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Santen, S.S. van; Olsson, D.S.; Hammarstrand, C.; Wijnen, M.; Fiocco, M.; Heuvel-Eibrink, M.M. van den; ... ; Neggers, S.J.C.M.M.

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Body Composition and Bone Mineral Density in Craniopharyngioma Patients: A Longitudinal Study Over 10 Years

Selveta S. van Santen,[1,2,5] Daniel S. Olsson,[3,4] Casper Hammarstrand,[3,4] Mark Wijnen,[1,2] Marta Fiocco,[5,6,7] Marry M. van den Heuvel-Eibrink,[2,5] Gudmundur Johannsson,[3] Joseph AMJL Janssen,[1] Aart J van der Lely,[1] and Sebastian J.C.M.M. Neggers[1,2,5]

[1]Department of Medicine, Endocrinology; Erasmus Medical Center, Rotterdam, The Netherlands; [2]Department of Paediatric Oncology/Haematology, Erasmus MC—Sophia Children's Hospital, Rotterdam, The Netherlands; [3]Department of Medicine, Endocrinology; Sahlgrenska University Hospital, Gothenburg, Sweden; [4]Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [5]Princess Máxima Center for Paediatric Oncology, Utrecht, The Netherlands; [6]Mathematical Institute, Leiden University, Leiden, The Netherlands; and [7]Department of Biomedical Data Sciences, Medical Statistics Section, Leiden University Medical Center, Leiden, The Netherlands

ORCiD numbers: 0000-0001-8818-6759 (S. S. van Santen); 0000-0002-9734-0786 (D. S. Olsson); 0000-0001-7294-413X (C. Hammarstrand); 0000-0002-7760-879X (M. M. van den Heuvel-Eibrink); 0000-0003-3484-8440 (G. Johannsson).

Abbreviations: AO, adulthood onset; BF%, body fat percentage; BMD, bone mineral density; BMI, body mass index; CO, childhood onset; CP, craniopharyngioma; DI, diabetes insipidus; DXA, dual X-ray absorptiometry; FMI, fat mass index; FFMI, fat free mass index; GHRT, growth hormone replacement therapy.

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Abstract

Context: Patients with craniopharyngioma suffer from obesity and impaired bone health. Little is known about longitudinal changes in body composition and bone mineral density (BMD).
Objective: To describe body composition and BMD (change).
Design: Retrospective longitudinal study.
Setting: Two Dutch/Swedish referral centers.
Patients: Patients with craniopharyngioma (n = 112) with a dual X-ray absorptiometry (DXA) scan available (2 DXA scans, n = 86; median Δtime 10.0 years; range 0.4-23.3) at age ≥ 18 years (58 [52%] male, 50 [45%] childhood onset).
Main outcome measures: Longitudinal changes of body composition and BMD, and associated factors of ΔZ-score (sex and age standardized).
Results: BMI (from 28.8 ± 4.9 to 31.2 ± 5.1 kg/m^2, $P < .001$), fat mass index (FMI) (from 10.5 ± 3.6 to 11.9 ± 3.8 kg/m^2, $P = .001$), and fat free mass index (FFMI) (from 18.3 ± 3.2

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to 19.1 ± 3.2 kg/m^2, $P < .001$) were high at baseline and increased. Fat percentage and Z-scores of body composition did not increase, except for FFMI Z-scores (from 0.26 ± 1.62 to 1.06 ± 2.22, $P < .001$). Z-scores of total body, L2-L4, femur neck increased (mean difference 0.61 ± 1.12, $P < .001$; 0.74 ± 1.73, $P < .001$; 0.51 ± 1.85, $P = .02$). Linear regression models for ΔZ-score were positively associated with growth hormone replacement therapy (GHRT) (femur neck: beta 1.45 [95% CI 0.51–2.39]); and negatively with radiotherapy (femur neck: beta –0.79 [–1.49 to –0.09]), glucocorticoid dose (total body: beta –0.06 [–0.09 to –0.02]), and medication to improve BMD (L2-L4: beta –1.06 [–1.84 to –0.28]).

Conclusions: Z-scores of BMI, fat percentage, and FMI remained stable in patients with craniopharyngioma over time, while Z-scores of FFMI and BMD increased. Higher glucocorticoid dose and radiotherapy were associated with BMD loss and GHRT with increase.

Freeform/Key Words: craniopharyngioma, DXA, body composition, sarcopenia, bone mineral density, longitudinal study

Patients with craniopharyngioma (CP) suffer from a tumor that may affect the pituitary, optic nerve, and hypothalamus, causing damage and impaired function of these important structures (1). The age at presentation of the disease has a bimodal distribution, with incidence peaks observed in children aged 5 to 14 years (childhood onset [CO] patients with CP) and in adults aged 50 to 74 years (adulthood onset [AO] patients with CP) (2, 3). Patients with CP have excess mortality (1, 3, 4), especially due to obesity-related disorders (standardized mortality ratio 3.2-19) (3-7). Neurological or endocrinological dysfunction may increase fracture risk (8) and obesity. Obesity was reported in up to 75% of the patients (9). Several factors may contribute to obesity in patients with CP, such as endocrine aberrations related to hypopituitarism, visual and neurological sequelae with decreased sympathetic nerve activity, sleep disturbances, and daytime somnolence (10). The simplest way to investigate obesity is to calculate body mass index (BMI): it is noninvasive and inexpensive. Unfortunately, it does not well differentiate body fat from fat free mass (11). Dual X-ray absorptiometry (or DXA scan) is considered a reliable method to determining body composition in case of suspected discordance of BMI and adiposity (9, 12), and can be used to measure bone mineral density (BMD) (13). Only a couple of small studies have published cross-sectional data on DXA scan–derived body composition measures in patients with CP (14-17). In a study including 11 patients with CP, it was found that resting energy rate was significantly reduced in obese subjects, even after controlling for fat free mass (16). In another study with 185 CO patients with CP, obesity was found to be associated with higher BMI at diagnosis, higher maternal BMI, presence of ventriculoperitoneal shunts, and hypothalamic tumor involvement (18).

