Diagnosing metabolic syndrome in craniopharyngioma patients: body composition versus BMI

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Abstract

Objective: Craniopharyngioma patients often have poor metabolic profiles due to hypothalamic–pituitary damage. Previously, using BMI as obesity marker, the occurrence of the metabolic syndrome in these patients was estimated at 46%. Our aim was to determine if dual X-ray absorptiometry (DXA) scan in evaluation of obesity and metabolic syndrome would be superior.

Design: Retrospective study of craniopharyngioma patients for whom DXA scan results were available.

Methods: BMI, fat percentage and fat mass index were used to evaluate obesity and as components for obesity in metabolic syndrome.

Results: Ninety-five craniopharyngioma patients were included (51% female, 49% childhood-onset disease). Metabolic syndrome occurred in 34–53 (45–51%) subjects (depending on the definition of obesity, although all definitions occurred in higher frequency than in the general population). Metabolic syndrome frequency was higher if obesity was defined by fat percentage (52 vs 42%) or fat mass index (51 vs 43%) compared to BMI. Misclassification appeared in 9% (fat percentage vs BMI) and 7% (fat mass index vs BMI) for metabolic syndrome and 29 and 13% for obesity itself, respectively. For metabolic syndrome, almost perfect agreement was found for BMI compared with fat percentage or fat mass index. For obesity, agreement was fair to moderate (BMI vs fat percentage).

Conclusion: Using BMI to evaluate obesity underestimates the true prevalence of metabolic syndrome in patients with craniopharyngioma. Furthermore, fat percentage contributes to a better evaluation of obesity than BMI. The contribution of DXA scan might be limited for identification of the metabolic syndrome.

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Introduction

Craniopharyngiomas (CPs) are tumors in the (supra)sellar region that occur both in children and adults, with peak incidences between ages 5–9 and 40–44 years (1, 2). These tumors are rare with an estimated incidence rate of 1.7 per million person years (1, 2) and relatively high 10-year survival rates at between 77 and 93% (2, 3). Still, the burden

to patients, their families (2, 4) and to the community is substantial, particularly because of the increased risk of long-term morbidity (2, 5, 6) and mortality compared to the general population (2, 3, 5, 7). The standardized mortality ratio from cardio- and cerebrovascular disease has been reported to be between 3.2 and 19.4 (2, 6, 8).

Although histologically benign, CP can physically disturb important neurovascular structures (9), particularly the hypothalamus, pituitary and optic nerves (3, 9). The hypothalamus plays a major role in integrating hormonal, metabolic and neural signals for energy homeostasis (7). Failure of the hypothalamo–pituitary axis is strongly linked with the development of obesity, metabolic syndrome (3, 7, 10, 11, 12) and subsequent cardiovascular disease (8, 13). Visual impairment (i.e. due to tumor growth near the optic nerve) occurs in approximately 75% of the patients (3) and is a barrier to engage in physical activity.

Up to two-thirds of the patients are found to be overweight or obese (3, 14), and in a study of 224 Dutch and Swedish patients, 9% has been diagnosed with type II diabetes mellitus (T2D) (5). Obesity and T2D are both associated with cardiovascular disease and cerebral infarction (15, 16); the latter has been shown to be an important cause of mortality (5). Severe weight gain is especially seen in the first year after the operation (17). Both levels of physical activity and basal metabolic rate are low in patients with CP (7, 18).

Obesity is an important contributor to the metabolic syndrome (MetS) in CP survivors (6). Many definitions of MetS have been formulated, but all include obesity, dyslipidemia, hypertension and altered glucose metabolism as components (6). MetS and T2D are two important risk factors for cardiovascular disease, giving a two-fold and five-fold elevated risk respectively (19). MetS is associated with an increase in all-risk mortality (20). The prevalence of MetS has been estimated to be 46% in a previous study of CP survivors (6). This is very high compared to the general population (15% in the Swedish and the 26% in Dutch populations of that age) (6). Obesity rates in the previous study were estimated based on BMI. BMI is the most accessible method for estimating obesity in a clinical setting, but does not take into account an altered body composition. Dual X-ray absorptiometry (DXA scan) is considered the gold standard for determining body composition where there is suspected discordance between BMI and adiposity (21). Furthermore, compared with measurement of body fat percentage (BF%) by DXA scan, BMI has been found to underestimate obesity in adult, non-CP childhood cancer survivors (22). Therefore, considering the relatively substantial contribution of adiposity to MetS in CP survivors, we hypothesized that the occurrence of MetS defined using BMI is underestimated in our cohort of CP patients due to their altered body composition.

