight. Genotype (deletion vs mUPD) was not significantly related to osteoporosis or osteopenia (adjusted $P = .86$).

Risk Factors for Osteoporosis

Use of alcohol (7%) and tobacco (9%) was not significantly related to osteoporosis or osteopenia (Table 2). Hypogonadism, irrespective of treatment with SHRT, was the most prevalent risk factor (with a prevalence of 93% in males and 80% in females), followed by insufficient physical exercise (present in 40%). No significant association was found between (un)treated hypogonadism and normal BMD, osteopenia, or osteoporosis. Use of GHt at some point in life (ie, either current use or use in

Table 4. Comparison of individuals with PWS with and without scoliosis

	Number of observations	No scoliosis (n = 66)	Number of observations	Scoliosis (n = 263)	*P* value
Age in years, median (IQR)[a]	66	30.1 (24.8-36.8)	263	31.4 (25.4-40.2)	.33
Male sex	66	34 (52)	263	106 (40)	.10
Height in m, median (IQR)	66	1.58 (1.51-1.69)	263	1.56 (1.48-1.64)	**.007**[b]
Weight in kg, median (IQR)	66	85.2 (71.4-104.8)	263	79.7 (66.2-95.3)	**.006**[c]
BMI in kg/m^2, median (IQR)	66	33.7 (28.6-42.5)	263	32.6 (26.5-40.1)	.21
Deletion vs mUPD	59	39 (66) del/20 (34) mUPD	243	166 (68) del/77 (32) mUPD	.74
GHt					
Ever	66	42 (64)	263	179 (68)	.49
During childhood[d]	57	33 (58)	222	138 (62)	.56
During adulthood[e]	52	28 (54)	183	99 (54)	.97
Current	66	23 (35)	252	82 (33)	.72
Hypogonadism males	34	31 (91)	104	98 (94)	.53
Ever received SHRT	32	25 (78)	105	72 (69)	.30
Hypogonadism females	30	23 (77)	155	136 (88)	.11
Ever received SHRT	29	22 (76)	151	108 (72)	.63

Data are presented as n (%), unless otherwise specified. *P* values are calculated using a chi-squared test for dichotomous variables and a Mann–Whitney U test for continuous variables. Bold *P* values represent statistically significant differences.
As not all variables were available for all included patients, we display the number of observations, representing the number of patients for whom that variable was known.
Abbreviations: BMI, body mass index; del, deletion; GHt, growth hormone treatment; IQR, interquartile range; mUPD, maternal uniparental disomy; SHRT, sex hormonal replacement therapy.
[a]Current age or age of death for deceased patients.
[b]$P < .001$ after adjusting for GHt (ever received).
[c]$P = .004$ after adjusting for GHt (ever received).
[d]During childhood includes all patients who had received GHt at some point during childhood, independent of whether the patient received GHt as an adult compared with patients who never received GHt.
[e]During adulthood includes all patients who had received GHt at some point when they were 18 years old, or older, independent of GHt during childhood compared with patients who never received GHt.

the past) was lower in patients with osteoporosis than in patients with normal bone density (45% vs 65%, $P = .020$). However, after adjusting for age, height, weight, and sex, this difference was no longer statistically significant ($P = .88$). GHt during childhood was not significantly related to osteoporosis after correction for age, sex, weight, and height either ($P = .45$). Only 4 patients had hyperthyroidism and 3 had hyperparathyroidism. Scoliosis was not significantly more prevalent in adults with osteopenia (85%) or osteoporosis (86%) than in those with normal bone density (74%, adjusted $P = .061$). Eleven percent of the cohort used corticosteroids, either daily or only during physical or psychological stress. Corticosteroid use was not significantly related to osteoporosis or osteopenia (adjusted $P = .14$). Osteoporosis showed no correlation with gastrointestinal comorbidities or surgery either (adjusted $P = .16$ and $P = .23$ respectively).

Fractures

Ten of 326 (3%) patients had previously suffered at least one vertebral fracture. In six patients, the fractures were spontaneous, in other words, not caused by any (observed or reported) mechanical trauma. Fifty-nine (17%) of all patients had suffered from a nonvertebral fracture at any point in life. In eight patients (14%), this was a spontaneous fracture without previous (observed or reported) adequate trauma. Forty-five patients had had a single fracture; the remaining 14 patients suffered from multiple fractures, either at different time points or simultaneously. The maximum number of fractures in one patient was six. This patient had osteoporosis and received SHRT for hypogonadism. Four patients, all previously diagnosed with osteoporosis, had suffered from both vertebral and at least one nonvertebral fracture. Fractures (both vertebral and nonvertebral) were more frequent in patients with a current diagnosis of osteoporosis. However, after correcting for age, sex, weight, and GHt, only nonvertebral fractures remained significantly associated with osteoporosis ($P = .003$). Patients with (vertebral or nonvertebral) fractures were significantly older than adults without fractures ($P < .001$ and $P = .001$ respectively, Table 3). GHt was not associated with either vertebral or nonvertebral fractures after correcting for age, sex, height, and weight. We did not find any association between (vertebral or nonvertebral) fractures and hypogonadism or SHRT in either of the sexes.

Scoliosis

Scoliosis was present in the majority of patients (80%, 263 out of 329 patients) with a median Cobb angle of 23.0 (IQR 13.0-41.5) degrees. Table 4 shows the clinical characteristics of adults with PWS with and without scoliosis. No significant difference was found for age, sex, BMI, genotype (deletion vs mUPD), GHt at any point in life, GHt during childhood, hypogonadism, or SHRT between patients with and without scoliosis. Scoliosis was not related to osteoporosis or fractures.

Results of the Literature Review

Our search resulted in 1464 articles. A total of 1289 articles were excluded based on title and abstract. The remaining

Table 5. Results of studies reporting on osteoporosis and bone mineral density in adults with Prade–Willi syndrome

Author (year)	Country	Patient characteristics	Methods	Outcome	Influencing factors	Remarks
Butler et al (2002) (11)	UK	N: 58 Age range: 18-46 years Sex: 32M, 26F Mean BMI: 35 kg/m^2 Genotype: NA GHt: NA SHRT: 13%	Cross-sectional study. Semistructured interviews with family or caregivers	Osteoporosis: 1/58 (2%) History of any fractures: 25/58 (43%) History of >1 fractures: 13/58 (22%)	—	Not all cases with PWS were genetically confirmed. No systematic BMD assessment
Sinnema et al (2011) (10)[a]	NL	N: 102 Mean age: 36 years (range 18-66) Sex: 49M, 53F Mean BMI: 32 kg/m^2 (range 17-52 kg/m^2) Genotype: 55 del, 44 mUPD, 3 ICD GHt: 5%, past 8% SHRT: males: current 16%, past 14% females: current 17%, past 9%	Cross-sectional study. Semistructured interviews with caregivers and review of medical files	Osteoporosis: 16/102 (16%)	Osteoporosis more prevalent in del (13/55, 24%) compared with mUPD (2/44, 5%, $P = .02$) No significant different was found in the prevalence of osteoporosis for different age groups or sex	No systematic BMD assessment
Butler et al (2013) (65)	USA	N: 11 Mean age: 32 years (range 23-50) Sex: 5M, 6F BMI: 34.5 kg/m^2 Genotype: 9 del, 1 mUPD, 1 ICD GHt: no prior GHt SHRT: NA, but evidence of hypogonadism and low sex steroid levels were present	Cohort study. 12 months GHt followed by 12 months no GHt. BMD assessment by DXA at baseline and 12 and 24 months	Osteoporosis: NA Total body BMD (mean ± SE) at baseline: 1.14 ± 0.05 g/cm^2	—	—
Jørgensen et al (2013) (67)[a]	Scandinavia	N: 42 Mean age: 28.5 years Sex: 21M, 21F Mean BMI: 28.1 kg/m^2 Genotype: NA GHt: no GHt at least 12 months before study, none during adulthood SHRT: not started at least 12 months before study 43%M, 29%F	Double blind RCT for GHt vs placebo for 12 months, open label, GHt for additional 24 months Controls were 15 healthy age-, weight-, and sex matched Norwegian subjects Bone density assessment by DXA at baseline, 12, 24, and 36 months	Osteoporosis: NA BMD lumbar spine: 1.038 ± 0.138 g/cm^2 BMD total hip: 0.864 ± 0.120 g/cm^2 Z-score lumbar spine, mean (95% CI): −1.4 (−1.8 to −1.0) Z-score total hip, mean (95% CI): −1.5 (−1.8 to −1.3) Z-score total body, mean (95% CI): −1.0 (−1.4 to −0.6) Compared with healthy controls, BMD of lumbar spine and BMD Z-score were significantly lower in adults with PWS; however, BMD was not significantly different after correction for height	Z-scores of men at lumbar spine and total body were significantly lower than Z-scores of women (lumbar spine, mean (95% CI): −1.9 (−2.5 to −1.3) vs −1.0 (−1.5 to −0.5), $P < .05$, total body, mean (95% CI): −1.5 (−2.0 to −1.0) vs −0.5 (−0.9 to 0.0), $P < .01$). No significant difference was found for total hip BMD Z-score of eugonadal women at baseline were normal and higher than hypogonadal women (mean (95% CI): 0.0 (−0.6 to 0.6) vs −1.0 (−1.7 to −0.4), $P < .05$) A BMI >30 kg/m^2 was associated with higher baseline BMD of the lumbar spine ($P < .01$), total hip ($P < .01$) and total body ($P < .05$) Regression analysis showed baseline BMD as a predictor of total hip BMD ($P =$	—