Studies in patients with CP investigating the longitudinal changes in BMI (18-21) or body composition (15) are scarce. Weight gain in patients with CP was observed mostly before (19) or in the first year after treatment/diagnosis (18, 19, 22, 23). The only study investigating changes in body fat percentage (BF%) in 19 patients with CP receiving growth hormone replacement treatment (GHRT) reported no change in BF% after 60 months of follow-up (15). To the best of our knowledge, no longitudinal studies in patients with CP on sarcopenia or BMD change and influencing factors for BMD change have been performed to date (1, 24-28). Therefore, the aim of the present study was to describe the course of body composition and BMD in patients with CP, during follow-up, and to identify potential influencing factors for BMD changes.

Materials and Methods

This longitudinal retrospective study included patients who were treated for craniopharyngioma either at the Erasmus MC (Rotterdam, The Netherlands), or Sahlgrenska University Hospital (Gothenburg, Sweden). Only DXA scans from patients over 18 years of age were included in the study. The research proposal was approved by the Ethics Review Board of the Erasmus MC and the Regional Ethics Review Board of the Gothenburg University; all patients gave their informed consent.

Data collection and patient identification methods have previously been described (4, 8, 24). Data were collected from the first and most recent DXA scan regardless of scanner type. DXA scan data included pooled data of Lunar DPXL, Lunar iDXA, Lunar Prodigy. The study evaluated the Lunar DPXL and Lunar Prodigy data separately, since different scanner types might generate different results (8). We

did not do this for the Lunar iDXA because there was only a limited number of results from this scanner type. Gathered data existed of body composition measures (such as BF%, fat mass index [FMI] and fat free mass index [FFMI]), BMI, and BMD values and corresponding sex-specific T-scores and sex- and age-specific Z-scores as described in DXA scanner reports. The mean of the differences between first and last DXA scan was calculated. Furthermore, sex- and age-specific Z-scores were computed (29-38); for body composition measures, Swedish references were used if Dutch references were unavailable (9, 34).

All definitions were previously described (8). Hypothalamic damage was defined as tumor- and/or treatment-related injury to the hypothalamus and/or third ventricle as visualized by neuroimaging (9, 24). In our analysis we evaluated patients who had radiotherapy and hypothalamic damage together as 1 group, as we assumed that they had hypothalamic dysfunction. Medication to improve BMD was defined as current or past use of bisphosphonates, vitamin D, or calcium (gonadal axis replacement therapy or other hormonal replacement therapy were excluded for this definition). Patients were categorized as using high or low glucocorticoid dose, where patients with mean or higher glucocorticoid dose (17.7 mg of hydrocortisone equivalent dose) were considered to have a high dose. FFMI was calculated as lean mass and mineral bone mass (kg) per square height (meters); FMI as body fat mass (kg) per square height (meters); and BMI as total body weight per square height (meters).

Cut-offs of categories for BMD (osteopenia and osteoporosis) (39) and for high or low body composition measures are shown in Table 1 and (40). All supplementary material and figures are located in a digital research materials repository (40). BMD categories may be specified through single or multiple sites (at either of femur neck, L2-L4, and/or total body). Patients were considered as obese based on BMI Z-scores >2.0.

Table 1. Definitions of cut-offs for body composition and BMD measures

	Male	Female
Body composition		
High BMI	≥ 30 kg/m^2 or Z-score ≥2	≥ 30 kg/m^2 or Z-score ≥2
High BF%	≥26% if aged 20-39 years old or ≥29% if aged 40-59 years old, or Z-score ≥2 (38)	≥39% if aged 20-39 years old; ≥41% if aged 40-59 years old, or Z-score ≥2
High FMI	≥ 9 or Z-score ≥2 (37)	≥ 13 or Z-score ≥2
Low FFMI	Z-score ≤–2	Z-score ≤–2
BMD		
Osteopenia	T-score –1 to –2.5 or Z-score –1 to –2	
Osteoporosis	T-score ≤–2.5 or Z-score ≤–2	

Abbreviations: BF%, body fat percentage; BMD, bone mineral density; BMI, body mass index; FMI, fat mass index; FFMI, fat free mass index.

Statistical analysis

Statistical analysis was performed using Version 25.0 of IBM SPSS Statistics for Windows, and Graphpad Version 8.01. Data are presented as mean and standard deviation (SD) unless stated otherwise. $P < .05$ were considered significant. Comparisons of proportions were performed by using either the χ^2 test, the Fisher's exact test or McNemar's test as appropriate. For normally distributed data, the T-test was used for group comparisons, while nonparametric equivalents were used in case of violation of the normality assumption. Univariable and multivariable linear regression models were estimated to investigate determinants of changes in BMD Z-scores; baseline Z-scores and age at first DXA scan were incorporated in each model. The model with the biggest R^2 and most significant variables was ultimately chosen. A diagnostic check was performed on model fitting, homoscedasticity, multicollinearity, influential cases, and outliers.

Results

Baseline characteristics of subjects

Baseline characteristics of 112 included patients with CP are shown in Table 2. Most of the included patients originate from a previously reported cohort (4, 24). Patients were previously treated with surgery (n = 108; in 64 patients a transsphenoidal approach and in 29 patients a transcranial approach), radiotherapy (n = 61), and yttrium (n = 13). The median number of surgical procedures was 1 (mean 1.3 ± 0.9, range 0-5). The median age at first presentation of CP was 25 years (range 0-73). Mean follow-up time was 19 ± 11 years (range 1-62). At last follow-up, 15 patients (13%) had died. Men received less often medication to improve BMD (4 [7%] vs 12 [22%], $P = .02$) than women (as previously reported) (8). Gonadal deficiencies were not different between men and women (95% vs 85%, $P = .15$). Gonadal axis replacement therapy was more often administered to men than women (91% vs 57% $P < .001$) but not different if postmenopausal women (defined as >51 years) were excluded (91% vs 94%, $P = 1.00$). Of 105 growth hormone deficient patients, 93 were using GHRT (89%). Patients diagnosed before the year 2000 or from 2000 and onwards did not show any differences in body composition or BMD, except for total body BMD Z-score (–0.22 ± 1.48 vs 0.51 ± 1.24, $P = .04$) (40).

