Journal of Bone Research
ISSN: 2572-4916
OPEN ACCESS Freely available online
Research Article

Are Childhood-Onset Craniopharyngioma Patients at Risk for Low Bone Mass? Insights into Adiposity, Hypogonadism and Growth Hormone

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ABSTRACT

Background: Bone mass may be compromised in childhood-onset craniopharyngioma patients due to different factors. The aim of this study was to evaluate the effect of adiposity, hypogonadism and growth hormone on bone mass in craniopharyngioma patients.

Methods: A cross-sectional study of 46 patients, aged between 6.6 and 32.1 years, 7.5 years from diagnosis, 63% male, 39.1% underwent surgery followed by cranial radiotherapy, assessed according to body fat, lumbar spine and total body bone mineral density through dual energy X-ray absorptiometry, computed tomography scan-derived abdominal adipose tissue, and adipokines by univariate and multivariate regression analyses.

Results: Craniopharyngioma patients presented with decreased lumbar spine and total body bone mass related to therapy (cranial radiotherapy and combinations), but no fractures so far. The body mass index Z score at assessment had a positive mechanical effect on total body bone mass. The replacement of sex steroids at or above 3 years increased bone mass at the total body site. The presence of diabetes insipidus and initiating growth hormone at or above 11.8 years of age had a negative impact on lumbar spine bone mass. Regarding cutoffs, 21.7% of patients presented with decreased lumbar spine bone mass and 10.9% at the total body site, but no differences were observed in spite of growth hormone, sex steroid or sex.

Conclusion: Hypothalamic obesity, therapy, and hormone deficiencies may determine bone mass among craniopharyngioma patients. All these factors might be monitored during follow-up, as they could possibly explain linking mechanisms between bone, metabolism and cancer.

Keywords: Craniopharyngioma; Bone density; Adiposity; Gonadal steroid hormones; Growth hormone/deficiency

INTRODUCTION

Craniopharyngioma (CP) is a benign tumor of the sellar or suprasellar region that accounts for 1-15% of intracranial tumors in children. Resection followed by adjuvant Cranial Radiotherapy (CRT) and/or intracystic chemotherapy (Interferon-α, IFN-α) is the common type of treatment [1-3]. As a consequence of hypothalamic damage, CP patients may develop neurologic and hormone abnormalities, and the so-called hypothalamic obesity [4-8]. Children treated for any type of cancer may have their bone mass compromised [9-17]. Nonetheless, unlike other childhood cancers, particularly Acute Lymphocytic Leukemia (ALL), few studies have focused on bone metabolism and hypopituitarism so far. Along with genetic background, the disease itself and/or consequences of treatment, many other factors have been hypothesized to be associated with bone derangement in CP patients [14-17].

CP patients are extremely obese and frequently develop Metabolic Syndrome (MS) traits [7,8]. Obesity may have a beneficial influence on bone health as a consequence of the positive effect of mechanical loading on bone formation. On the other

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Received: 05-Jul-2022; Manuscript No. BMRJ-22-18422; **Editor assigned:** 08-Jul-2022; PreQC. No. BMRJ-22-18422 (PQ); **Reviewed:** 22-Jul-2022; QC. No. BMRJ-22-18422; **Revised:** 29-Jul-2022; Manuscript No. BMRJ-22-18422 (R); **Published:** 05-Aug-2022, DOI: 10.35248/2572-4916.22.10.180.

Citation: Siviero-Miachon AA, Tosta-Hernandez PDC, da Silva NS, Cappellano A, de Medeiros Pinheiro M, Spinola-Castro AM (2022) Are Childhood-Onset Craniopharyngioma Patients at Risk for Low Bone Mass? Insights into Adiposity, Hypogonadism and Growth Hormone. J Bone Res. 10:180.

hand, fat accumulation may also affect bone through the direct effect of adipokines or indirectly through the state of chronic inflammation [9,13,18-22]. Several studies have evaluated the relationship between adiposity, including adipokines, and Bone Mineral Density (BMD) in cancer survivors [9,13,22], but no study has evaluated this association among CP patients. Thus, the goal of this study was to investigate whether adiposity and hormone deficiencies may affect bone mass in childhood-onset CP patients.

MATERIALS AND METHODS

Subjects

This was a comparative cross-sectional study of a selected sampling of CP patients. This study complies with the Declaration of Helsinki and was performed according to the ethics committee approved (approval number 743.617). Written informed consent was obtained from all patients or parents and/or legal guardians prior to enrollment. CP diagnosis was based on clinical, radiological and histological findings [8]. The inclusion criteria comprised chronological age of at least two years, minimal follow-up of six months after diagnosis, and satisfactory hormone replacement. Characteristics of host/disease were assessed from medical records and clinical examinations. Hypothalamic involvement was classified according to Puget's criteria [23].

CP subjects were treated according to the following modalities: total or partial surgery, fractionated CRT, with a mean dosage of 54 Gy, and intracystic chemotherapy comprising IFN-α and/or bleomycin, alone or in various combinations [8,24]. Patients were stratified into six categories (the so-called therapy group): IFN-α; surgery; CRT/none; surgery+CRT; surgery+IFN-α; and surgery+CRT+IFN-α/bleomycin. Anterior pituitary hormone deficiencies (excluding Growth Hormone, GH) were considered as the respective replacement at study assessment, including Glucocorticoid (GC), Levothyroxine Sodium (LT4), and sex steroid. To simplify the analyses, the number of anterior pituitary deficiencies was considered (none or one deficiency, two or three deficiencies). The presence of diabetes insipidus (Yes or No) was analysed separately.