(*continued*)

Table 5. Continued

Author (year)	Country	Patient characteristics	Methods	Outcome	Influencing factors	Remarks
					.028). Lumbar spine BMD predictors were BMI ($P = .010$) and sex ($P = .026$)	
Kido et al (2013) (69)	Japan	N: 22 Age range: 16-48 years Sex: 22M Mean BMI: 33.6 kg/m^2 Genotype: 21 del, 1 mUPD GHt: 9% Hypogonadism: 100% SHRT: 0% at baseline, then SHRT was initiated in 100%	Observational cohort study. BMD assessment by DXA	Osteoporosis: NA At baseline (before start of SHRT): Lumbar spine BMD: 0.8505 ± 0.0426 g/cm^2 (n = 18) Lumbar spine T-score: −1.547 ± 1.871 Lumbar spine Z-score: −1.510 ± 1.871	2 years of monthly intramuscular testosterone injections of 125 mg significantly increased lumbar spine BMD (to 0.9035 ± 0.0465 g/cm^2, $P = .036$), lumbar spine T-scores (to −1.092 ± 1.333, $P = .036$) and lumbar spine Z-scores (to −0.934 ± 1.333, $P = .036$)	—
Longhi et al (2015) (70)[a]	Italy	N: 41 Mean age: 29.4 years Sex: 17M, 24F Mean BMI: males 41.6 kg/m^2, females 41.2 kg/m^2 Genotype: 33 del, 8 mUPD GHt: current 34%, 22% past SHRT: 6%M, 54%F	Cross-sectional study. Controls matched for age and sex. BMD assessment by DXA scan	Osteoporosis: NA No significant difference between PWS and controls In total body BMD (1.13 ± 0.01 vs 1.07 ± 0.16 g/cm^2), L2-L4 (1.04 ± 0.14 vs 1.21 ± 0.13 g/cm^2) or femur neck (0.89 ± 0.14 vs 1.02 ± 0.17 g/cm^2) after correcting for height	No significant differences found between BMD total body, L2-L4 or femur neck for patients with and without SHRT	Control group had a lower BMI (mean BMI 24.5 kg/m^2 in males and 21.1 kg/m^2 in females) than patients with PWS
Donze et al (2018) (71)[a]	NL	N: 27 Mean age: 17.2 years Sex: 8M, 19F Mean BMI SDS: 0.9 Genotype: 9 del, 15 mUPD, 2 ICD, 1 translocation GHt: 100% at time of inclusion Hypogonadism: 88%M and 84%F SHRT: 38%M, 42%F	Baseline characteristics of a crossover GHt RCT BMD assessment by DXA scan. Compared with age- and sex-matched references	Osteoporosis: NA At adult height, total body BMD SD (Z-score) was −0.7 ± 1.1, which was significantly lower than in healthy peers ($P < .01$) 4/27 (15%) had total body BMD SD of <−2.0	There was no significant difference in total body BMD SDS between hypogonadal adults with and without SHRT ($P = .49$ and $P = .39$ respectively)	All patients had received GHt during childhood Not clear if all patients were aged >15 years
van Nieuwpoort et al (2018) (68)	NL	N: 15 Median age: 22.0 years (range 19.2-42.9) Sex: 4M, 11F Median BMI: 27.5 kg/m^2 Genotype: 93.3% del, 6.7% mUPD GHt: current 0%, past 27% Hypogonadism: 87% SHRT: 54%	Cross-sectional study. BMD assessment by DXA scan	Osteoporosis: Lumbar spine: 2 (13%) Total hip: 2 (13%) Osteopenia: Lumbar spine: 6 (40%) Total hip: 10 (67%) Median lumbar spine BMD: 0.91 (IQR 0.17) g/m^2 Median T-score lumbar spine: −1.4 (IQR 2.0) Median Z-score lumbar spine: −1.7 (IQR 1.4) Median total hip BMD: 0.76 (IQR 0.10) g/m^2 Median T-score total hip: −1.6 (IQR 0.9) Median Z-score total hip: −1.5 (IQR 1.1)	Lumbar spine and total hip T-scores were significantly lower in men (median T-scores −2.6 and −2.0 respectively) than in women (median T-scores −0.9 and −1.2 respectively, $P < .05$). BMD for lumbar spine, hip, and total body and Z-scores were not significantly different	Criteria for osteoporosis not specified DXA scans only performed in 11 patients

(*continued*)

Table 5. Continued

Author (year)	Country	Patient characteristics	Methods	Outcome	Influencing factors	Remarks
				Median total body BMD: 0.99 (IQR 0.13) g/cm^2		
Viardot et al (2018) (72)	Australia	N: 11 Mean age: 27.6 years Sex: 7M, 4F Mean BMI: 37.4 kg/m^2 Genotype: NA GHt: 0% SHRT: 71%M, 25%F	Cross-sectional study. BMD assessment by DXA scan 2 control groups: 1 obese (n = 12) and 1 lean (n = 10) group	Osteoporosis: NA Total body BMD (mean ± SE): PWS: 1.21 ± 0.07 g/cm^2 Obese controls: 1.25 ± 0.07 g/cm^2 Lean controls: 1.13 ± 0.06 g/cm^2 No significant differences between PWS and the control groups in total body BMD	Multiple linear regression in all (PWS and non-PWS) included individuals showed that total lean mass was a significant predictor of BMD (coefficient 0.005, P = .024), while having obesity, having PWS, fat mass, height, and age were not	No DXA results for lumbar spine or hip. SHRT no included in multiple regression model Matching was performed by recruiting control groups with similar baseline characteristics to the PWS group rather than case to case matching. Unknown how patients with similar characteristics were selected
Baraghithy et al (2019) (73)	Israel	N: 30 Mean age: 29.9 years Sex: 60% M Mean BMI: 28.4 kg/m^2 Genotype: 16 del, 13 mUPD, 1 ICD GHt: NA SHRT: NA	Cross-sectional study. BMD assessment by DXA scan. Compared with 28 age- and BMI-matched controls	Osteoporosis: NA Z-scores of Patients with PWS significantly lower than controls (femoral neck: −1.6 ± 1.0 vs 0.2 ± 1.2, P < .001, total hip −1.3 ± 1.4 vs 0.4 ± 1.1, P < .001, lumbar spine −1.6 ± 1.3 vs −0.4 ± 1.3, P = .001 and forearm −2.4 ± 1.2 vs −0.4 ± 0.7 P < .001)	—	—
Damen et al (2021) (74)[a]	NL	N: 43 Mean age (range): 19.5 years (18.7-20.7) for males and 18.4 years (15.8-23.8) for females Sex: 18M, 25F Mean BMI: 24.5 kg/m^2 Genotype: 18 del, 20 mUPD, 4 ICD, 1 translocation GHt: 100% Hypogonadism: 93% SHRT: 83% Hypogonadal without SHRT: 16%	Baseline characteristics of a prospective cohort study on GHt. BMD assessment with DXA scans, compared with age- and sex-matched references	Osteoporosis: NA Total body BMD (median [IQR]) was 1.15 (1.08 to 1.19) g/cm^2, total body SDS −0.78 (−1.31 to 0.11), which was significantly lower than in the reference group (P < .01) 9/43 (21%) patients total body SD <−2.0 Lumbar spine BMD (median [IQR]): 1.19 (1.09 to 1.26) g/	—	All patients had received GHt for at least 5 years during childhood No baseline characteristics of controls

(*continued*)

Table 5. Continued

Author (year)	Country	Patient characteristics	Methods	Outcome	Influencing factors	Remarks
				cm^2, lumbar spine SDS −0.62 (−1.16 to −0.09) 1 patient (2%) had a fracture during the study		
Faienza et al (2021) (66)[a]	Italy	N: 52 Mean age: 30.6 years (SD 10.7 years) Sex: 22M, 30F Median BMI: 35.3 kg/m^2 Genotype: 32 del, 20 mUPD GHt: 6 SHRT: 5%M, 33%F Vitamin D: 50% supplementation	Cross-sectional study. Biochemical measurement from blood samples and DXA scans to asses BMD Compared with 54 normal weight adult controls	Osteoporosis: NA T-score BMD of lumbar spine (median [IQR]): −1.10 [0.20]) Lumbar spine BMD: 1.05 (0.06) g/cm^2 Total body less head BMD: 1.18 (0.08) g/cm^2 No significant difference between del and mUPD genotype 5 (10%) adults had a history of post-traumatic fractures	No significant difference between del and mUPD.	Controls are normal weight adults, while irisin is also released from adipose tissue Exclusion criteria: use of mineral or vitamin supplements (except for vitamin D), presence of chronic diseases with possible impact on bone metabolism, use of medication affecting bone turnover and fractures in the 6 months preceding the study
Noh et al (2022) (75)	Korea	N: 68 Age range: 19-34 years Sex: 39M, 29F Mean BMI: 35 kg/m^2 Genotype: 44 del, 24 other GHt: 48 previous, 10 current SHRT: NA	Cross-sectional study. Data collection from patient records Compared with 204 age, sex and BMI-matched controls BMD assessment by DXA scan	Decreased bone density: 18/68 (26%) in Adults with PWS compared with 2/204 (1%) in controls ($P < .001$)	Decreased bone density according to GHt: Without GHt: 2/10 (20%) Previous GHt: 14/48 (29%) Current GHt: 2/10: (20%) $P > .05$ for all comparisons	—

Data are presented as mean ± SD, unless otherwise specified. When articles reported subgroup analysis for adults and children or patients >16 years old and patients <16 years old, only information for the adults or patients >16 years old are reported here whenever possible.
Abbreviations: BMI, body mass index; BMD, bone mineral density; del, deletion; DXA, dual-energy X-ray absorptiometry; F, females; GHt, growth hormone treatment; ICD, imprinting center defect; IQR, interquartile range; M, males; mUPD, maternal uniparental disomy; NA, not available; N, number of patients; RCT, randomized controlled trial; SHRT, sex hormone replacement therapy with estrogen or testosterone; SD, standard deviation; SDS, standard deviation score; SE, standard error; NL, The Netherlands;; WHO, World Health Organization.
[a]Partly overlapping study population as current study.