Table 2. Baseline characteristics of craniopharyngioma patients

	All patients with CP (n = 112)	Males	Females	*P* value
Age at last follow-up (years)[a]	49 (16-82)	52 (16-78)	47 (18-82)	.36
Age at presentation (years)[a]	25 (0-73)	27 (0-62)	23 (6-73)	.93
(Female/corresponding) gender, n (%)	54 (48)	58 (100)	54 (100)	.78
Childhood onset disease, n (%)	50 (45)	24 (41)	26 (48)	.47
Tumor location at last follow-up, n (%)				
Intrasellar	2 (2)	1 (2)	1 (2)	1.0
Suprasellar	45 (40)	22 (38)	23 (43)	.50
Intra-/suprasellar	63 (56)	35 (60)	28 (52)	.49
CP treatment				
Surgery	108 (96)	58 (100)	50 (93)	.05
Radiation	62 (55)	31 (53)	31 (57)	.71
Pituitary deficiencies				
GH deficiency[c]	105 (94)/93 (83)	53 (91)/48 (83)	52 (96)/45 (83)	.44
TSH deficiency[c]	107 (96)/107 (96)	58 (100)/58 (100)	49 (91)/49 (91)	**.02**
Hypogonadism[cb]	102 (91)/84 (75)	55 (95)/53 (91)	47 (87)/31 (57)	.19
Corticotropic deficiency[c]	95 (85)/92 (84)	53 (91)/50 (89)	42 (78)/42 (78)	.045
ADH deficiency[c]	76 (68)/75 (67)	40 (69)/40 (69)	36 (67)/35 (65)	.80
Medical history				
Recurrence/progression	40 (36)	19 (33)	21 (39)	.54
Hypothalamic damage	38 (36)	21 (38)	17 (35)	.77
Hydrocephalus ever	26 (23)	11 (19)	15 (28)	.29
Visual impairment	81 (76)	42 (76)	39 (75)	.99
Epilepsy	14 (13)	5 (9)	9 (17)	.20
Diabetes mellitus	13 (12)	7 (12)	6 (11)	.85
Fracture in history	21 (19)	16 (28)	5 (9)	**.01**
BMD medication	16 (14)	4 (7)	12 (22)	**.02**

The bold values indicate that they are statistically significant ($P < 0.05$). Tumor location and recurrence or progression were unknown in 2 and 1 patient(s), respectively.
Abbreviations: ADH, antidiuretic hormone; BMD medication, bone mineral density increasing medication; CP, Craniopharyngioma; GH, growth hormone; N, number; TSH, thyroid stimulating hormone.
[a]Median (range).
[b]In females aged 50 years or younger and men, 83/90 subjects (92%) used gonadal hormone replacement therapy.
[c]All/using replacement therapy.

Baseline values and longitudinal change in body composition

Median age at first DXA scan was 36 years (range 18-79) and age at last follow-up was 49 years (range 16-82). The median time since first tumor related treatment at first DXA scan was 9.9 years (range –9.2 to 47.0) and the median time between the first and last DXA scan was 10.0 years (range 0.41-23.3). The proportion of patients with obesity increased when defined by BMI Z-scores (from 28 [41%] to 38 [55%], $P = .02$) and FMI Z-scores (from 28 [48%] to 36 [61%], $P = .04$); other definitions of obesity did not change during follow-up (Table 3). Unstandardized values of BMI (from 28.8 ± 4.9 to 31.2 ± 5.2 kg/m^2, $P < .001$), FMI (from 10.5 ± 3.6 to 11.9 ± 3.8 kg/m^2, $P = .001$) and FFMI (from 18.3 ± 3.2 to 19.1 ± 3.2 kg/m^2, $P < .001$) were high at baseline and increased significantly (Table 4, Fig. 1, and (40)). However, if standardized, only FFMI Z-scores increased (from 0.26 ± 1.62 to 1.06 ± 2.22, $P < .001$) (Fig. 2). BF% (Z-scores) did not change (Table 4). There was no difference in change of body composition measures or body composition Z-scores between men and women over time (Figs. 1 and 2). Patients treated for CP before 2000 had longer time difference from first to last DXA scan (12.4 ± 6.5 vs 6.3 ± 4.2, $P < .001$) but no differences in BMI or body composition values at first DXA scan, last DXA scan or change over time (data not shown).

Subgroups: childhood onset vs adulthood onset patients

The follow-up time since first presentation was significantly longer in CO patients than AO patients (22.7 ± 12.4 vs 16.3 ± 9.0 years, $P = .03$). At baseline, CO patients had a higher proportion of subjects with normal BMI than AO patients (30% vs 10%, $P = .02$) and had higher BF% (39.5 ± 13.2 vs 34.2 ± 9.2, $P = .048$), but lower FFMI (16.6 ± 2.8 vs 19.7 ± 3.0, $P < .001$) and FFMI Z-score values (–0.8 ± 1.4 vs 0.7 ± 1.4, $P < .001$) than AO

Table 3. Baseline DXA scan and changes of BMD and body composition categories

	All CP		
	First DXA scan	Last DXA scan	*P*
Age (years)	37 ± 15	48 ± 16	**<.001**
Osteoporosis (T/Z-score)	19/79 (24)	20/79 (25)	1.00
Osteoporosis (T-score)	13/75 (17)	18/75 (24)	.38
Osteoporosis (Z-score)	19/77 (25)	13/77 (17)	.24
Osteopenia (T/Z-score)	47/78 (60)	42/79 (53)	.41
Osteopenia (T-score)	38/75 (51)	27/75 (36)	**.04**
Osteopenia (Z-score)	39/77 (51)	34/77 (44)	.46
BMI	28.8 ± 4.9	31.2 ± 5.1	**<.001**
BMI Z-score	1.4 ± 1.9	1.5 ± 1.6	.38
Low BMI	2/69 (3)	1/69 (1)	1.00
Normal BMI	12/69 (17)	5/69 (7)	**.04**
Overweight	27/69 (39)	25/69 (36)	.83
Obese	28/69 (41)	38/69 (55)	**.02**
FMI			
Low FMI	0/59 (0)	0/59 (0)	NA
Normal FMI	10/59 (17)	6/59 (10)	.29
Excess fat FMI	21/59 (36)	17/59 (29)	.48
Obese FMI	28/59 (48)	36/59 (61)	**.04**
FFMI			
Low FFMI	5/41 (12)	2/41 (5)	.25
Normal FFMI	29/41 (71)	29/41 (71)	1.00
High FFMI	7/41 (17)	10/41 (24)	.25
BF%			
Low BF%	0/48 (0)	0/48 (0)	NA
Normal BF%	16/48 (33)	12/49 (25)	.34
High BF%	31/48 (65)	36/48 (75)	.18