Sex steroid was administered as a standard protocol, according to sex and chronologic age. For those CP subjects with delayed puberty (absence of signs of puberty above 13 years in females and 14 years in males) who had not attained final height, the appropriate gonadal steroid (estrogens in females or testosterone in males) was initiated and progressively increased up to maintenance doses. For those patients who had already attained adult height, presented with hypogonadism (or secondary amenorrhea), gonadal steroids were maintained and adjusted according to individual needs. To analyse the effect of sex steroids, the following parameters were considered: sex steroid replacement therapy (Yes or No), age at initiation (no use, below 16.2, and at or above 16.2 years), and time receiving sex steroids (no use, below 3.0, and at or above 3.0 years). The cutoffs of 16.2 and 3.0 years were obtained from the median values, in spite of sex.

All CP patients presented with GH deficiency, diagnosed according to standard criteria [25-27]. Patients were treated with recombinant human GH (rhGH) at a dose of 0.12-0.15 IU/kg if they presented with poor growth velocity and/or predicted final height below target height, along with altered GH status (GH peak ≤ 5 ng/mL). Patients who showed normal Z height and growth velocity despite presenting altered GH status and/or low insulin-like growth factor-1 (IGF-1) did not receive rhGH and were classified as a group named non-rhGH. Thus, patients were stratified into three groups (the so-called GH group): Non-rhGH, current therapy with rhGH (rhGH-c), and previous therapy with rhGH (rhGH-p). To analyse the effect of rhGH, the following parameters were considered: age at initiation (no use, below 11.8, and at or above 11.8 years) and time receiving rhGH (no use, below 2.6, and at or above 2.6 years). The cutoffs of 11.8 and 2.6 years were obtained from the median values, in spite of sex.

Measurements

Body composition: Body Mass Index (BMI), calculated as the weight in kilograms divided by height in meters squared (kg/m^2) converted into Z scores (Z BMI), based on the World Health Organization (WHO) [25,26]; total fat mass and lean mass, analysed as their indexes, respectively Fat Mass Index (FMI) and Lean Mass Index (LMI), both calculated by means of fat mass or lean mass in kilograms divided by height in meters squared (kg/m^2), obtained by dual x-ray absorptiometry, GE-Lunar Radiation corporation (iDXA, USA model) [28,29].

Fat distribution: waist-to-height ratio and Computed Tomography (CT) scan-derived abdominal adipose tissue, Visceral Adipose Tissue (VAT), and Subcutaneous Adipose Tissue (SAT) were measured according to the method described elsewhere [30].

Adipokines: leptin (ng/mL), adiponectin (μg/mL), resistin and visfatin (both in ng/mL), and their respective assays information were published elsewhere [13].

Bone mineral density: lumbar spine L1-L4 and total body (with head) BMD evaluated by GE-Lunar Radiation corporation (iDXA, USA model), and converted to Z scores. Lumbar spine and total body BMD Z scores were stratified into two groups as follows: low BMD for chronological age, encompassing Z scores less than or equal to -2.0, and BMD within the inferior limit of normality, comprising Z scores between -1.0 and -2.0 [31,32].

Statistical analysis

Statistical analysis was initially performed descriptively using summary measures: Mean ± Standard Deviation (SD), median, minimum and maximum, absolute and relative frequencies. Categorical variables comprised sex, hypothalamic involvement, therapy, hormone replacement, diabetes insipidus, sex steroid replacement, age at initiation and time receiving sex steroid and rhGH. Numerical variables included age, Z BMI and Z height (at CP diagnosis and assessment), FMI, LMI, waist-to-height ratio, VAT, SAT, adipokines, lumbar spine and total body BMD Z scores. The inferential analyses were as follows:

• Chi-squared test or Fisher's exact test to compare categorical variables, according to GH group.

• One-way Analysis of Variance (ANOVA), with Bonferroni post hoc test for pairwise comparisons if statistically significant in the comparison of numerical variables, according to GH group.

• Fisher´s exact test to compare lumbar spine and total body BMD cutoffs, according to GH group, sex steroid replacement, and sex.

• Multiple linear regressions were adjusted to evaluate the simultaneous effects of predictor variables on lumbar spine L1-L4 and total body BMD Z score (dependent variables). Due to the large number of variables and the sample size, those significant at 10% in the simple linear regression were selected for the multivariate initial models, and then the variables not significant at 5% were excluded one by one in order of significance (backward method), except for Z BMI and Z height at assessment, age at initiation of rhGH, and time receiving sex steroid, which were all considered regardless of their significance due to clinical relevance. Lumbar spine and total body BMD Z scores are indexes already corrected for sex and chronological age. Thus, sex and age were considered as control variables merely for the analyses of adipokines.

The Kolmogorov-Smirnov test was used to verify the normal distribution of variables. In all findings, the significance level of alpha was 5%. Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS) version 20.0.

RESULTS

Subjects' characteristics

The selected sample consisted of 46 CP patients, 29/46 (63%) male, aged [mean ± SD] 9.5 ± 4.2 years at CP diagnosis, 17.0 ± 5.8 years at assessment, and 7.5 ± 4.0 years from diagnosis. Regarding hypothalamic involvement, 36/46 (78.2%) patients were grade 1 or 2 according to Puget's score. Concerning therapy, 18/46 (39.1%) underwent surgery followed by CRT, and 5/46 (10.9%) CP patients received IFN-α as a monotherapy. Regarding hormone replacement, 43/46 (93.5%) received at least two hormones (excluding rhGH). In relation to the GH group, 25/46 (54.3%) CP subjects were classified as non-rhGH, 15/46 (32.6%) as rhGH-c, and 6/46 (13%) as rhGH-p (Table 1).

The results related to GH group are presented in the following sequence: Non-rhGH, rhGH-c, and rhGH-p.

Regarding age at diagnosis [11.1 ± 4.2 *vs.* 6.2 ± 2.5 *vs.* 10.8 ± 2.9 years; P=0.001] and study assessment [18.3 ± 6.8 *vs.* 13.6 ± 2.8 *vs.* 20.2 ± 1.6 years; P<0.001], non-rhGH and rhGH-p presented with similar means but were older than rhGH-c (Table 2).