Table 6. Results of studies reporting on growth hormone treatment in relation to bone mineral density in adults with Prader–Willi syndrome

Author (year)	Country	Patient characteristics	Methods	Outcome	Influencing factors	Remarks
Butler et al (2013) (65)	USA	N: 11 Mean age: 32 years (range 23-50) Sex: 5M, 6F BMI: 34.5 kg/m^2 Genotype: 9 del, 1 mUPD, 1 ICD GHt: no prior GHt SHRT: NA, but evidence of hypogonadism and low sex steroid levels were present	Cohort study. 12 months GHt, followed by 12 months without GHt BMD assessment by DXA at baseline and 12 and 24 months	Total BMD (mean ± SE) At baseline: 1.14 ± 0.05 g/cm^2 At 12 months: 1.12 ± 0.05 g/cm^2 At 24 months: 1.15 ± 0.05 g/cm^2 No significant change in BMD was found during follow-up	—	All low plasma IGF-1 level at baseline
Jørgensen et al (2013) (67)[a]	Scandinavia	N: 42 Mean age: 28.5 years Sex: 21M, 21F BMI: 28.1 kg/m^2 Genotype: GHt: no GHt at least 12 months before study, none during adulthood SHRT: 43% M, 29% F, not started at least 12 months before study	Double-blind RCT for GHt vs placebo for 12 months, open-label GHt for additional 24 months Controls were 15 healthy age, weight, and sex matched Norwegian subjects Bone density assessment by DXA at baseline, 12, 24, and 36 months	12 months of GHt significantly decreased Z-score of lumbar spine (−2.1%±3.4%) compared with placebo (+1.9% ±3.4%, $P < .01$). No other changes in BMD at other sides or any significant changes after 24 months of GHt were found	After 24 months of GHt, Z-score of men remained significantly lower than women. Lumbar spine, mean (95% CI): −2.2 (−2.8 to −1.6) vs −1.1 (−1.6 to −0.5), $P < .05$. Total body, mean (95% CI): −1.7 (−2.2 to −1.1) vs −0.5 (−0.9 to 0.0), $P < .01$)	Patients lost to follow-up were excluded from analysis
Khare et al (2014) (77)	USA	N: 18 Mean age: >15 years old Sex: NA BMI: NA Genotype: 9 del, 8 mUPD, 1 unknown GHt: 0% prior to study SHRT: NA	Cross-sectional study; 7 subjects received GHt and 11 subjects had never received GHt Assessment of BMD by DXA scan	BMD Z-score of the spine was significantly higher in the GHt group than in the no GHt group ($P = .021$)	There was no statistically significant difference in BMD Z-score of the spine between patients with a del or mUPD	—
Longhi et al (2015) (70)[a]	Italy	N: 41 Mean age 29.4 years Sex: 17M, 24F BMI: males 41.6 kg/m^2, females 41.2 kg/m^2 Genotype: 33 del, 8 mUPD GHt: current 34%, 22% past SHRT: 6%M, 54%F	Cross-sectional study comparing previous or current GHt (n = 23) vs no GHt (n = 18) BMD assessment by DXA scan	No significant difference between GHt and no GHt Patients with PWS in BMD (g/cm^2) of total body (1.11 ± 0.09 vs 1.15 ± 0.12), lumbar spine (1.02 ± 0.12 vs 1.05 ± 0.16) or femur neck (0.86 ± 0.13 vs 0.91 ± 0.16)	—	No distinction between current and past GHt
Donze et al (2018) (71)[a]	NL	N: 27 Mean age: 17.2 years Sex: 8M, 19F Mean BMI SDS: 0.9 Genotype: 9 del, 15 mUPD, 2 ICD, 1 translocation GHt: 100% at time of inclusion Hypogonadism: 88% M and 84%F SHRT: 38%M, 42% F	Double blind RCT 1 year GHt vs placebo followed by crossover to the alternative treatment for 1 year BMD assessment by DXA scan at baseline, 6, 12, 18, and 24 months	GHt did not affect BMD measurements No significant difference was found in total body and lumbar spine BMD SDS after 12 months of GHt compared with placebo ($P = .51$ and $P = .37$ respectively). After 2 years, BMD of total body SDS did not change significantly ($P = .20$), but BMD SDS of the lumbar spine corrected for	SHRT did influence BMD measurements Independent of GHt or placebo, total body BMD SDS did not change significantly in hypogonadal patients without SHRT (−0.8 to −0.9, $P = .11$), while there was a significant increase in total body BMD SDS from −1.1 to −0.7 ($P < .01$) in patients with SHRT after 2 years. SDS of the BMD of the lumbar	All patients had received GHt during childhood Not clear if all patients were aged >15 years

(*continued*)

Table 6. Continued

Author (year)	Country	Patient characteristics	Methods	Outcome	Influencing factors	Remarks
				bone size declined significantly, independent of GHt ($P < .01$). There was no significant difference in change in BMD SDS for total body and BMD SWS for lumbar spine corrected for bone size between GH and placebo There were no bone fractures during the study period	spine corrected for bone size decreased from −0.2 to −0.6 in hypogonadal patients without SHRT ($P = .01$), while it remained similar in patients with SHRT (−0.5 at baseline and after 2 years, $P = 0.79$)	
Damen et al (2021) (74)[a]	NL	N: 43 Mean age (range): 19.5 years (18.7-20.7) for males and 18.4 years (15.8-23.8) for females Sex: 18M, 25F Mean BMI: 24.5 kg/m^2 Genotype: 18 del, 20 mUPD, 4 ICD, 1 translocation Hypogonadism: 93% SHRT: 83% Hypogonadal without SHRT: 16%	Open-label prospective cohort study, patients received GHt during 3 years BMD assessment with DXA scans	No significant difference were found for BMD of total body at start and after 3 years (SDS −0.76 (−1.11 to −0.41) vs −0.90 (−1.27 to −0.54), $P = .11$)	In men, a significant decrease in SDS BMD of total body after 3 years was found (−1.10 (−1.70 to −0.49) vs −1.46 (−1.94 to −0.98), $P = .008$). In women, no significant different was found in total body BMD SDS ($P = .78$) No significant different was found in total body BMD of 33 male and female subjects with SHRT after 3 years ($P = .37$). In men receiving SHRT, a significant decrease in total body BMD was found during 3 years from −1.33 (−1.96 to −0.69) to −1.59 (−2.15 to −1.01), $P = .014$. In women, no difference was found ($P = .72$) Regression analysis showed and association between female sex and higher BMD total body at baseline ($\beta = 1.956$, $P < .001$) and after 3 years ($\beta = 2.100$, $P < .001$) No associated was found between age and genetic subtypes	All patients had received GHt for at least 5 years during childhood No baseline characteristics of controls

Data are presented as mean ± SD, unless otherwise specified.
Abbreviations: BMI, body mass index; BMD, bone mineral density; del, deletion; DXA, dual-energy X-ray absorptiometry; ICD, imprinting center defect; F, females; GHt, growth hormone treatment; M, males; mUPD, maternal uniparental disomy; NA, not available; N, number of patients; SHRT, sex hormone replacement therapy; SDS, standard deviation score; SE, standard error; NL, The Netherlands.
[a]Partly overlapping study population as current study.

175 articles underwent full-text screening. One article was excluded because the full-text was unavailable. Another 149 articles were excluded when, after reading the full-text, it turned out they did not meet the inclusion criteria. Twenty-six articles were included in the review.