Baseline first DXA scan and changes during follow-up (Δ). Data are presented as mean ± SD or n/n (%) as applicable. The bold values indicate that they are statistically significant ($P < 0.05$). For applied cutoffs, see Table 1 and (40). There are no significant differences between male and females at first or last DXA scan.
Abbreviations: BF%, body fat percentage; BMI, body mass index; DXA, dual X-ray absorptiometry scan; FFMI, fat free mass index; FMI, fat mass index; NA, not applicable (empty groups).

Table 4. DXA results of any DXA scanner type—bone mineral density and body composition in all patients with craniopharyngioma

	First DXA scan	Last DXA scan	Δ	*P*
Age (years)	37.0 ± 14.9	48.0 ± 16.5	11.0 ± 6.5	**<.001**
Bone				
Bone mineral density				
Total body	1.17 ± 0.13	1.19 ± 0.16	0.04 ± 0.10	**.001**
L2-L4	1.13 ± 0.19	1.22 ± 0.26	0.11 ± 0.17	**<.001**
Femur neck	0.96 ± 0.18	0.99 ± 0.22	0.04 ± 0.26	.29
Femur	1.03 ± 0.21	1.04 ± 0.21	0.03 ± 0.32	.70
T-score				
Total body	–0.10 ± 1.49	0.43 ± 1.68	0.66 ± 1.07	**<.001**
L2-L4	–0.70 ± 1.57	0.14 ± 2.03	0.78 ± 1.63	**<.001**
Femur neck	–0.64 ± 1.48	–0.40 ± 1.60	0.23 ± 1.95	.44
Femur	–0.27 ± 1.61	–0.10 ± 1.52	0.26 ± 2.19	.53
Z-score				
Total body	–0.49 ± 1.37	–0.05 ± 1.44	0.61 ± 1.12	**<.001**
L2-L4	–0.77 ± 1.59	–0.03 ± 1.97	0.74 ± 1.73	**<.001**
Femur neck	–0.62 ± 1.32	–0.09 ± 1.33	0.51 ± 1.85	**.02**
Femur	–0.32 ± 1.44	–0.01 ± 1.35	0.29 ± 2.11	.55
Body composition				
BMI	28.8 ± 4.9	31.2 ± 5.1	2.01 ± 3.36	**<.001**
BMI Z-score	1.39 ± 1.92	1.52 ± 1.55	0.09 ± 1.41	.38
FMI	10.5 ± 3.6	11.9 ± 3.8	0.97 ± 2.43	**.001**
FMI Z-score	1.37 ± 1.41	2.14 ± 1.46	0.10 ± 0.90	.43
FFMI	18.3 ± 3.2	19.1 ± 3.2	1.13 ± 1.87	**<.001**
FFMI Z-score	0.26 ± 1.62	1.06 ± 2.22	0.91 ± 1.39	**<.001**
BF%	36.4 ± 11.6	37.5 ± 8.4	0.28 ± 9.37	.15
BF% Z-score	1.41 ± 1.06	1.62 ± 0.96	-0.02 ± 0.73	.61

Data are expressed as mean ± SD. The bold values indicate that they are statistically significant ($P < 0.05$).
Abbreviations: Δ, mean difference; BF%, body fat percentage; BMD, bone mineral density; BMI, body mass index; DXA, dual X-ray absorptiometry; FFMI, fat free mass index; FMI, fat mass index; N, number.

patients. During follow-up, CO patients increased more in BMI than AO patients (mean difference 2.8 ± 3.9 vs 1.3 ± 2.9, $P = .008$) and increased in BF% Z-scores while AO patients decreased (mean difference 0.2 ± 0.9 vs –0.3 ± 0.6, $P = .04$).

Subgroups: patients with vs without radiotherapy/hypothalamic damage

This group consisted of 34 patients who had radiotherapy only, 16 patients who had hypothalamic damage only, and of 22 patients who had both. At baseline, patients with radiotherapy or hypothalamic damage had a significant higher BMI (29.6 ± 5.1 vs 27.2 ± 4.3, $P = .02$), higher BMI Z-scores (1.7 ± 1.9 vs 0.7 ± 1.7, $P = .004$), and higher FMI Z-scores (1.6 ± 1.5 vs 1.0 ± 1.2, $P = .06$). As a group, they had an increase in BF% Z-scores instead of a decrease in patients without radiotherapy or hypothalamic damage (mean change 0.1 ± 0.7 vs –0.3 ± 0.8, $P = .02$) and increased more in FMI (mean change 1.3 ± 2.6 vs 0.2 ± 2.1, $P = .03$). At last DXA scan, patients with radiotherapy or hypothalamic damage had not only a higher total body mass and fat-related body composition measures (BMI 32.3 ± 5.6 vs 29.2 ± 3.5, $P = .01$; BMI Z-scores 1.8 ± 1.7 vs 1.0 ± 1.2, $P = .01$; BF% Z-scores 1.8 ± 0.8 vs 1.3 ± 1.1, $P = .03$; FMI Z-scores 2.5 ± 1.6 vs 1.4 ± 1.3, $P = .007$), but also higher muscle mass-related measures (FFMI Z-scores 1.5 ± 2.6 vs 0.3 ± 1.4, $P = .03$) than patients without radiotherapy or hypothalamic damage.