The rhGH-p group presented with more patients receiving all anterior pituitary hormones (except rhGH) compared to the other groups [16/25 (64%) *vs.* 5/15 (33.3%) *vs.* 5/6 (83.3%); P=0.029]. Additionally, in this group there were more patients receiving sex steroids [17/25 (68.0%) *vs.* 5/15 (33.3%) *vs.* 6/6 (100.0%); P=0.011], at or above 16.2 years [10/25 (40.0%) *vs.* 1/15 (6.7%) *vs.* 3/6 (50.0%); P=0.017], and at or above 3.0 years of therapy [10/25 (40.0%) *vs.* 1/15 (6.7%) *vs.* 4/6 (66.7%); P=0.015] (Table 1).

Patients in the rhGH-p group also started rhGH at or above 11.8 years [0/25 (0.0%) *vs.* 5/15 (33.3%) *vs.* 6/6 (100.0%); P<0.001] and received rhGH up to 2.6 years compared to rhGH-c [0/25 (0.0%) *vs.* 7/15 (46.7%) *vs.* 3/6 (50.0%); P<0.001] (Table 1).

Height, adiposity indexes, and bone mass

At diagnosis, the non-rhGH group presented with an increased Z height compared to the groups that received rhGH [-0.19 ± 1.22 *vs.* -1.74±1.29 *vs.* -2.36 ± 1.45; P<0.001]. Non-rhGH also showed an increase in Z BMI while compared to rhGH-p [1.44 ± 1.57 *vs.* 0.77 ± 1.57 *vs.* -0.30 ± 1.10; P=0.044].

At assessment, non-rhGH presented with an increased Z height compared to rhGH-p [-0.55 ± 0.89 *vs.* -1.25 ± 1.25 *vs.* -1.64 ± 1.16; P=0.034]. Nonetheless, Z BMI showed no differences between groups [2.67 ± 1.15 *vs.* 1.85 ± 2.20 *vs.* 1.42 ± 1.75; P=0.143].

FMI [23.0 ± 8.6 *vs.* 15.8±7.5 *vs.* 19.8 ± 7.3 kg/m^2; P=0.039] and VAT [282.3 ± 140.7 *vs.* 139.3 ± 83.3 *vs.* 200.1 ± 93.5 cm^3; P=0.003] were both increased in non-rhGH compared to rhGH-c.

Leptin [30.4 ± 6.0 *vs.* 22.5 ± 11.6 *vs.* 25.9±7.5 ng/mL; P=0.039] and leptin-to-adiponectin ratio [18.88 ± 14.20 *vs.* 7.98 ± 6.11 *vs.* 8.70 ± 5.89 ng/μg; P=0.011] were both increased in non-rhGH compared to rhGH-c, whereas adiponectin was decreased in both non-rhGH and rhGH-c compared to rhGH-p [2.2 ± 1.1 *vs.* 3.6 ± 1.8 *vs.* 7.5 ± 9.3 μg/mL; P=0.005] (Table 2).

Multiple linear regressions

Lumbar spine L1-L4 bone mineral density Z score: In the final multivariate model, the following variables remained significant: Age at initiation of rhGH at or above 11.8 years (β=-0.938; P=0.025), therapy: Surgery+CRT+IFN-α/bleomycin (β=-1.012; P=0.003) and the presence of diabetes insipidus (β=-0.816; P=0.043). CP patients who started rhGH at or above 11.8 years, subjected to surgery+CRT+IFN-α/bleomycin, and with diabetes insipidus showed a decrease in lumbar spine BMD (Table 3).

Total body bone mineral density Z score: In the final multivariate model, the following variables remained significant: Z BMI at assessment (β=0.188; P=0.025), therapy: CRT/none (β=-1.546; P=0.021), surgery+CRT+IFN-α/bleomycin (β=-0.958; P=0.003), and time receiving sex steroids at or above 3 years (β=0.858; P=0.022). In CP patients, an increase in Z BMI at assessment and exposition to sex steroids at or above 3 years played a positive effect on total body BMD. However, CP patients subjected to CRT/none and the combination of surgery+CRT+IFN-α/bleomycin presented a decrease in total body BMD. To date, the CRT/none group was composed of only two patients (Table 4).

Bone mineral density cutoffs: Low BMD for chronologic age was detected in 21.7% of patients at the lumbar spine and 10.9% at the total body. There were no significant differences in BMD Z score cutoffs as regards GH group (Table 5), sex steroid replacement therapy or sex (data not shown).

Table 1: General traits, hypothalamic involvement, therapy, and hormone replacement of CP patients, according to GH group.