Osteoporosis and Bone Mineral Density

Table 5 shows the results of the literature review of articles reporting on osteoporosis and BMD in adults with PWS. Osteoporosis was present in 2% to 26% of adults with PWS. Sinnema et al (10) reported that osteoporosis was

Table 7. Results of studies reporting on vitamin D and bone related factors in adults with Prader–Willi syndrome

Author (year)	Country	Patient characteristics	Methods	Outcome	Influencing factors	Remarks
Jørgensen et al (2013) (67)[a]	Scandinavia	N: 42 Mean age: 28.5 years Sex: 21M, 21F BMI: 28.1 kg/m^2 Genotype: NA GHt: no GHt at least 12 months before study, none during adulthood SHRT: 43%M, 29%F, not started at least 12 months before study	Randomized controlled double blind for GHt vs placebo for 12 months, open label GHt for additional 24 months Blood samples were collected for biochemical essay	At baseline: P1NP was at the high end of normal (73.8 ± 36.6 µg/L), osteocalcin was low (4.1 ± 2.8 µg/L), cross-linked *N*-telopeptides of type I collagen was in the upper range of expected (20.7 ± 6.2 nM)	GHt for 12 months increased P1NP levels ($P < .001$) and normalized osteocalcin levels ($P < .05$). Cross-linked *N*-telopeptides of type I collagen did not change significantly	Patients lost-to-follow-up were excluded from analysis
Longhi et al (2015) (70)[a]	Italy	N: 41 Mean age: 29.4 years Sex: 17M, 24F BMI: males 41.6 kg/m^2, females 41.2 kg/m^2 Genotype: 33 del, 8 mUPD GHt: 34% current, 22% past SHRT: 6%M, 54%F	Cross-sectional study. Controls matched for age and sex. Blood samples were taken for 25(OH) vitamin D, intact PTH and BAP measurements	Vitamin D levels of Patients with PWS were significantly lower than controls (19.8 ± 9.7 vs 36.2 ± 16.7 µg/L, $P < .01$) patients with PWS showed significantly higher value of BAP (15.1 ± 7.7 vs 12.2 ± 3.8 µg/L, $P < .05$) than controls	—	Control group had a lower BMI (mean BMI 24.5 kg/m^2 in males and 21.1 kg/m^2 in females) than patients with PWS Use of vitamin D supplements unknown
Purtell et al (2016) (29)	Australia	N: 10 Mean age: 27.9 years Sex: NA Mean BMI: 37.0 kg/m^2 Genotype: NA GHt: 0%	Cross-sectional study. Blood samples were taken for analysis 2 control groups: 1 obese (n = 12) and 1 lean (n = 10) group	No significant differences between 25(OH) vitamin D levels between the lean (23.4 ± 4.4 ng/mL), obese (18.6 ± 3.1 ng/mL) and PWS group (12.7 ± 1.5 ng/mL). The mean vitamin D level in PWS was in the range of mild to moderate vitamin D deficiency	—	Unknown if any individuals used vitamin D supplements
Brunetti et al (2018) (78)	Italy	N: 14 Mean age: 29.5 years (SD 7.2 years) Sex: 5M, 9F Mean BMI: 44.6 kg/m^2 Genotype: 12 del, 2 mUPD GHt: 43% SHRT: 0%M, 43%F	Cross-sectional study. Venous blood samples were collected to assess blood values BMD assessed by DXA scan 15 normal weight controls matched for sex and age	25(OH) vitamin D (ng/mL), osteocalcin (ng/mL), OPG (pg/mL) and sclerostin (pg/mL) levels significantly lower in adults with PWS than in controls (25.17 ± 11.83 vs 35.2 ± 5.8, $P < .001$, 7.91 ± 7.94 vs 21.3 ± 3.21, $P < .01$, 317.2 ± 77.5 vs 443.5 ± 116, $P < .006$ and 1298 ± 318 vs 1906 ± 698, $P < .01$ respectively) RANKL (pg/mL) significantly higher in adults with PWS than controls (77.5 ± 42.2 vs 51.8 ± 20.9, $P < .004$). However, this was no longer significant after correction for GHt and SHRT CTX and DKK-1 were not significantly different between PWS and controls	Multivariate analysis showed no correlation between RANKL and T-score of lumbar spine BMD (β = −0.033, $P = .134$) but a positive correlation between OPG and T-score of lumbar spine BMD (β = 1.521, $P = .0001$) and sclerostin and T-score of lumbar spine BMD (β = 0.331, $P = .0001$)	Patients and controls who used vitamin D or mineral supplements, had chronic diseases impacting bone metabolism, used medications affecting bone turnover, or had a fracture in the 6 months preceding the study were excluded
Baraghithy et al (2019) (73)	Israel	N: 30 Mean age: 29.9 years Sex: 18M, 12F Mean BMI: 28.4 kg/m^2 Genotype: 16 del, 13 mUPD, 1 ICD GHt: NA SHRT: NA	Cross-sectional study. Measurement of *N*-oleoyl serine, 25(OH) vitamin D, calcium, alkaline phosphatase and phosphatase in venous blood. Assessment of Z-scores by DXA scan	Vitamin D levels in PWS were 74.5 ± 79.3 ng/mL *N*-oleoyl serine was significantly lower in PWS than in controls (1.4 ± 0.7 pmol/mL vs 2.4 ± 0.95 pmol/mL, $P < .001$) No significant differences in 25(OH) vitamin D, calcium, alkaline phosphatase, and phosphatase between patients with and without PWS	*N*-oleoyl serine was positively associated with Z-scores of femoral neck (r = 0.405, $P = .0018$), total hip (r = 0.439, $P = .0007$), lumbar spine (r = 0.296, $P = .0251$) and forearm (r = 0.349, $P = .0186$)	Use of vitamin D supplements unknown.
Barrea et al (2020) (79)	Italy	N: 15 Mean age: 28 years (range 19-41 years) Sex: 6M, 9F Mean BMI: 44 kg/m^2 Genotype: NA GHt: none current, 100% past	Cross-sectional study. Data collected by interview, physical examination and biochemical essays Compared with 15 age-, sex-, and BMI-matched controls	Vitamin D deficiency: 15/15 (100%) Dietary vitamin D intake was significantly lower in adults with PWS than controls (4 ± 1 µg/1.000 kcal vs 5 ± 1 µg/1.000 kcal, $P = .01$). 25(OH) vitamin D in adults with	25(OH) vitamin D levels were significantly associated with BMI (r = −0.52, $P = .04$), waist circumference (r = −0.56, $P = .03$), fat mass (r = −0.52, $P = .04$), and dietary vitamin D intake (r = 0.91, $P < .001$)	Many exclusion criteria, including current therapy with calcium, osteoporosis therapies, and medications that may affect vitamin absorption of metabolism like SHRT

(*continued*)

Table 7. Continued

Author (year)	Country	Patient characteristics	Methods	Outcome	Influencing factors	Remarks
				PWS significantly lower than controls (22 ± 7 vs 35 ± 10, $P = .001$), regardless of BMI or fat mass category		Inclusion period October to March
Damen et al (2021) (74)[a]	NL	N: 43 Mean age (range): 19.5 years (18.7-20.7) for males and 18.4 years (15.8-23.8) for females Sex: 18M, 25F Mean BMI: 24.5 kg/m^2 Genotype: 18 del, 20 mUPD, 4 ICD, 1 translocation Hypogonadism: 93% SHRT: 83% Hypogonadal without SHRT: 16%	Open-label, prospective cohort study, patients received GHt during 3 years Biochemical measurement from blood samples	25(OH) vitamin D levels at baseline (mean [range]): 66.0 (55.3-88.8) nmol/L	No significant difference was found in 25(OH) vitamin D levels after 3 years of GHt	All patients had received GHt for at least 5 years during childhood
Faienza et al (2021) (66)[a]	Italy	N: 52 Mean age: 30.6 years (SD 10.7 years) Sex: 22M, 30F Median BMI: 35.3 kg/m^2 Genotype: 32 del, 20 mUPD GHt: 6 SHRT: 5%M, 33%F Vitamin D: 50% supplementation	Cross-sectional study. Biochemical measurement from blood samples and DXA scans to asses BMD Compared with 54 normal weight adult controls	25(OH) vitamin D: Median (IQR) vitamin D level in adults with PWS was 28.8 (9.2) ng/mL Irisin: No significant difference between Adults with PWS and controls (6.65 ± 4.49 µg/mL vs 7.24 ± 5.20 µg/mL)	After adjusting for age, irisin in adults with PWS the best predictors for irisin levels were the genetic background ($\beta = -0.365$, $P = .0001$), 25(OH) vitamin D levels ($\beta = 0.346$, $P = .0001$), GHt ($\beta = -0.139$, $P = .0001$), age at start ($\beta = -0.317$, $P = .0001$) and duration of GHt ($\beta = -0.139$, $P = .0001$ age at start of SHRT ($\beta = -0.324$, $P = .0001$), IQ ($\beta = 0.910$, $P = .0001$) and total body BMD adjusted for height ($\beta = 0.412$, $P = .0001$) 25(OH) vitamin D: No significant difference between 25(OH) vitamin D levels of adults with deletion and mUPD genotype (31.6 ± 9.2 vs 28.7 ± 10.5 ng/mL) Irisin: Significantly reduced in del compared with controls ($P < .04$), but not in mUPD compared with controls Patients with PWS without vitamin D supplementation had a significant reduction in irisin compared with controls ($P < .001$) and patients with supplementation ($P < .02$), for both the del ($P < .004$) and mUPD ($P < .001$) genotype	Controls are normal weight adults, while irisin is also released from adipose tissue Exclusion criteria: use of mineral or vitamin supplements (except for vitamin D), presence of chronic diseases with possible impact on bone metabolism, use of medication affecting bone turnover and fractures in the 6 months preceding the study Study population might overlap with Brunetti et al (78)
Casamitjana et al (2022) (80)	Spain	N: 27 Median age: 26 years (all >18 years) Sex: 12M, 15F Median BMI: 34.5 kg/m^2 Genotype: 18 del, 6 mUPD, 3 ICD GHt: 0% at baseline SHRT: 8 M, 7F	Cohort study with GHt for 12 months in the adults with PWS Fasting blood samples were collected for biochemical essay Control group: 22 volunteers from hospital staff or acquaintances, median age 27.5 years, 13 women	At baseline: Median (IQR): Irisin was 982.3 (519.4-1789.6) ng/mL in adults with PWS compared with 89.8 (41.8-219.4) ng/mL in controls ($P < .0001$) Myostatin and IL-6 did not differ significantly between Adults with PWS and controls ($P > .05$)	After 12 months of GHt the median (IQR) irisin level was 906.8 (583.5-1770.4) ng/mL ($P = .76$ compared to baseline) No significant change was observed for myostatin and IL-6 ($P > .05$ for both)	—

Data are presented as mean ± SD, unless otherwise specified. When articles reported subgroup analysis for adults and children or patients >16 years old and patients <16 years old, only information for the adults or patients >16 years old are reported here whenever possible.