Our aim was to investigate the value of DXA scan in cardiovascular risk assessment in CP patients. Our main

objective was to compare the relative effectiveness of BMI and DXA scan-derived body composition measures such as BF% and fat mass index (FMI) in the evaluation of MetS. Our secondary objective was also to determine influencing factors of obesity and MetS in CP survivors. Our approach was to determine the agreement between methods and to perform logistic regression models.

Subjects and methods

Patients and study design

The study had a cross-sectional and retrospective design. Patients treated for CP at the Erasmus University Medical Center (Erasmus MC, Rotterdam, the Netherlands) and Sahlgrenska University Hospital (Gothenburg, Sweden) were included as described before (6). Only patients with at least one DXA scan available were included in the study (included, $n=95$; excluded, $n=61$, description shown in Supplementary Table 1, see section on [supplementary data](#) given at the end of this article). The decision to perform a DXA scan was made by the physicians in the context of general care. Although it was not possible to retrieve much information on why the decision was made, it may be assumed this was done to evaluate bone mineral density (BMD). If BMD was not of interest, bio-electrical impedance analysis measurements were an option in the Erasmus MC, which are less costly, easier to plan and do not involve any radiation. The most frequently used DXA scanners were Lunar DPXL, Lunar Prodigy and Lunar iDXA (see Supplementary Table 2). The study was approved by the Ethical Review Board of Erasmus MC and the Regional Ethical Review Board, Gothenburg University. All patients gave their informed consent.

Data collection

The methods and definitions for data collection were described previously (6). Hypothalamic damage is defined as tumor- and/or treatment-related injury to the hypothalamus and/or third ventricle as visualized by neuroimaging (6). If patients were treated for ACTH deficiency with cortisone acetate, the dose was converted to a hydrocortisone equivalent dose (described previously (23)). For the current study, the presence of MetS criteria was evaluated as close as possible (± 3 years) to the last DXA scan. The results of DXA scan, including BMI, FMI and BF% were gathered. If patients had more than one scan, data from the first and last DXA scan were gathered.

Table 1 Definition of the metabolic syndrome: adjustments to the joint interim statement (6).

At least three of the following five criteria:

- Obesity defined by high BMI or defined by high body fat percentage (BF%) or defined by high fat mass index (FMI)
- Fasting glucose ≥ 5.6 mmol/L (or corresponding HbA1c of $\geq 5.2\%$ or 33.3 mmol/mol) or drug treatment for increased glucose
- Triglycerides ≥ 1.7 mmol/L or drug treatment for elevated triglycerides
- HDL cholesterol < 1.0 mmol/L in males and < 1.3 mmol/L in females or drug treatment for reduced HDL cholesterol
- Blood pressure $\geq 130/85$ mmHg or drug treatment for hypertension

HDL, high-density lipoprotein.

BMI was calculated by dividing the weight (kg) per squared height (meters). FMI was calculated by total fat mass (kg) per square height (meters). Obesity (high BMI): defined by BMI > 30 , or by ≥ 2 SDS score. Obesity (high BF%): defined by high BF% with limits defined according to sex and age (for females as a BF% $\geq 39\%$ if aged 20–39 years old or $\geq 41\%$ between 40 and 59 years old, and for males $\geq 26\%$ if 20–39 years old or $\geq 29\%$ in the age category of 40–59, or by SDS-score ≥ 2). Obesity (high FMI): defined by high FMI with limits defined according to sex and age (for adult females ≥ 13 ; for males ≥ 9).