Variable	GH group			Total (n=46) n (%)	P-value
	Non-rhGH (n=25) n (%)	rhGH-c (n=15) n (%)	rhGH-p (n=6) n (%)		
Sex					>0.999
Female	9 (36.0)	6 (40.0)	2 (33.3)	17 (37.0)	
Male	16 (64.0)	9 (60.0)	4 (66.7)	29 (63.0)	
Hypothalamic involvement (grade)					0.907
1	2 (8.0)	1 (6.7)	0 (0.0)	3 (6.5)	
2	17 (68.0)	12 (80.0)	4 (66.7)	33 (71.7)	
NA	6 (24.0)	2 (13.3)	2 (33.3)	10 (21.7)	
Therapy					0.249
IFN-α	1 (4.0)	2 (13.3)	2 (33.3)	5 (10.9)	
Surgery	2 (8.0)	1 (6.7)	1 (16.7)	4 (8.7)	
CRT	1 (4.0)	0 (0.0)	0 (0.0)	1 (2.2)	
Surgery+IFN-α	4 (16.0)	0 (0.0)	0 (0.0)	4 (8.7)	
Surgery+CRT	9 (36.0)	8 (53.3)	1 (16.7)	18 (39.1)	
Surgery+CRT+IFN-α	6 (24.0)	4 (26.7)	1 (16.7)	11 (23.9)	
Surgery+CRT+bleomycin	2 (8.0)	0 (0.0)	0 (0.0)	2 (4.3)	
None	0 (0.0)	0 (0.0)	1 (16.7)	1 (2.2)	
Hormone replacement therapy, except rhGH					0.029
LT4	1 (4.0)	1 (6.7)	0 (0.0)	2 (4.3)	
LT4+GC	7 (28.0)	9 (60.0)	0 (0.0)	16 (34.8)	
GC+sex steroid	1 (4.0)	0 (0.0)	0 (0.0)	1 (2.2)	
LT4+GC+sex steroid	16 (64.0)	5 (33.3)	5 (83.3)	26 (56.5)	
None	0 (0.0)	0 (0.0)	1 (16.7)	1 (2.2)	
Diabetes insipidus					0.067
No	3 (12.0)	1 (6.7)	3 (50.0)	7 (15.2)	
Yes	22 (88.0)	14 (93.3)	3 (50.0)	39 (84.8)	
Sex steroid replacement therapy					0.011
No	8 (32.0)	10 (66.7)	0 (0.0)	18 (39.1)	
Yes	17 (68.0)	5 (33.3)	6 (100.0)	28 (60.9)	
Age at initiation of sex steroid (years)					0.017
No use	8 (32.0)	10 (66.7)	0 (0.0)	18 (39.1)	
<16.2 (median)	7 (28.0)	4 (26.7)	3 (50.0)	14 (30.4)	
≥ 16.2	10 (40.0)	1 (6.7)	3 (50.0)	14 (30.4)	
Time receiving sex steroid (years)					0.015
No use	8 (32.0)	10 (66.7)	0 (0.0)	18 (39.1)	
<3.0 (median)	7 (28.0)	4 (26.7)	2 (33.3)	13 (28.3)	
≥ 3.0	10 (40.0)	1 (6.7)	4 (66.7)	15 (32.6)	
Age at initiation of rhGH (years)					<0.001
No use	25 (100.0)	0 (0.0)	0 (0.0)	25 (54.3)	
<11.8 (median)	0 (0.0)	10 (66.7)	0 (0.0)	10 (21.7)	
≥ 11.8	0 (0.0)	5 (33.3)	6 (100.0)	11 (23.9)	
Time receiving rhGH (years)					<0.001
No use	25 (100.0)	0 (0.0)	0 (0.0)	25 (54.3)	
<2.6 (median)	0 (0.0)	7 (46.7)	3 (50.0)	10 (21.7)	
≥ 2.6	0 (0.0)	8 (53.3)	3 (50.0)	11 (23.9)	

Note: Chi-squared test or Fisher´s exact test. Subgroup percentages may not total 100% due to rounding. **Abbreviations:** CP: Craniopharyngioma, GH: Growth Hormone, rhGH: Recombinant human GH, c-rhGH: Current therapy with rhGH, p-rhGH: Previous therapy with rhGH, NA: Not available, IFN-α: Interferon-α, CRT: Cranial radiation therapy, LT4: Levothyroxine sodium, GC: Glucocorticoid.

Table 2: General characteristics, adiposity indexes, and bone mass variables of CP patients, according to GH group.

Variable	n	Non-rhGH (GI)		n	rhGH-c (GII)		n	rhGH-p (GIII)		P-value	P GIxGII	P GIxGIII	P GIIxGIII
		Mean ± SD	Median (min; max)		Mean ± SD	Median (min; max)		Mean ± SD	Median (min; max)				
At diagnosis													
Age (years)	25	11.1 ± 4.2	10.6 (4.9; 23.0)	15	6.2 ± 2.5	6 (1.9; 11.1)	6	10.8 ± 2.9	11.6 (5.5; 13.7)	0.001	<0.001	>0.999	0.025
Height (Z score)	25	-0.19 ± 1.22	-0.36 (-2.25; 2.34)	15	-1.74 ± 1.29	-1.98 (-4.42; 0.17)	6	-2.36 ± 1.45	-2.55 (-4.63; -0.74)	<0.001	0.001	0.001	0.938
BMI (Z score)	25	1.44 ± 1.57	1.8 (-3.50; 3.39)	15	0.77 ± 1.57	0.86 (-1.43; 4.77)	6	-0.30 ± 1.10	-0.35 (-2.19; 0.91)	0.044	0.550	0.037	0.438
At assessment													
Age (years)	25	18.3 ± 6.8	17.3 (6.6; 32.1)	15	13.6 ± 2.8	13.7 (9; 17.4)	6	20.2 ± 1.6	20.3 (18.3; 22.3)	<0.001	0.024	>0.999	0.036
Height (Z score)	25	-0.55 ± 0.89	-0.58 (-2.32; 1.89)	15	-1.25 ± 1.25	-1.15 (-3.85; 0.71)	6	-1.64 ± 1.16	-1.61 (-3.08; 0.28)	0.034	0.132	0.023	>0.999
BMI (Z score)	25	2.67 ± 1.15	2.64 (0.28; 4.21)	15	1.85 ± 2.20	1.62 (-1.66; 7.11)	6	1.42 ± 1.75	1.91 (-1.40; 3.10)	0.143	0.383	0.277	>0.999
FMI (kg/m²)	25	23.0 ± 8.6	23.2 (8.1; 37.7)	14	15.8 ± 7.5	15.1 (3.0; 30.6)	6	19.8 ± 7.3	19.7 (9.7; 30.3)	0.039	0.025	>0.999	0.946
LMI (kg/m²)	25	26.9 ± 6.8	27.8 (14.6; 38.4)	14	22.4 ± 4.9	22 (13.4; 31.6)	6	24.8 ± 7.0	23.9 (17.6; 35.0)	0.115	0.100	>0.999	>0.999
Waist-to-height ratio	25	0.66 ± 0.08	0.66 (0.50; 0.79)	15	0.62 ± 0.14	0.60 (0.45; 0.99)	6	0.62 ± 0.08	0.62 (0.51; 0.73)	0.493	0.835	>0.999	>0.999
Visceral adipose tissue (cm³)	25	282.3 ± 140.7	285.1 (21.2; 603.0)	15	139.3 ± 83.3	127.7 (15.6; 294.4)	6	200.1 ± 93.5	182.5 (104.3; 375.3)	0.003	0.001	0.391	0.864
Subcutaneous adipose tissue (cm³)	25	681.2 ± 353.5	677.9 (126.4; 1478.1)	15	501.8 ± 361.1	359.5 (73.9; 1,313.2)	6	764.6 ± 462.4	781 (177.2 ; 1,414.0)	0.233	0.435	>0.999	0.428
Leptin (ng/mL)	25	30.4 ± 6.0	31.6 (10.4; 36.6)	15	22.5 ± 11.6	29.9 (5.0; 33.8)	6	25.9 ± 7.5	28.5 (14.3; 33.1)	0.039	0.013	0.723	>0.999