Abbreviations: BMI, body mass index; BAP, bone alkaline phosphatase; BMD, bone mineral density; CTX-1, C-terminal telopeptide of type I collagen; del, deletion; DKK-1, Dickkopf-1; DXA, dual-energy X-ray absorptiometry; F, females; GHt, growth hormone treatment; M, males; mUPD, maternal uniparental disomy; N, number of patients; NA, not available; P1NP, *N*-terminal propeptide of type I procollagen; OPG, osteoprotegerin; RANKL, receptor activator of nuclear factor-κB ligand; SHRT, sex hormone replacement therapy; 25(OH) vitamin D, 25-hydroxy vitamin D.

[a]Partly overlapping study population as current study.

Table 8. Results of studies reporting on scoliosis and other orthopedic conditions in adults with Prader–Willi syndrome

Author (year)	Country	Patient characteristics	Methods	Prevalence scoliosis and orthopedic conditions	Influencing factors	Remarks
Holm et al (1981) (35)	USA	N: 10 Mean age: 28 years (range 20-41 years) Sex: 6M, 4F BMI: NA Genotype: NA GHt: NA	Cross-sectional study. Cobb angle of ≥10° on spinal X-ray	Scoliosis: 10/10 (100%). Average Cobb angle: 22.5° Kyphosis: 5/10 (50%) Mean curve kyphosis: 61°	—	Diagnosis PWS based on clinical criteria instead of genetic tests
Partsch et al (2000) (81)	Germany	N: 19 Mean age: 23 years (range 18-34 years) Sex: 7M, 12F Mean BMI 46 kg/m^2, range 31-74 kg/m^2 Genotype: All deletion or mUPD GHt: 0%	Cross-sectional study. Data collection from patient records	Scoliosis: 7/19 (37%) Kyphosis: 19/19 (100%) Gonarthrosis: 1/19 (5%)	—	Unknown whether spinal X-ray was performed
Butler et al (2002) (11)	UK	N: 58 (information about scoliosis known for 56) Age range: 18-46 years Sex: 32M, 26F Mean BMI: 35 kg/m^2 Genotype: NA GHt: NA	Cross-sectional study. Semistructured interview with family or carers	Suspected scoliosis/kyphosis: 23/56 (41%) Scoliosis observed by a professional: 19/56 (34%) Serious scoliosis or intervention for scoliosis: 7/56 (13%)	Scoliosis more prevalent in females than in males (1.23:1 and 2.3:1 for severe deformity). BMI not significantly associated with scoliosis	Not all cases with PWS were genetically confirmed. No spinal X-ray
Nakamura et al (2009) (39)	Japan	N: 34 Age range: 16-50 years Sex: 67M, 34F[b] BMI: NA Genotype: 80 del, 21 no del[b] GHt: 57%[b]	Retrospective cohort study. Cobb angle of ≥10° on spinal X-ray	Scoliosis: 16/34 (47%). Mean Cobb angle: 27° Severe scoliosis: 3/34 (9%) Surgery for scoliosis: 1/34 (3%)	Genotype and GHt were not significantly associated (analysis in entire group of children and adults)	—
Sode-Carlsen et al (2011) (64)[a]	Scandinavia	N: 43 Mean age: 29.5 years (range 16-42) Sex: 19M, 24F Mean (SD) BMI at baseline 28.9 (19.4-44.8) kg/m^2 Genotype: NA SHRT: 47%M, 25%F	Multicenter international RCT. GHt vs placebo for 1 year, followed by open-label GHt for all patients for 1 year (GHt group) or 2 years (placebo group), until all patients had received GHt for 2 years in total Scoliosis evaluated by spinal X-ray and defined as Cobb angle >10° and progression as a change of ≥+5° change in Cobb angle	Scoliosis: 23/38 (61%) Median Cobb angle: 13° Operation for scoliosis: 2/38 (5%)	After 2 years of GHt, 6 patients (16%) showed progression of scoliosis and 3 (8%) showed a decrease of Cobb angle >5°	Unknown GHt prior to study, but none was treated for at least 1 year preceding the study 4 patients did not complete the study
Sinnema et al (2011) (10) and Sinnema et al (2013) (82)[a]	NL	N: 102 Mean age: 36 years (range 18-66 years) Sex: 49M, 53F Mean BMI: 32 kg/m^2 (range 17-52 kg/m^2) Genotype: 55 del, 44 mUPD, 3 ICD GHt: 5% current, 8% past	Cross-sectional study. Semistructured interviews with caregivers and review of medical files	Scoliosis: 57/102 (56%) Foot problems: 81/102 (79%) Knee problems: 6/102 (6%) Hip problems: 9/102 (9%) Surgery for musculoskeletal conditions: 28/102 (27%) Of which: Surgery for scoliosis: 11/102 (11%) Hip surgery: 4/102 (4%)	Patients with a deletion had more knee problems than other genotypes (11% vs 0%, $P = .02$), there was no difference in scoliosis, foot problems or hip problems BMI and age were not associated to any orthopedic conditions	Unknown if scoliosis was confirmed by spinal X-ray in all cases

(*continued*)

Table 8. Continued

Author (year)	Country	Patient characteristics	Methods	Prevalence scoliosis and orthopedic conditions	Influencing factors	Remarks
				Arthroscopy: 4/102 (4%) Knee surgery: 3/102 (3%) Osteosynthesis: 3/102 (3%) Foot surgery: 3/102 (3%)		
Laurier et al (2015) (37)[a]	France	N: 154 Mean age: 28 years (range 16-54 years) Sex: 68M, 86F Mean BMI ± SD: 42 ± 11 kg/m^2 Genotype: 101 del, 24 mUPD, 3 ICD, 3 translocation, 18 AMP non del, 5 AMP GHt 14% current, 24% past	Cross-sectional study. Spinal X-ray	Scoliosis: 95/126 (75%)	No association with genotype (del vs mUPD) or age	—
Coupaye et al (2016) (84)[a]	France	N: 73 Mean age: 25 years (range 16-58 years) Sex: 35M, 38F Mean BMI ± SD: del-group: 41 ± 11 kg/m^2 mUPD-group: 35 ± 10 kg/m^2 Genotype: 47 del, 26 mUPD GHt: 15% current, 36% past	Cross-sectional study. Systematic examination at outpatient clinic	Scoliosis: 57/73 (78%) Severe/operated scoliosis: 16/73 (22%)	No association between scoliosis and genotype, but severe/operated scoliosis was more prevalent in mUPD (9/26, 35%) than del (7/47, 15%, $P = .047$)	Unknown if spinal X-rays were performed
Woods et al (2018) (83)	USA	N: 19 Mean age: 34.5 (range 18-62 years) Sex: 11M, 8F Mean BMI: 27 kg/m^2 (range 19.5-35.0 kg/m^2) Genotype: NA GHt: NA	Cross-sectional study. Questionnaires filled in by guardians or caregivers	Scoliosis: 1/19 (5%)	—	Unknown if PWS was genetically confirmed
Pellikaan et al (2020) (8)[a]	NL	N: 115 Median age: 29 years (range 18-72 years) Sex: 56M, 59F Median BMI: 29 kg/m^2 (IQR 26-35 kg/m^2) Genotype: 64 del, 41 mUPD, 3 ICD, 7 unknown GHt: 36% current	Cross-sectional study Spinal X-ray if gibbus deformity present during physical examination	Scoliosis after systematic screening: 83/112[c] (74%) Scoliosis was undiagnosed before systematic health screening in 22 (20%) patients	Scoliosis was more frequent in patients with an mUPD (59%) than with a deletion (81%, $P = .02$). Scoliosis was not associated with BMI, age, sex, or living situation	—
Crinò et al (2022) (40)		N: 74 Age range: 18-50 years Sex: 34M, 40F Mean BMI ± SD: 36 ± 9 kg/m^2 Genotype: 46 del, 28 mUPD GHt: 53 current or past	Cross-sectional study Observation of the standing and sitting posture, Adam's forward bend test, and spinal X-ray	Scoliosis: 87.8%	—	—

(*continued*)