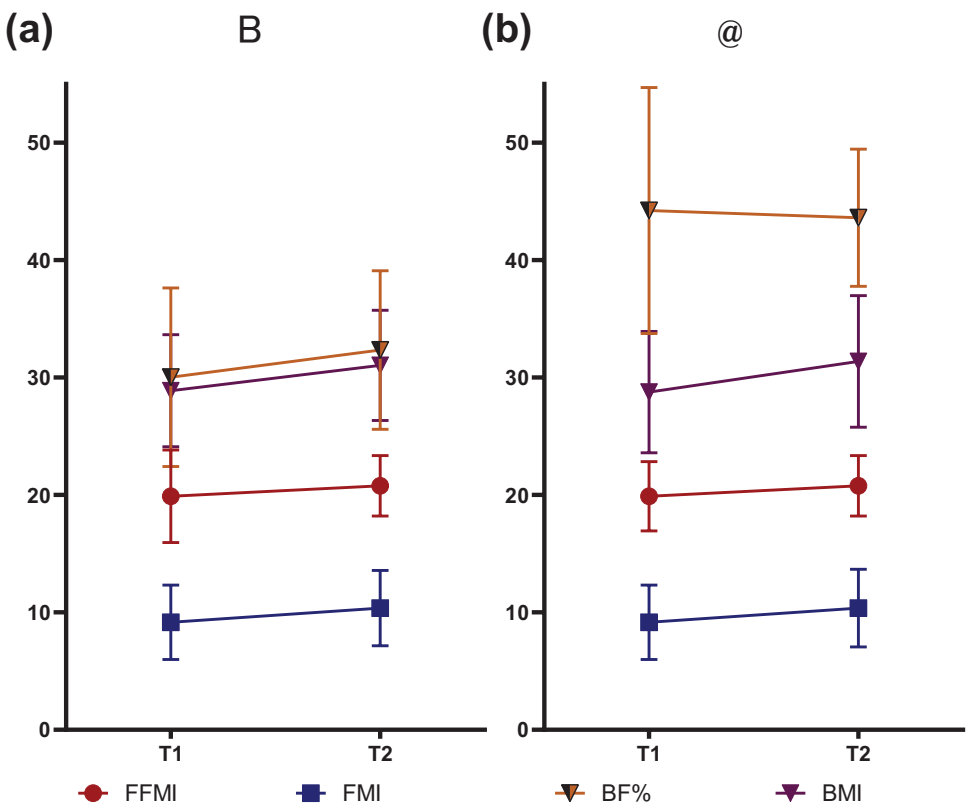

Figure 1. Body composition measures men and women with craniopharyngioma. Unstandardized mean and SD of fat free mass index (FFMI; red circles), fat mass index (FMI; blue squares), body fat percentage (BF%; black/orange triangles), and body mass index (BMI; purple triangles) are shown at the first dual X-ray absorptiometry (DXA) scan (T1) and last DXA scan (T2) in male (A) and female (B) patients with craniopharyngioma. As expected, men had significantly lower FMI values than women at T1 and T2 ($P \leq .001$), lower BF% ($P < .001$), and higher FFMI ($P < .001$); there was no difference in BMI or in changes from T1 to T2. There was a significant increase from T1 to T2 in all patients in BMI ($P < .001$), FMI ($P = .001$), and FFMI ($P < .001$), but not BF% ($P = .15$).

Subgroups: patients with vs without certain pituitary hormone deficiencies

Patients with gonadal axis deficiency increased in BMI Z-scores (mean difference 0.2 ± 1.4 vs –0.7 ± 1.0, $P = .03$) and increased more in higher FFMI at last DXA scan than patients without gonadal axis deficiency (mean change 1.4 ± 1.9 vs –0.2 ± 1.2, $P = .009$). Patients with adrenocorticotropin deficiency increased during follow-up in BMI Z-scores (mean difference 0.2 ± 1.5 vs –0.6 ± 1.0, $P = .03$) and FMI Z-scores (mean difference 0.1 ± 0.7 vs –0.4 ± 1.5, $P = .03$). If patients with diabetes insipidus (DI) were compared with patients without DI, they increased more in BMI (mean difference 2.6 ± 3.6 vs 0.8 ± 2.6, $P = .02$), FMI Z-scores (mean difference 0.2 ± 0.7 vs –0.2 ± 1.1, $P = .006$), and FFMI Z-scores from first to last DXA scan (mean difference 1.4 ± 1.4, vs 0.1 ± 1.1, $P = .005$). Patients with high glucocorticoid dose had no significant differences from patients with low glucocorticoid dose except for higher unstandardized FFMI at first DXA scan (19.0 ± 3.2 vs 16.9 ± 2.6, $P = .003$) and at last DXA scan (19.6 ± 3.3 vs 18.1 ± 2.7, $P = .04$).

Longitudinal change in BMD

BMD, and corresponding T- and Z-scores were slightly below average at baseline, but increased for total body and L2-L4, and the Z-score for femur neck as well (mean difference Z-scores 0.61 ± 1.12, $P < .001$; 0.74 ± 1.73, $P < .001$; 0.51 ± 1.85, $P = .02$, respectively) (Table 4 and Fig. 3). There was no significant difference in (change in) Z-scores between patients with or without radiotherapy, with or without hypothalamic damage, with or without tumor progression, or CO or AO patients (Fig. 3). There was a decrease in osteopenia rates from first to last DXA scan in the entire group if it defined by low T-score (38 [51%] vs 27 [36%], $P = .04$) but no difference in proportion of osteoporosis at first (19 [24%]) or last (20 [24%]) DXA scan ($P = 1.00$) (Table 3). Patients treated for CP before 2000 had lower total body Z-scores at first (–0.77 ± 1.30 vs 0.11 ± 1.36, $P = .02$) and last (–0.22 ± 1.48 vs 0.51 ± 1.24, $P = .04$) DXA scan than patients treated from 2000 and onwards. Other BMD-related values did not differ (data not shown).