Adiponectin (µg/mL)	25	2.2 ± 1.1	2.1 (0.4; 5.0)	15	3.6 ± 1.8	3.1 (1.7; 7.4)	6	7.5 ± 9.3	2.9 (1.2; 24.9)	0.005	0.688	0.002	0.048
Leptin-to-adiponectin ratio (ng/µg)	25	18.88 ± 14.20	15.69 (2.07; 66.67)	15	7.98 ± 6.11	5.86 (1.36; 19.72)	6	8.70 ± 5.89	10.37 (0.77; 16.16)	0.011	0.010	0.146	1.000
Resistin (ng/mL)	25	13.0 ± 4.8	11.7 (6.9; 28.6)	15	10.3 ± 2.0	10.3 (7.2; 14.0)	6	14.6 ± 6.2	13 (9.6; 26.3)	0.163	0.183	>0.999	0.119
Visfatin (ng/mL)	25	21.9 ± 24.4	17.3 (1.6; 128.8)	15	20.8 ± 13.3	17.3 (4.3; 46.4)	6	21.1 ± 12.1	22.1 (6.2; 35.9)	0.987	>0.999	>0.999	>0.999
Lumbar spine L1-L4 BMD (Z score)	25	-0.89 ± 1.07	-0.80 (-3.00; 1.10)	15	-1.31 ± 1.14	-1.40 (-3.20; 0.50)	6	-1.45 ± 0.94	-1.70 (-2.60; 0.20)	0.351	0.695	0.765	>0.999
Total body BMD (Z score)	25	-0.16 ± 1.00	0.00 (-2.00; 1.70)	15	-0.48 ± 1.11	-0.10 (-2.50; 1.80)	6	-0.63 ± 1.54	-0.65 (-2.40; 1.10)	0.531	>0.999	>0.999	>0.999

Note: Analysis of Variance (ANOVA) with Bonferroni post-hoc test.

Abbreviations: CP: Craniopharyngioma, GH: Growth Hormone, rhGH: Recombinant human GH, c-rhGH: Current therapy with rhGH, p-rhGH: Previous therapy with rhGH, SD: Standard Deviation, min: Minimum value, max: Maximum value, BMI: Body Mass Index, FMI: Fat Mass Index, LMI: Lean Mass Index, BMD: Bone Mineral Density.

Table 3: Estimated parameters from L1-L4 BMD Z score linear regression models, among CP patients.

	Univariate model		Multivariate model			
			Initial		Final	
	β (CI95%)	P	β (CI95%)	P	β (CI95%)	P
GH group (reference=Non-rhGH)		0.351		-		-
rhGH-c	-0.421 (-1.132; 0.289)	0.238	-	-	-	-
rhGH-p	-0.558 (-1.547; 0.431)	0.261	-	-	-	-
Age at initiation of rhGH (years)-reference (No use)		0.080		0.096		0.058
<11.8 (mean)	-0.038 (-0.824; 0.748)	0.923	0.132 (-0.649; 0.914)	0.732	0.099 (-0.664; 0.863)	0.794
≥ 11.8	-0.844 (-1.605; -0.084)	0.030	-0.871 (-1.72; -0.022)	0.045	-0.938 (-1.753; -0.124)	0.025
Time receiving rhGH (years)-reference (No use)		0.327		-		-
<2.6 (mean)	-0.348 (-1.160; 0.464)	0.392	-	-	-	-
≥ 2.6	-0.563 (-1.348; 0.223)	0.156	-	-	-	-
Age at diagnosis (years)	0.039 (-0.038; 0.116)	0.317	-	-	-	-
Z BMI at diagnosis	-0.093 (-0.296; 0.111)	0.363	-	-	-	-
Z BMI at assessment	0.194 (0.007; 0.382)	0.042	0.096 (-0.086; 0.278)	0.292	0.114 (-0.062; 0.290)	0.199
Z height at assessment	0.167 (-0.124; 0.458)	0.253	0.045 (-0.248; 0.338)	0.758	0.017 (-0.272; 0.306)	0.907
FMI (kg/m^2)	0.01 (-0.028; 0.049)	0.587	-	-	-	-