Table 8. Continued

Author (year)	Country	Patient characteristics	Methods	Prevalence scoliosis and orthopedic conditions	Influencing factors	Remarks
Noh et al (2022) (75)	Korea	N: 68 Age range: 19-34 years Sex: 39M, 29F Mean BMI: 35 kg/m^2 Genotype: 44 del, 24 other GHt: 48 previous, 10 current	Cross-sectional study. Data collection from patient records	Scoliosis: 41/68 (60%)	—	Unknown whether spinal X-ray was performed

Data are presented as mean ± SD, unless otherwise specified. When articles reported subgroup analysis for adults and children or patients >16 years old and patients <16 years old, only information for the adults or patients >16 years old are reported here whenever possible.
Abbreviations: AMP, abnormal methylation profile; BMI, body mass index; del, deletion; F, females; GHt, growth hormone treatment; IQR, interquartile range; M, males; mUPD, maternal uniparental disomy; N, number of patients; NA, not available.
[a]Study population partly overlapping with current study.
[b]Data for the entire cohort of 101 patients, which also included patients <16 years old.
[c]Scoliosis was missing for three patients.

more prevalent in adults with PWS with a deletion. However, Faienza et al (66) did not find a significant association between genotype and osteoporosis. Jørgensen et al (67) reported that Z-scores of men were significantly lower than those in women with PWS and that a BMI > 30 kg/m^2 was associated with a higher BMD. Van Nieuwpoort et al (68) reported that male sex was associated with lower lumbar spine T-scores. In this study, 87% of patients (both male and female) had hypogonadism, of whom 54% were treated with SHRT. Information on (the treatment of) hypogonadism was not given for males and females separately.

A prospective cohort study by Kido et al (69) found that testosterone replacement therapy increased BMD after 2 years. Donze et al (71) found a significant increase in SDS of total body BMD after 2 years of SHRT. However, Longhi et al (70) did not find an association between SHRT and BMD.

Growth Hormone Treatment in Relation to Bone Health

Table 6 shows the studies reporting on the effect of GHt on skeletal problems (osteoporosis and/or scoliosis). Previous literature remains controversial regarding the effects of GHt. Several studies (65, 71–76) did not find any significant effect of GHt on BMD. Other studies showed conflicting results (67, 77).

Vitamin D Levels and Bone Markers and Bone-related Factors

Table 7 summarizes the results of the studies that investigated 25(OH) vitamin D and the bone related factors irisin, *N*-terminal propeptide of type I procollagen (P1NP), osteocalcin, Receptor activator of nuclear factor-κB Ligand (RANKL), osteoprotegerin (OPG), and *N*-oleoyl serine in patients with PWS (66, 67, 73, 78).

Longhi et al (70) and Brunetti et al (78) found lower levels of vitamin D in adults with PWS than in controls. However, Purtell et al (29) did not find any association. According to Faienza et al (66) vitamin D levels were not related to genotype.

Scoliosis

According to our literature review, the prevalence of scoliosis in adults with PWS is 5% to 100% Table 8. The large variation in this prevalence could be explained by underestimation of the prevalence due to the use of interviews and/or questionnaires (without physical examination or X-ray) to diagnose scoliosis in some studies (10, 11, 81–83). Studies that systematically screened for scoliosis by physical examination and/or spinal X-ray reported a prevalence between 47% and 100%. Some studies reported a significantly higher prevalence of scoliosis in females (10, 11, 82) and patients with an mUPD (8). However, not all studies replicated these findings (10, 37, 39, 82, 84). Sode-Carlsen et al (64) found that 16% of patients receiving GHt had progression of scoliosis (ie, increase in the Cobb angle) and 8% had a decrease in the Cobb angle after 2 years of GHt.

Discussion

In this study, we showed that osteoporosis, osteopenia, and scoliosis are common skeletal problems in adults with PWS. Modifiable risk factors for osteoporosis such as hypogonadism, insufficient dairy intake, sedentary lifestyle, and corticosteroid use were often present, but we did not find modifiable risk factors for scoliosis.

The prevalence of osteoporosis found in this study is in line with previous studies in adults with PWS that showed a prevalence of 2% to 26% (8, 10–12, 75). However, not all studies performed a systematic screening for osteoporosis using DXA scans, likely leading to an underestimation of the true prevalence in these studies. Osteoporosis was more prevalent in males than in females, and this remained significant even after correction for age, height, weight, and genotype. In a previous study, males and females differed with regard to the use of psychotropic medication, which was slightly increased in males (85). As the use of some types of psychotropic medication is related to decreased BMD (86, 87), this might partly explain this difference. Fractures were more prevalent in males. Behavioral challenges are comparable between males and females, which

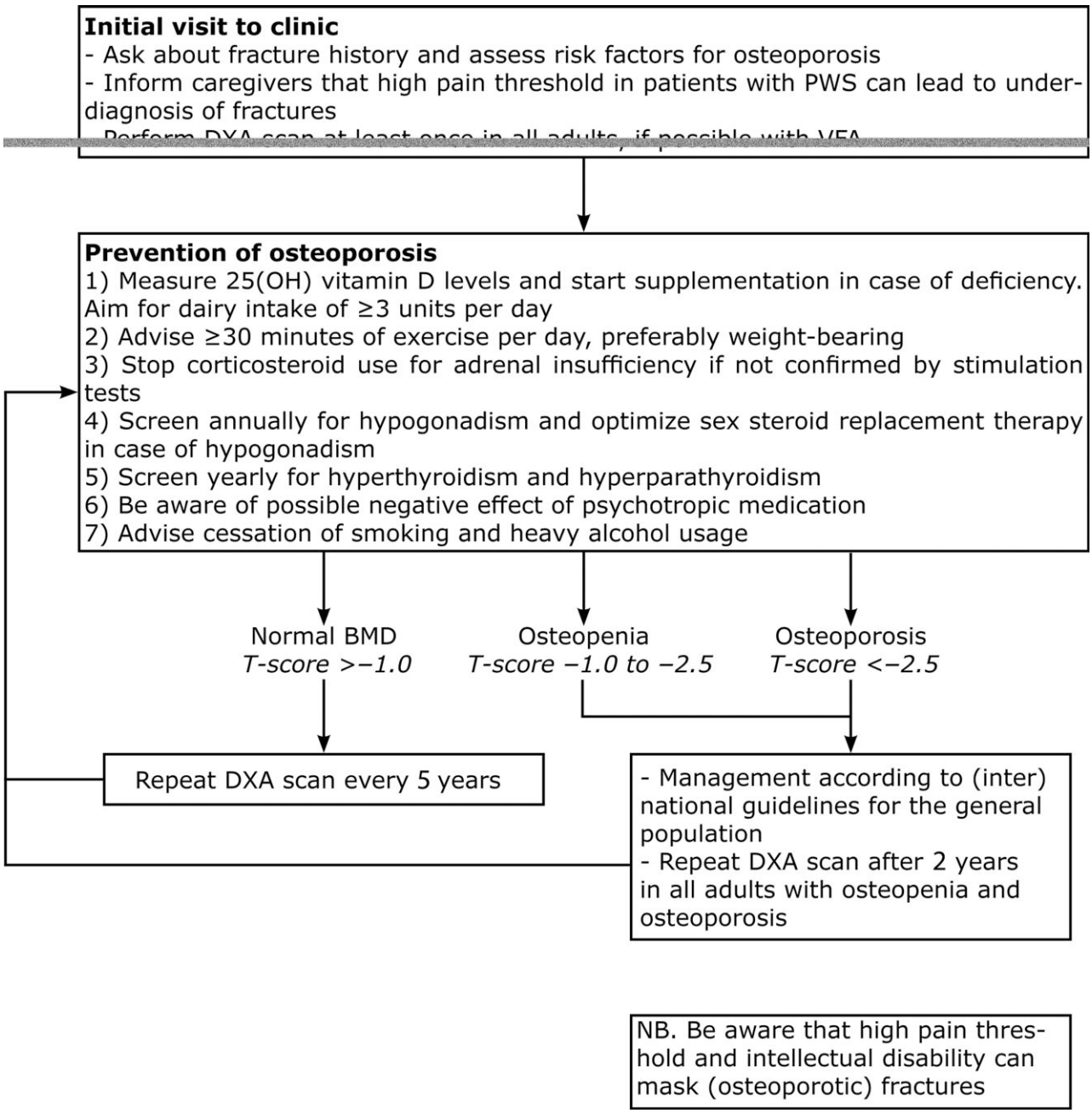

Figure 1. Recommendations for the prevention, detection, and treatment of osteoporosis in adults with PWS (49, 95, 96). Abbreviations: DXA, dual-energy X-ray absorptiometry; PWS, Prader–Willi syndrome; VFA, vertebral fracture assessment.

suggests that the increased risk of fractures in males is not due to temper outburst (88, 89).

GHt may increase BMD and decrease the risk of osteoporosis in patients with PWS (77), although results are inconclusive (65, 67, 70, 76, 82). In our study, GHt was not associated with a decreased risk of osteoporosis. However, Longhi et al showed that adults with PWS have unfavorable bone geometry and reduced bone strength, leading to an increased risk of fractures independent of BMD. GHt improves bone geometry, possibly reducing fracture risk without increasing BMD (70).