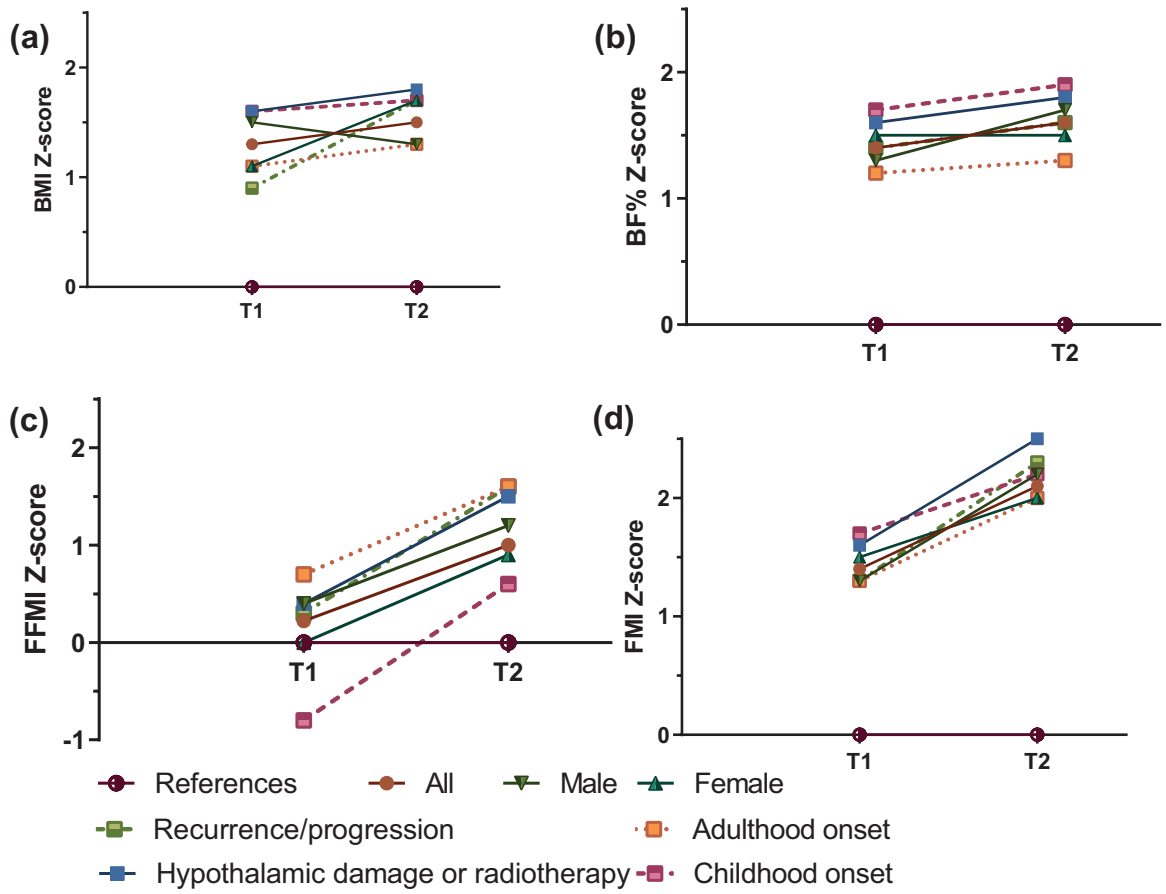

Figure 2. BMI Z-scores at first and last dual X-ray absorptiometry (DXA) scan. Sex- and age-standardized Z-scores are presented for (A) body mass index (BMI), (B) body fat percentage (BF%), (C) fat free mass index (FFMI), and (D) fat mass index at first (T1) and last (T2) DXA scan. Data are given as mean ± standard deviation. Male and female patients did not differ in body composition Z-scores. Patients with recurrence or progression of disease increased in BMI Z-scores while patients without recurrence or progression decreased (mean change 0.7 ± 1.3 vs –0.3 ± 1.4, $P = .04$). Patients with hypothalamic damage or radiotherapy had higher BMI Z-scores at T1 (1.7 ± 1.9 vs 0.7 ± 1.7, $P = .004$) and T2 (1.8 ± 1.7 vs 1.0 ± 1.2, $P = .01$), higher BF% Z-scores at T1 (1.6 ± 1.0 vs 1.1 ± 1.2, $P = .03$) and T2 (1.8 ± 0.8 vs 1.3 ± 1.1, $P = .03$), and differed in change of BF% Z-scores from T1 to T2 (0.1 ± 0.7 vs –0.3 ± 0.8, $P = .02$). They also had a higher FMI Z-scores at T1 (1.6 ± 1.5 vs 1.0 ± 1.2, $P = .06$) and T2 (2.5 ± 1.4 vs 1.4 ± 1.3, $P = .007$), and FFMI Z-scores at T2 (1.5 ± 2.6 vs 0.3 ± 1.4, $P = .03$). Childhood-onset patients had higher BF% Z-scores at T2 (1.9 ± 0.8 vs 1.3 ± 1.0, $P = .02$) than adult-onset patients and increased instead of decreased in BF% Z-scores from T1 to T2 (mean difference 0.2 ± 0.9 vs –0.3 ± 0.6, $P = .04$). They also had lower FFMI Z-scores at T1 (–0.8 ± 1.4 vs 0.7 ± 1.4, $P < .001$) and borderline lower FFMI Z-scores at T2 (0.6 ± 2.4 vs 1.6 ± 2.0, $P = .07$).

Prodigy and DPXL

Using the Lunar Prodigy, almost all body composition results increased significantly, but not using DPXL (40). The BMD results follow a similar pattern, except for femur neck: femur neck BMD, T-scores, and Z-scores significantly improved if measured using Lunar DPXL, in contrast to Lunar Prodigy.

Effect of prognostic factors for change in BMD Z-scores

Univariable and multivariable linear regression models were estimated to identify possible predictors of changes in total body Z-score, L2-L4 Z-score, and femur neck Z-score (Table 5).