LMI (kg/m^2)	0.025 (-0.025; 0.075)	0.323	-	-	-	-
Waist-to-height ratio	2.146 (-0.918; 5.211)	0.165	-	-	-	-
VAT (cm^3)	0.001 (-0.002; 0.004)	0.452	-	-	-	-
SAT (cm^3)	0.000 (0.000; 0.001)	0.365	-	-	-	-
Therapy group (reference=surgery+CRT)		0.039		0.034		
IFN-α	-0.072 (-1.089; 0.944)	0.887	-0.491 (-1.621; 0.639)	0.383	-	-
Surgery	-0.972 (-2.084; 0.139)	0.085	-0.687 (-1.740; 0.367)	0.194	-	-
CRT/none	-0.222 (-1.721; 1.277)	0.766	-1.401 (-3.172; 0.370)	0.117	-	-
Surgery+IFN-α	0.353 (-0.759; 1.464)	0.525	-0.198 (-1.484; 1.089)	0.757	-	-
Surgery+CRT+IFN-α/ bleomycin	-1.072 (-1.804; -0.340)	0.005	-1.281 (-2.059; -0.502)	0.002	-1.012 (-1.666; -0.358)	0.003
Number of hormone replacement (reference=3)		0.240		-	-	-
0 to 1	-0.178 (-1.493; 1.136)	0.786	-	-	-	-
2	0.536 (-0.137; 1.208)	0.116	-	-	-	-
Diabetes insipidus	-0.778 (-1.650; 0.095)	0.079	-1.226 (-2.307; -0.146)	0.027	-0.816 (-1.606; -0.026)	0.043
Leptin (ng/mL)[a]	0.016 (-0.024; 0.057)	0.416	-	-	-	-
Adiponectin (µg/mL)[a]	0.028 (-0.061; 0.117)	0.534	-	-	-	-
Leptin-to-adiponectin ratio (ng/µg)[a]	0.013 (-0.016; 0.043)	0.368	-	-	-	-
Resistin (ng/mL)[a]	-0.009 (-0.086; 0.068)	0.817	-	-	-	-
Visfatin (ng/mL)[a]	0.001 (-0.017; 0.019)	0.906	-	-	-	-
Sex steroid replacement therapy (reference=No use)	-0.350 (-1.007; 0.306)	0.288	-	-	-	-
Age at initiation of sex steroid (years) - reference (No use)		0.253		-	-	-
<16.2 (median)	-0.611 (-1.38; 0.158)	0.116	-	-	-	-
≥ 16.2	-0.090 (-0.859; 0.68)	0.815	-	-	-	-
Time receiving sex steroid (years) - reference (No use)		0.236		0.645	-	0.780
<3.0	-0.642 (-1.426; 0.143)	0.106	0.143 (-0.66; 0.945)	0.720	0.001 (-0.766; 0.769)	0.997
≥ 3.0	-0.098 (-0.851; 0.656)	0.795	0.434 (-0.524; 1.392)	0.364	0.225 (-0.543; 0.993)	0.556
R^2	-		50.0%		43.8%	
R^2 adjusted	-		31.6%		31.6%	

Note: n=46 to initial and final multiple linear models. Kolmogorov-Smirnov test for normality of initial (P=0.724) and final multivariate model (P=0.581). [a]Adjusted for sex and age at assessment.

Abbreviations: BMD: Bone Mineral Density, CP: Craniopharyngioma, CI: Confidence Interval, GH: Growth Hormone, rhGH: Recombinant Human GH, c-rhGH: Current Therapy with rhGH, p-rhGH: Previous Therapy with rhGH, BMI: Body Mass Index, FMI: Fat Mass Index, LMI: Lean Mass Index, VAT: Visceral Adipose Tissue, SAT: Subcutaneous Adipose Tissue, CRT: Cranial Radiation Therapy, IFN-α: Interferon-α.

Table 4: Estimated parameters from total body BMD Z score linear regression models, among CP patients.

	Univariate model		Multivariate model			
			Initial		Final	
	β (CI95%)	P	β (CI95%)	P	β (CI95%)	P
GH group (reference=Non-rhGH)		0.531		-		-
rhGH-c	-0.316 (-1.046; 0.414)	0.387	-	-		-
rhGH-p	-0.469 (-1.485; 0.546)	0.357	-	-		-
Age at initiation of rhGH (years)-reference (No use)		0.036		0.131		0.077
<11.8 (median)	0.214 (-0.571; 0.999)	0.585	0.570 (-0.214; 1.354)	0.148	0.624 (-0.081; 1.329)	0.081
≥ 11.8	-0.881 (-1.641; -0.122)	0.024	-0.462 (-1.295; 0.37)	0.265	-0.389 (-1.141; 0.363)	0.301
Time receiving rhGH (years)-reference (No use)		0.150		-		-
<2.6 (median)	0.044 (-0.768; 0.856)	0.913	-	-	-	-
≥ 2.6	-0.727 (-1.512; 0.058)	0.069	-	-	-	-
Age at diagnosis (years)	0.024 (-0.056; 0.103)	0.551	-	-	-	-
Z BMI at diagnosis	0.109 (-0.097; 0.315)	0.294	-	-	-	-
Z BMI at assessment	0.283 (0.102; 0.463)	0.003	0.010 (-0.576; 0.596)	0.973	0.188 (0.025; 0.351)	0.025
Z height at assessment	0.364 (0.085; 0.643)	0.012	0.341 (-0.025; 0.707)	0.067	0.255 (-0.009; 0.519)	0.058
FMI (kg/m^2)	0.039 (0.001; 0.077)	0.044	-0.058 (-0.182; 0.066)	0.345	-	-
LMI (kg/m^2)	0.056 (0.007; 0.106)	0.027	0.045 (-0.035; 0.126)	0.262	-	-
Waist-to-height ratio	3.350 (0.330; 6.370)	0.030	6.999 (-7.219; 21.217)	0.323	-	-
VAT (cm^3)	0.002 (-0.001; 0.004)	0.177	-	-	-	-
SAT (cm^3)	0.001 (0.000; 0.002)	0.170	-	-	-	-
Therapy group (reference=surgery+CRT)		0.068		0.018		0.003
IFN-α	0.228 (-0.824; 1.28)	0.664	0.526 (-0.412; 1.464)	0.262	-	-
Surgery	-0.497 (-1.648; 0.653)	0.388	-0.211 (-1.265; 0.843)	0.685	-	-
CRT/none	-1.172 (-2.724; 0.379)	0.135	-1.557 (-3.023; -0.09)	0.038	-1.546 (-2.842; -0.250)	0.021
Surgery+IFN-α	0.853 (-0.298; 2.003)	0.142	-0.273 (-1.532; 0.985)	0.661	-	-
Surgery+CRT+IFN-α/bleomycin	-0.726 (-1.484; 0.032)	0.060	-1.065 (-1.827; -0.303)	0.008	-0.958 (-1.566; -0.351)	0.003
Number of hormone replacement (reference=3)		0.293		-		-
0 to 1	-0.696 (-2.04; 0.647)	0.302	-	-	-	-
2	0.327 (-0.36; 1.015)	0.342	-	-	-	-
Diabetes insipidus	0.219 (-0.697; 1.136)	0.632	-	-	-	-
Leptin (ng/mL)[a]	-0.002 (-0.044; 0.040)	0.922	-	-	-	-
Adiponectin (μg/mL)[a]	-0.06 (-0.149; 0.029)	0.178	-	-	-	-
Leptin-to-adiponectin ratio (ng/μg)[a]	0.012 (-0.018; 0.043)	0.415	-	-	-	-
Resistin (ng/mL)[a]	0.054 (-0.023; 0.131)	0.161	-	-	-	-
Visfatin (ng/mL)[a]	-0.002 (-0.020; 0.016)	0.834	-	-	-	-
Sex steroid replacement therapy (reference=No use)	-0.320 (-0.990; 0.349)	0.340	-	-	-	-