Risk factors for osteoporosis were prevalent. However, in our cohort many well-known risk factors for osteoporosis were not significantly related to osteoporosis or osteopenia. This is could be caused by lack of statistical power due to early treatment of risk factors such as hypogonadism or hyperthyroidism, leading to small numbers of untreated patients. Additionally, some risk factors were rare, also resulting in low statistical power.

In our cohort, vertebral fractures were found in 3%, which is similar to the prevalence found by Waterloo et al (90) for vertebral fractures in the general population before the age of 60. However, the patients in our cohort were relatively young with a median age of only 31 years (IQR 25-40), with only a few patients who were above 50 years old. Therefore, we were not able to investigate the prevalence of fractures in older adults. Moreover, data on vertebral fracture assessments were not available for all patients, possibly leading to an underestimation.

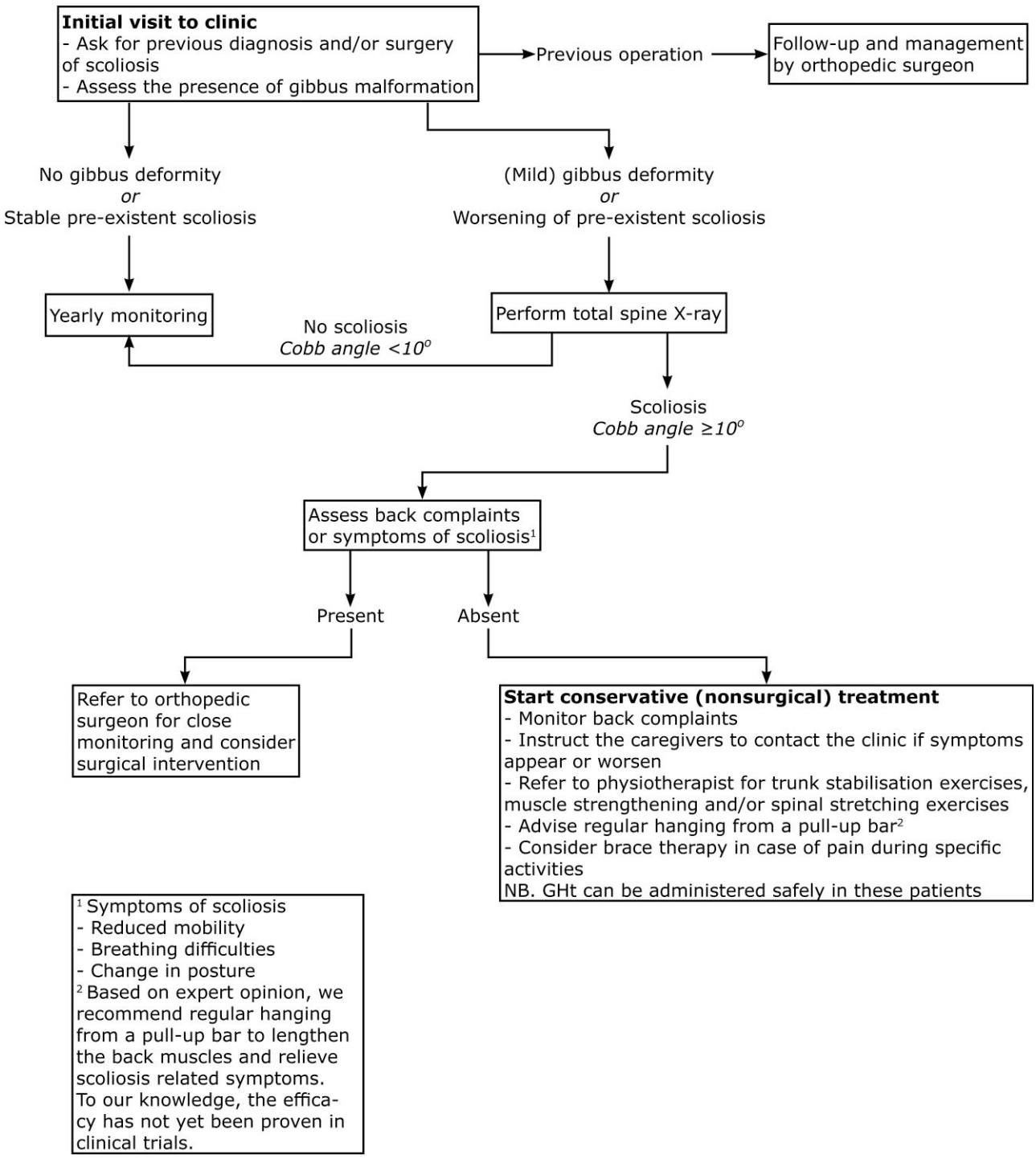

Figure 2. Recommendations for the detection, monitoring of progression, and treatment of scoliosis in adults with PWS (97–9997–99). Abbreviation: GHt, growth hormone therapy.

The prevalence of scoliosis found in this study was 80%. Previous research reported a prevalence of scoliosis between 5% and 100% (Table 8). Scoliosis is thought to be related to obesity and hypotonia of (paravertebral) muscles (35, 38). However, in our cohort, scoliosis was not significantly related to BMI and hypotonia was not assessed. According to Burwell et al, childhood GHt could be related to an increased risk of scoliosis due to increased growth velocity (91). Sode-Carlson et al found a progression of the Cobb angle of >5° in 16% of patients with PWS after 2 years of GHt, although no control group was available (64). However, in our study, childhood GHt was not associated with scoliosis. This is in line with previous pediatric studies that reported no effect of GHt on onset of scoliosis, curve progression or need for surgery in patients with PWS (38, 92, 93).

Although the median age of our cohort was only 31 years, we already found a high prevalence of osteoporosis (14%) and osteopenia (54%). Due to improved health care, life expectancy of patients with PWS has drastically increased (94). Therefore, early prevention and detection is crucial to prevent complications later in life.

Clinical Recommendations

Due to the complexity of the syndrome, patients with PWS are preferably treated in a PWS reference center. However, reference centers are not always available. Therefore, we have defined practical clinical recommendations for the optimization of skeletal health in adults with PWS (Figs. 1 and 2) that can be used in any clinical setting.

We recommend screening for osteoporosis and scoliosis in all adults with PWS and assessing risk factors for osteoporosis. The screening should consist of a DXA scan (if possible, with vertebral fracture assessment) every 5 years in patients with normal BMD on the previous DXA scan and every 2 years in patients with osteopenia or osteoporosis. For scoliosis, yearly evaluation should be performed. We want to stress the fact that osteoporotic fractures can be easily missed due to the high pain threshold and intellectual disability often present in patients with PWS. Preventive measures to avoid the development of osteoporosis in adults with PWS include (1) optimizing calcium and vitamin D intake, (2) optimizing physical activity, (3) avoidance of unnecessary use of corticosteroids, (4) yearly screening for (and treatment of) hypogonadism, (5) yearly screening for hyperthyroidism and hyperparathyroidism, (6) extra caution in patients using psychotropic medication, and (7) cessation of smoking and alcohol use.

Recommendation 1: Optimizing Calcium and Vitamin D Intake

In our study, we showed that 78% of participants used vitamin D supplements and 14% had a dairy intake of ≥3 units/day. Vitamin D has a direct effect on osteocytes, osteoblasts, and osteoclasts and regulates calcium and phosphate metabolism (100, 101). In the general population, vitamin D deficiency increases the risk of osteoporosis and studies with vitamin D supplementation show a reduced fracture risk and increased BMD (102, 103). We did not find a difference in 25(OH) vitamin D levels or vitamin D supplementation between patients with and without osteoporosis, probably due to lack of power as few patients had low vitamin D levels and many patients already received vitamin D supplementation. However, previous studies reported reduced vitamin D levels in adults with PWS, especially in those with obesity (70, 78, 79). The reduced 25(OH) vitamin D levels could be related to reduced exposure to sunshine and an increased volume of distribution in adipose patients as vitamin D is fat soluble (104). We recommend yearly measurement of 25(OH) vitamin D levels in all adults with PWS not receiving vitamin D supplementation. We recommend starting vitamin D supplementation in patients with PWS with a vitamin D level below the reference, irrespective of DXA scan results. Additionally, we recommend a dairy intake of ≥3 units a day or calcium supplementation to ensure adequate calcium intake.

Recommendation 2: Optimizing Physical Activity

Many patients (39%) in our cohort exercised less than 30 minutes a day. In nonsyndromic pre- and postmenopausal women with osteoporosis, physical activity is known to improve bone mineral content and BMD, provided enough nutrients, calcium, and vitamin D are available (105). In children with PWS, Duran et al (26, 106) showed a positive association between moderate weight-bearing physical activity and hip BMD. The effect of physical activity on BMD in adults with PWS has, to our knowledge, not yet been studied in clinical trials. However, beside the (expected) possible positive effects on BMD, regular exercise is also important in patients with PWS to decrease body fat mass, increase lean body mass, and improve coordination to decrease fall risk (25). Therefore, we recommend regular physical activity of at least 30 minutes, but ideally at least 1 hour daily, preferably weight-bearing in order to maintain and possibly improve BMD and body composition. We also recommend aerobic and muscle strengthening exercises, but we realize this might be difficult due to hypotonia and challenging behavior.