In a univariable model, time from first to last DXA scan (beta 0.04 [0.003-0.08]), hydrocortisone equivalent dose (beta –0.06 [–0.10 to –0.02]) and medication to improve BMD (beta –0.95 [1.83 to –0.08]) were associated with change in total body Z-score. In the multivariable analysis, time from first to last DXA scan was not associated with change in total body Z-score (beta 0.03 [–0.005 to 0.07]) while hydrocortisone equivalent dose was (beta –0.06 [–0.09 to –0.02]). In a univariable model, medication to improve BMD and progression were not associated with change in L2-L4 Z-score (beta –1.30 [–2.78 to 0.18] and beta 0.86 [0.02-1.73], respectively). In multivariable analysis, medication to improve BMD was associated with change in L2-L4 Z-score (beta –1.06 [–1.84 to –0.28]), while tumor progression was not (beta 0.04 [–0.45 to 0.52]). In the univariable model for change in femur neck

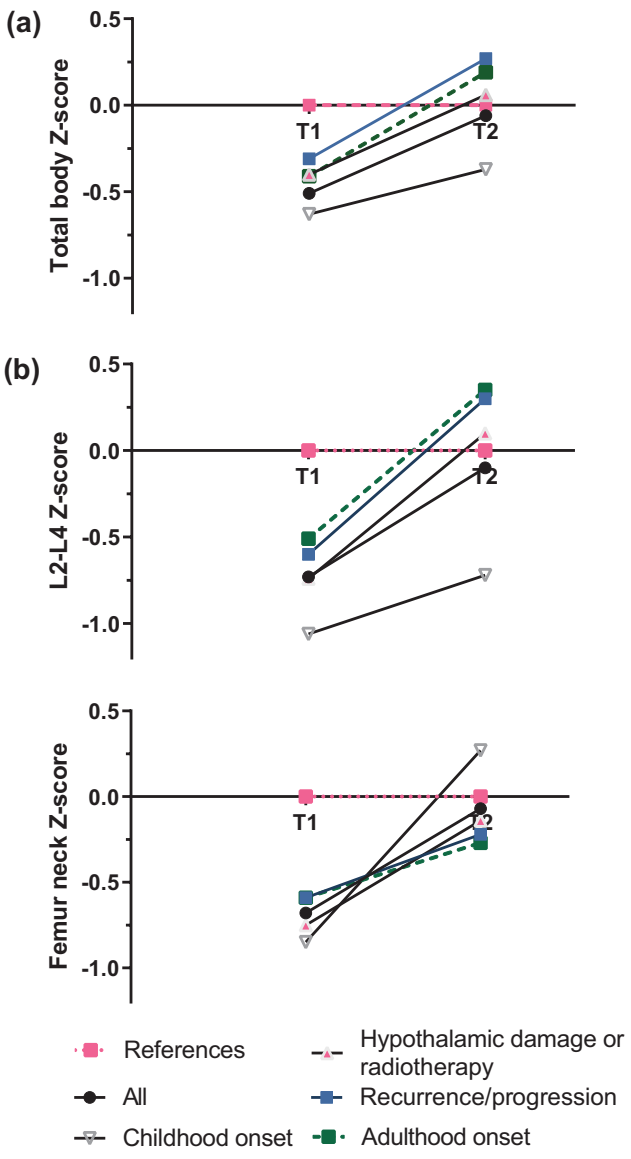

Figure 3. Total body, L2-L4 and femur neck Z-scores of the first and last dual X-ray absorptiometry scan (DXA). Z-scores at first (T1) and last (T2) DXA scan in all craniopharyngioma patients of (A) total body, (B) L2-L4, and (C) femur neck. Data are given as mean ± standard deviation. Z-scores improved significantly in all patients from T1 to T2 of total body (from –0.49 ± 1.37 to –0.05 ± 1.44, $P < .001$), L2-L4 (from –0.77 ± 1.59 to –0.03 ± 1.97, $P < .001$), and femur neck (from –0.62 ± 1.32 to –0.09 ± 1.33, $P = .02$). There was no significant difference in Z-scores between patients with or without radiotherapy/recurrence or progression/hypothalamic damage or patients with childhood- or adulthood-onset disease, at T1, T2, or change from T1 to T2.

Z-score, GHRT (beta 1.45 [0.51-2.39]) and previous radiotherapy (beta –0.79 [–1.49 to –0.09]) were significant explanatory variables. In multivariable analysis, GHRT and radiotherapy were however not identified as significant prognostic factors (with corresponding estimated regression coefficients of beta –0.37 [–1.27 to 0.53]) and –0.05 [–0.67 to 0.57]).

Discussion

This is the first study assessing longitudinally changes in 86 patients with CP, comparing anthropometric and BMD data, with a follow-up of 10 years. In addition, we investigated prognostic factors for BMD change.

Body composition improved in patients with CP during follow-up: FFMI increased and was relatively high, implying an improvement in muscle mass and bone mass, and suggesting that there was hardly any sign of sarcopenic obesity. This increase in age-standardized FFMI was peculiar, since in the general population FFMI usually decreases with advancing age (41, 42). One may suggest that this increase in muscle and bone mass might be related to physical functioning. However, it is unclear whether gain in muscle mass was a reflection of improved physical performance or sufficient hormonal replacement therapy. In the elderly general population, impaired physical activity performance was associated with FMI rather than with FFMI (43), and in the male general population, FFMI had a U-shaped relationship with mortality (44). It is unknown whether the increase in FFMI in our study population affected the mortality in any way. We observed an increase in unstandardized values of body mass and fat-related measures, but not in the age- and sex-specific scores, suggesting that patients did gain fat and total weight with aging, similarly as the general population does. Loss of fat mass is a desired goal of treatment, as obesity and the metabolic syndrome occur very frequently in patients with CP, making improvement of their cardiovascular risk profile an enormous challenge (9). Both physical activity level and basal metabolic rate are usually low in patients with CP, regardless of fat free mass (16, 23). Patients may already gain weight in the first year after onset and even before diagnosis (19). This underlines the difficulty of developing an effective strategy in patients with CP to prevent the development of obesity. Thus, anti-obesity treatment should ideally be started as soon as possible and preferably directly after confirmation of the CP diagnosis.

Interestingly, bone density of the total body, femur neck and L2-L4 improved during follow-up. Independent risk factors for a decrease in bone density scores were glucocorticoids, previous radiotherapy, and, remarkably, medication given to improve BMD. It is well known that excessive glucocorticoids can reduce bone mass (13). Cranial radiotherapy is not only an important risk for pituitary deficiencies and hypothalamic dysfunction (45), but also for obesity (45). The authors hypothesized that the improvement in BMD in our cohort was explained by the high obesity rates in patients with CP, as obesity can induce an increase in bone mass and is generally considered to be a protective factor for osteoporosis (43).