Age at initiation of sex steroid (years) - reference (No use)		0.488		-		-
<16.2 (median)	-0.474 (-1.268; 0.321)	0.236	-	-	-	-
≥ 16.2	-0.167 (-0.961; 0.628)	0.674	-	-	-	-
Time receiving sex steroid (years) - reference (No use)		0.109		0.350		0.035
< 3.0 (mean)	-0.736 (-1.520; 0.048)	0.065	0.184 (-0.730; 1.097)	0.684	0.091 (-0.618; 0.799)	0.797
≥ 3.0	0.040 (-0.713; 0.793)	0.915	0.743 (-0.376; 1.862)	0.185	0.858 (0.129; 1.586)	0.022
R^2	-		59.4%		53.7%	
R^2 adjusted	-		40.4%		43.7%	

Note: n=46 to initial and final multiple linear models. Kolmogorov-Smirnov test for normality of initial (P=0.868) and final multivariate model (P=0.864).
[a]Adjusted for sex and age at assessment.
Abbreviations: BMD: Bone Mineral Density, CP: Craniopharyngioma, CI: Confidence Interval, GH: Growth Hormone, rhGH: Recombinant human GH, c-rhGH: Current therapy with rhGH, p-rhGH: Previous therapy with rhGH, BMI: Body Mass Index, FMI: Fat Mass Index, LMI: Lean Mass Index, VAT: Visceral Adipose Tissue, SAT: Subcutaneous Adipose Tissue, CRT: Cranial Radiation Therapy, IFN-α: Interferon-α.

Table 5: L_1-L_4 and total body BMD Z score cutoffs of CP patients, according to GH group.

Variable	GH group			Total (n=46) n (%)	P-value
	Non-rhGH (n=25) n (%)	rhGH-c (n=15) n (%)	rhGH-p (n=6) n (%)		
Lumbar spine L1-L4					0.169
≥ -1.0	15 (60.0)	6 (40.0)	1 (16.7)	22 (47.8)	
-2.0 to -1.0	6 (24.0)	4 (26.7)	4 (66.7)	14 (30.4)	
≤ -2.0	4 (16.0)	5 (33.3)	1 (16.7)	10 (21.7)	
Total body					0.284
≥ -1.0	19 (76.0)	9 (60.0)	3 (50.0)	31 (67.4)	
-2.0 to -1.0	5 (20.0)	4 (26.7)	1 (16.7)	10 (21.7)	
≤ -2.0	1 (4.0)	2 (13.3)	2 (33.3)	5 (10.9)	

Note: Fisher´s exact test. Subgroup percentages may not total 100% due to rounding.
Abbreviations: BMD: Bone Mineral Density, CP: Craniopharyngioma, GH: Growth Hormone, rhGH: Recombinant human GH, c-rhGH: Current therapy with rhGH, p-rhGH: Previous therapy with rhGH.

DISCUSSION

This study investigated whether body composition, sex steroid and/or rhGH replacement influenced BMD in CP patients. The main finding of this study was that CP patients subjected to CRT combined with surgery and intracystic therapy presented with decreased lumbar spine and total body BMD. On the other hand, increased Z BMI at assessment had a positive effect on total body BMD. While considering hormone deficiencies, age at initiation of rhGH at or above 11.8 years and the presence of diabetes insipidus played a negative effect on lumbar spine BMD. Nonetheless, receiving sex steroid replacement at or above 3 years was considered a beneficial factor for total body BMD.

Along with genetic background, the disease itself and/or treatment, a combination of factors, including hypothalamic involvement, obesity, leptin resistance, insufficient sex steroid supplementation, and GH deficiency may determine BMD in CP patients [4-8,14-17]. Patients treated for CP frequently receive a combination of either total or subtotal surgery, CRT and/or intracystic IFN-α, which has been administered as a monotherapy with good results and reduced complications (in this study in 10.9% of CP subjects). Intracystic bleomycin used to be administered locally, but it was discontinued due to its adverse effects, particularly neurotoxicity, and frequent leakage into the brain parenchyma [8,24,33].

In this sample, the combination of surgery+CRT+intracystic IFN-α/bleomycin was a predisposing factor to decrease BMD in the lumbar spine and total body. The negative effect of therapy is in discordance with a recent statement, in which surgery was considered an independent protective factor for fractures in CP patients. It seems that the combination of CRT with additional types of therapies may decrease bone mass. However, it is difficult to assess the real role of each independent factor. The synergistic effect of the disease itself and therapy may be an important factor to decrease bone mass, considering that the majority of CP patients in this sample have a serious hypothalamic injury according to Puget's system [16,23]. Nonetheless, the group exposed to CRT only and/or nontherapy was composed of only two patients, which is not clinically important so far.