Recommendation 3: Avoidance of Unnecessary Corticosteroid use in Central Adrenal Insufficiency

One in 10 adults in our cohort used corticosteroid replacement, mostly only during physical or psychological stress. Few patients had proven central adrenal insufficiency; most patients received corticosteroids as part of local guidelines for the treatment of PWS.

Corticosteroid-induced osteoporosis is the most common cause of secondary osteoporosis in the general population (107, 108). Glucocorticoid use increases the risk of fractures (109, 110), which can occur as early as 3 months after start of corticosteroids and even with low doses of steroids (eg, 2.5-7.5 mg of prednisone daily) (111). In our clinical experience, when adults with PWS are prescribed corticosteroid stress doses, these stress doses are sometimes frequently administered due to recurrent episodes of psychological stress. As we previously showed that central adrenal insufficiency is rare in adults with PWS (1.2%) (112), we strongly recommend refraining from routine corticosteroid "stress-doses" in adults with PWS. In order to prevent secondary osteoporosis due to corticosteroid use, we advise only prescribing corticosteroids when central adrenal insufficiency is proven.

Recommendation 4: Yearly Screening for (and Treatment of) Hypogonadism

Hypogonadism was prevalent in both males (93%) and females (86%). Hypogonadism is a well-known risk factor for osteoporosis and timely treatment with hormone replacement therapy can reduce this risk (113–115). In this study we did not find an association between hypogonadism or SHRT and osteoporosis. However, as all patients were treated in a PWS reference center, untreated hypogonadism was rare, resulting in low statistical power. Previous research has shown a significant improvement in BMD in men (69) and women (71) with PWS after the start of SHRT. Therefore, we recommend yearly screening for hypogonadism. If hypogonadism is present, adequate SHRT should be started as soon as possible to avoid the negative effects of hypogonadism on BMD (69, 70). As starting and maintaining SHRT can be challenging, we have previously defined practical recommendations for hormone replacement therapy in males (15) and females (16).

Recommendation 5: Yearly Screening for Hyperthyroidism and Primary Hyperparathyroidism

The prevalence of hyperthyroidism in this study was 1.1%, which is similar to the prevalence in the general population in Europe (<1%) and the United States (1.3%) (116, 117). The prevalence of primary hyperparathyroidism found in the current study was 0.8%, which is in line with prevalence in the general adult population (0.1-0.7%) (118–121). Patients with PWS are already at risk of developing

osteoporosis and they might be unable to express the subtle complaints of hyperthyroidism and hyperparathyroidism due to intellectual disability. Therefore, we recommend yearly screening for hyperthyroidism and hyperparathyroidism by measuring thyroid-stimulating hormone, free thyroxine, and serum calcium levels. In case of hypercalcemia, parathyroid hormone (PTH) should also be measured. Depending on local hospital policy and the costs of PTH measurement, yearly (simultaneous) screening for both calcium and PTH could also be performed.

Recommendation 6: Extra Caution in Patients Using Psychotropic Medication

Psychiatric disorders, such as manic or depressive episodes with psychotic features are common in PWS, with an estimated prevalence of 16% to 28% (122–125). Psychotic features are most common in patients with an mUPD (122–125). Most psychotropic medications, such as selective serotonin reuptake inhibitors, benzodiazepines, tricyclic antidepressants, and conventional antipsychotics (eg, haloperidol) have been associated with an increased (osteoporotic) fracture risk in the general population (126–131). Furthermore, selective serotonin reuptake inhibitors, benzodiazepines, and atypical antipsychotics (eg, risperidone, clozapine) have been associated with a higher osteoporosis risk, though tricyclic antidepressants might reduce the risk for osteoporosis (86). It has been suggested that use of conventional antipsychotics may cause higher prolactin levels, possibly leading to hypogonadism and osteoporosis (131). There is conflicting evidence regarding the effect on BMD of antipsychotics that do not raise prolactin levels (132). The relationship between osteoporosis and the use of psychotropic medication in adults with PWS is still unknown. As current evidence is scarce, we suggest performing a DXA scan every 5 years in adults with PWS who are taking psychotropic medication, just like in adults who do not use psychotropic medication. We advise continuing psychotropic treatment as long as it is indicated, regardless of the BMD.

Recommendation 7: Cessation of Smoking and Alcohol use

In our cohort, there was no relation between alcohol usage and osteoporosis. However, adults with osteoporosis smoked significantly more cigarettes per week than those without osteoporosis. In the general population, smoking has been associated with low BMD (133–135) and increased fracture risk (133, 136). Cessation of smoking has been shown to increase BMD (137–139). Furthermore, chronic heavy alcohol usage has been associated with decreased BMD (140, 141). In contrast, light to moderate alcohol consumption might increase BMD in females (141, 142). We recommend that smoking and heavy alcohol usage is discouraged in all adults with PWS.

Awareness of High Pain Threshold and Intellectual Disability

Patients with PWS seldomly report pain. This can be due to their high pain threshold and intellectual disability (6, 143), which may impair their ability to express physical complaints. This may lead to delay in the diagnosis of (osteoporotic) fractures. In our cohort, several fractures had remained unnoticed for weeks, as the only symptoms had been change of behavior or walking pattern (personal communications). Therefore, it is important to keep in mind that patients with PWS may have an atypical presentation of fractures. Thorough physical examination should be performed in case of unexplained behavioral changes or refusal of physical activities to exclude underlying physical problems such as undiagnosed fractures. Additionally, when a DXA scan is performed, preferably a vertebral fracture assessment should also be performed to exclude undiagnosed vertebral fractures.

Yearly Screening for Scoliosis and Other Orthopedic Conditions

We recommend clinical assessment of scoliosis in all patients with PWS during yearly physical examination. Furthermore, we recommend that a standing full spine posterior-anterior X-ray is performed in case of doubt, progression, or when spine deformity surgery is considered (see Fig. 2). When scoliosis and low BMD are both present, complications of surgery such as iatrogenic instability and postoperative fractures are more prevalent (144, 145). Therefore, surgical correction of scoliosis is more challenging in patients with low BMD. Besides scoliosis, patients with PWS also have an increased risk of other orthopedic conditions, such as hip dysplasia, genu valgum, and kyphosis (146). In case of suspect kyphosis, a lateral view total spine X-ray should be performed. These conditions were not systematically documented in the medical records and could not be investigated in this retrospective study.

Strengths and Limitations

The current study is, to our knowledge, the first multicenter study on osteoporosis including more than 300 adults with PWS. We were able to assess not only the prevalence of scoliosis and osteoporosis, but also the risk factors for osteoporosis in this rare genetic syndrome. Additionally, we performed an extensive literature review on both osteoporosis and scoliosis in adults with PWS. However, our study also has some limitations. First, as data were collected retrospectively from patient records in different centers, screening and treatment protocols varied between centers. In particular, the assessment of vertebral fractures varied between centers, possibly leading to underdiagnosis of asymptomatic vertebral fractures in some centers. In some centers, DXA scans were only performed when risk factors for osteoporosis were present. As we only included patients for whom DXA scans results were available, the prevalence of osteoporosis and osteopenia we report might be an overestimation. Second, scoliosis was not systematically assessed using standing full spine X-rays in all patients, possibly leading to an underestimation of scoliosis prevalence. Third, as this was an international study, different DXA machines were used. To compare the results of different machines, the sBMD was calculated for all DXA scan results. However, earlier research has shown that a small bias might remain (147). Furthermore, the results could have been influenced by obesity, which might lead to an overestimation of BMD (12, 148). Moreover, previous research has shown that the true BMD might be underestimated in subjects with short stature (12, 149). As the median height in our cohort was 1.56 (IQR 1.49-1.64) meters, our reported prevalence of osteoporosis and osteopenia might be an overestimation. Uniform prospective studies are needed to overcome these limitations and to prospectively assess the fracture incidence.

Conclusion

In conclusion, osteoporosis, fractures, and scoliosis are common skeletal problems in adults with PWS. Male sex was associated with a higher prevalence of osteoporosis. In our cohort, the most prevalent modifiable risk factors for osteoporosis were (male and female) hypogonadism, insufficient dairy intake, sedentary lifestyle, and corticosteroid treatment. We did not identify any risk factors for scoliosis. In particular, GHt was not associated with scoliosis. Based on the cohort study and literature review, we provide practical clinical recommendations to prevent complications in this vulnerable patient population.

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Author Contributions

Conceptualization, K.P. and L.C.G.d.G.; methodology, D.v.A., K.P., and L.C.G.d.G.; formal analysis, D.v.A; investigation, D.v.A, K.P., M.C., C.H., T.M., G.G., A.C. (Antonino Crinò), A.C. (Assumpta Caixàs), C.P., H.M., T.W., and L.C.G.d.G.; resources, M.C., C.H., T.M., G.G., A.C. (Antonino Crinò), A.C. (Assumpta Caixàs), C.P., H.M., T.W., and L.C.G.d.G.; data curation D.v.A; writing—original draft preparation, D.v.A. and K.P.; writing—review and editing, all authors; visualization: D.v.A.; supervision, L.C.G.d.G. and A.J.v.d.L.; project administration, D.v.A., K.P., and L.C.G.d.G. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors have no conflict of interest to disclose.

Data Availability

The datasets used for analysis in this study are not published, however, they are available from the corresponding author on request.

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