Table 5. Linear regression model: univariable model and multivariable models of change in Z-scores of BMD

	Univariable linear regression model						Multivariable linear regression model					
	Δ Total body Z-score		Δ L2-L4 Z-score		Δ Femur neck Z-score		Δ Total body Z-score $R^2 = 0.23$		Δ L2-L4 Z-score $R^2 = 0.15$		Δ Femur neck Z-score $R^2 = 0.65$	
	Beta	95% CI	Beta	95% CI	Beta	95% CI	Beta	95% CI	Beta	95% CI	Beta	95%CI
Time from first to last DXA	0.04	0.003-0.08	0.02	–0.04-0.09	–0.02	–0.08-0.04	0.03	–0.005-0.07				
Time since first treatment at last DXA	0.01	–0.01-0.03	–0.01	–0.04-0.03	0.001	–0.03-0.03						
Female sex	–0.06	–0.57-0.44	0.05	–0.85-0.95	0.47	–0.26-1.19						
BMI at last DXA	0.03	–0.03-0.08	–0.002	–0.09-0.08	0.05	–0.03-0.12						
BMD medication	–0.95	–1.83 to –0.08	–1.30	–2.78-0.18	–0.67	–2.08-0.74			–1.06	–1.84 to –0.28		
Adulthood onset	0.35	–0.38-1.08	0.93	–0.36-2.22	–0.30	–1.32-0.73						
Hypothalamic damage	0.27	–0.31-0.85	–0.06	–1.06-0.95	–0.18	–1.04-0.68						
Growth hormone replacement therapy	0.40	–0.48-1.27	1.03	–0.31-2.38	1.45	0.51-2.39					–0.37	–1.27-0.53
Gonadal replacement therapy	0.49	–0.13-1.10	0.64	–0.38-1.66	–0.17	–1.01-0.68						
Hydrocortisone equivalent dose	–0.06	–0.10 to –0.02	–0.03	–0.10-0.05	0.05	–0.03-0.12	–0.06	–0.09 to –0.02				
Epilepsy medication	0.78	–0.01-1.57	0.15	–1.24-1.53	–0.14	–1.24-0.96						
Ever hydrocephalus	–0.16	–0.75-0.44	0.06	–1.01-1.12	0.18	–0.73-1.09						
Progression	0.31	–0.21-0.83	0.86	–0.02-1.73	–0.16	–0.89-0.59			0.04	–0.45-0.52		
Surgery	–0.29	–2.34-1.76	0.71	–2.77-4.18	1.11	–1.58-3.79						
Radiotherapy	–0.11	–0.61-0.39	0.14	–0.72-1.01	–0.79	–1.49 to –0.09					–0.05	–0.67-0.57
Yttrium	–0.32	–1.19-0.55	–0.05	–1.85-1.76	–0.22	–1.62-1.18						

All models are corrected for baseline Z-score and age at first DXA scan. Hydrocortisone dose is a hydrocortisone equivalent dose (mg).

Abbreviations: BMD medication, medication to improve bone mineral density; CI, Confidence Interval; DXA, dual X-ray Absorptiometry scan; BMI, body mass index;.

Factors involved in this increase of bone mass in obesity are augmented leptin levels and an increased peripheral conversions of androgens to estrogens (21). However, in our study, BMI was not associated with bone density change. This is in line with new findings on obesity, if implicated with low-grade inflammation, does not necessarily concur with benefits on bone mass (43). Obesity may cause a state of leptin resistance (43). Central leptin resistance or insensitivity due to hypothalamic damage could mediate negative effects of obesity on bone metabolism (43).

The unexpected finding that medication administered to improve BMD was associated with a decrease in BMD in our study might be due to bias by indication: this medication was likely to be given to patients who already had developed a poor bone health. Administration of GHRT was found to be associated with an increase in bone density. This is consistent with previous literature which describes that discontinuation of GHRT in CO patients before establishing peak bone mass in the first 3 decades of life may be associated with a high prevalence of pathological bone densities (21).

CO patients and patients with previous radiotherapy or hypothalamic damage seemed to be at higher risk for a less favorable body composition than their counter-subgroup. CO patients showed more increase in body mass, fat mass, and fat percentage, and less muscle mass at baseline than AO patients. This may have contributed to their previously found excess risk of diabetes mellitus type 2, cerebral infarction and total mortality (4), and of morbid obesity, and be related to the higher risk of hypothalamic involvement and panhypopituitarism of CO patients (24). In addition, the increase in FFMI Z-scores may be, at least partly, related to GHRT (28, 46, 47). Treatment of CP has changed from gross total resection to more conservative surgery (24), which could affect body composition and BMD. However, patients treated before and from 2000 onwards almost did not differ, except for total body Z-score, follow-up time, and cohort size.

There are some limitations in this research due to the retrospective design. As discussed before (8, 9), differences in observation can be perceived from different types of DXA scanners; in 15 out of 198 scan results, the scanner type was unknown due to a time period where both DPXL and Prodigy were used. We coped with this aspect by also analyzing data separately per DXA scanner for the most often used scanner types, and using Z-scores. This study is unique in reporting factors on BMD change in patients with CP, and it is one among few studies reporting longitudinal change in body composition, and represents a large cohort with an extensive follow-up.

Summarizing, patients with CP remained as stable in body composition as the general population over time, and even showed an increase in bone and muscle mass. Higher glucocorticoid dose and central nervous system irradiation negatively influenced this increase of BMD, while GHRT shows the opposite and it is associated with an increase in bone density. Even though these results are beneficial at glance, there still remains considerable need for improvement, as cardiovascular risk and fracture rates remain unacceptably high in patients with CP (4, 8). In addition, subgroups of CP patients such as those with CO disease and hypothalamic damage remain at high risk for adverse anthropometric effects. Future studies among patients with CP should therefore focus on development of methods for early prevention of obesity, interventions to influence body composition and improvement of bone quality in affected individuals, already from the diagnostic phase.

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Additional Information

***Correspondence and Reprint Requests*:** Dr. Sebastian JCMM Neggers, Erasmus Medical Center, Department of Internal Medicine, Endocrinology's Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands. Email: s.neggers@erasmusmc.nl.

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Data Availability: Restrictions apply to the availability of data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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