Regarding hormone replacement, the rhGH-p group presented with more anterior pituitary hormone deficiencies (except GH) compared to the remaining groups, which might be due to the older chronologic age as the degree of hypothalamic involvement was similar in all CP patients. The presence of

diabetes insipidus was a negative factor for lumbar spine bone mass, which is in accordance with a previous statement among patients with idiopathic central diabetes insipidus, in whom therapy with endonasal desmopressin at standard doses was not able to prevent or reverse bone impairment [14,34].

Sex steroid replacement was introduced according to the protocol presented. Nonetheless, due to relapses and/or other complications, some patients started this therapy older than recommended (median age 16.2 years). The rhGH-p group started replacement at or above 16.2 years and was replaced at or above 3 years. While considering the effect of these factors on BMD and/or the cutoffs, only time receiving sex steroids played a beneficial role on total body BMD. Even though rhGH-p started the induction of puberty at an older age, they had an adequate acquisition of bone mass. There were no differences between those patients with no replacement thus far, and the group receiving less than 3 years. Sex steroids influence the growth and maintenance of bones and muscles, and a decline in their levels may lead to loss of functional integrity in both tissues [14,35].

The replacement of rhGH in the rhGH-p group started at or above 11.8 years, and rhGH was given for less than 2.6 years, which played a negative role in determining lumbar spine BMD. GH promotes myogenesis and osteoblastogenesis, and induces chondrogenesis at the growth plate [36-38]. Notwithstanding, in a previous study with this CP cohort, rhGH also played a beneficial role in decreasing total body fatness and VAT, which is in accordance with prior data that showed that rhGH may prevent further fat gain. Additionally, starting rhGH therapy at a younger age and being replaced for more than 2.6 years might also have an extra beneficial effect on bone mass [8].

The non-rhGH group presented with a satisfactory growth velocity during follow-up, along with an increase in body fatness indexes and metabolic derangements (data already published) [8]. Nonetheless, this profile did not exert a negative effect on BMD thus far. This phenomenon is named "growth without GH" and involves several hormones, such as leptin and insulin, but is still not completely understood [39].

CP is considered a model for hypothalamic obesity, which is a devastating result of functional damage to the hypothalamus network, leading to a higher occurrence of MS traits and cardiovascular disease [5-8]. As CP patients are at an increased risk for this severe type of obesity, and there is an increased risk of fractures among them [16], one may suppose that adiposity should also be an important factor to explain this association [5-8,38]. Nonetheless, the relationship between bone, fatness and the impact of obesity during skeletal development is a matter of debate. Obesity has been considered a beneficial factor for bone health due to the positive effect of mechanical loading conferred by body weight on bone formation [38]. On the other hand, fat accumulation may also affect bone through the direct effect of adipokines or indirectly through the state of chronic inflammation associated with obesity, which may induce bone resorption [9,13,18-22].

In this CP cohort, Z BMI at assessment positively determined BMD at the total body site. Z height was maintained in the multivariate analysis to correct differences among GH group. The adiposity indexes FMI and VAT were increased in the non-rhGH group. However, fatness and lean mass have not played an important role in determining BMD in the multivariate models. Low bone mass, sarcopenia, and obesity are commonly observed in the process of aging, and recent evidence has suggested a potential interconnection between these compartments with common pathophysiology, even though this interaction is still poorly understood and not detected in this CP cohort thus far [15,40].

To date, there are few studies regarding BMD among CP patients [14-17], and no study has evaluated the relationship between adipokines and bone mass. Leptin and adiponectin are far the more studied in other cancer models. Nevertheless, their role in bone mass acquisition and metabolism is not clear so far. In this study sample, leptin and leptin-to-adiponectin ratio were both increased in the non-rhGH group, whereas adiponectin was decreased. However, in the multivariate model, adipokines did not play a role in determining BMD, while previous studies have identified leptin as a potent inhibitor of bone formation [9,13,22,41].

On the other hand, 21.7% of CP patients presented with low BMD at the lumbar spine and 10.9% at the total body, with no fractures so far, which is consistent with previous studies in which CP patients are at an increased risk for low BMD; however, the predominance between females was not detected in this CP cohort [14-17]. So far, a very low BMD seems not to be a good predictor for fracture risk in CP patients. Many reasons have already been described to explain decreased BMD; however, it appears that there is a combination of factors involved [4-8,14-17].

Considering study limitations, non-rhGH and rhGH-p group were older, which is not clinically relevant, as other important factors, such as obesity, therapy and hormone deficiencies were adequately adjusted. In addition, this is a sample from a single institution, and there is no information on physical activity, nutritional intake, and the use of anti-epileptic drugs so far.

CONCLUSION

In conclusion, childhood-onset CP patients at a mean of 7.5 years from diagnosis presented with low lumbar spine and total body BMD related to the type of therapy employed (CRT and combinations), but no fractures so far. Z BMI at assessment and the replacement of sex steroids at or above 3 years had a positive effect on total body site. On the other hand, the initiation of rhGH at an older age and the presence of diabetes insipidus had a negative effect on lumbar spine bone mass. A group of factors may determine BMD among CP subjects, reflecting an integration that could possibly explain unidentified mechanisms linking bone, metabolism and cancer.

ACKNOWLEDGEMENT

The authors greatly thank the patients and their families. The authors appreciate the technical assistance of Prof. Bruno Geloneze, M.D., Ph.D., and Antonio Ramos Calixto, Ph.D. for the adipokine evaluation; Ricardo Silva Ribeiro for performing the CT scans; and Mitti Koyama for the statistical revision.

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