The criteria used in the definition for MetS were according to the joint interim statement as described previously (6) with modification of the criterion of obesity and matching HbA1c values for high glucose (Table 1). MetS includes components of obesity, low high-density lipoprotein (HDL) cholesterol and high triglycerides, fasting glucose/HbA1c and blood pressure or pharmaceutical treatment (see below and Table 1). Three different definitions of obesity were used as criterion for MetS: based on high BMI, high BF% and high FMI. High BMI was defined as $> 30 \text{ kg/m}^2$ or SDS > 2 (24, 25). High BF% was defined through total body fat percentage as measured by DXA; for females as a BF% $\geq 39\%$ if aged 20–39 years old or $\geq 41\%$ if aged 40–59 years old. For males, this was $\geq 26\%$ if aged 20–39 years old or $\geq 29\%$ if aged 40–59 years old, or by SDS-score ≥ 2 (21). High FMI (kg fat mass/m^2 , measured by DXA scan) was defined for adult females as ≥ 13 , for adult males ≥ 9 (26) (Table 1). The MetS definitions are referred to as MetS (BMI), MetS (BF%) and MetS (FMI), since the obesity component is the only component varying. The cutoff value for BMI of $> 30 \text{ kg/m}^2$ was chosen, because this conforms with our previous research (6) and is an alternative for waist circumference according to the International Diabetes Federation (IDF) consensus (27) and World Health Organization (WHO) definition (28).

Standardized deviation scores (SDS) of BMI, FMI and BF% were calculated with the corresponding reference groups (29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40). For BF% in adults and FMI, data from a Swedish reference

group was used (29). If the patient was of a different ethnic background from the majority, a reference group from the country of origin was used instead, if available. DXA data from any type of scanner were accepted. When the age of our subjects at the moment of DXA scan conformed to the reference population (30–70 for the Dutch and 45–69 years for the Swedish population), a comparison of occurrence of MetS at last DXA scan was made and a weighted mean was calculated based on the sex and country of origin (30, 41). The same was done for the components of MetS; a comparison with the general population was made with two definitions for low HDL cholesterol and hypertension since the study (the NL de Maat study) used to compare the Dutch figures had different cutoff values and did not regard medication (30).

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 24.0 and Graphpad version 7.04. Unless stated otherwise, data are presented as mean and standard deviation (s.d.). Statistical significance was accepted at a $P \leq 0.05$. For normally distributed data, an unpaired *T*-test was used for group comparisons; Mann–Whitney *U* tests were used for non-normally distributed data. Comparisons of proportions were conducted using the Fisher's exact test or the χ^2 test as indicated. McNemar's test was performed in the case of two related dichotomous variables. The Kruskal–Wallis test was used to compare multiple groups and non-normally distributed outcomes. To identify risk factors for MetS and its components, a univariable logistic regression model was performed first; only significant predictors ($P < 0.05$) were entered in the multiple logistic regression analysis thereafter. Refinement was performed by adding variables with *P* values < 0.20 if the number of events allowed it (with rule of thumb ~ 10 events per variable). The most significant contributor was left in the model if more candidates were present than number of variables to fill; when equal options were available, the highest Nagelkerke R^2 and best discrimination was chosen. The dependent variables were studied with forced entry. The Student's *T*-test was used to compare normally distributed variables, and the Wilcoxon rank-sum test was used to compare non-normally distributed variables. The one sample binomial *T*-test was used to compare our data with the reference population. Bonferroni adjustments were used if applicable to correct for multiple testing. Cohen's kappa and the Altman–Bland method (with the difference of the mean of two methods)

were used to check for agreement between methods of measuring MetS and obesity to compare the definitions.

Results

Baseline characteristics

The baseline characteristics of the 95 CP patients included are shown in Table 2. Childhood onset (CO) of the disease was observed in 46 patients (49%) and 51% of all patients were female. The median follow-up time was 19 years (range 1–62). The median age at last follow-up was 45 years (range 16–78), mean age at first DXA scan was 35 years (range 11–79) and the mean time from first to last DXA scan was 10.4 years (range 0.1–23.3). The mean time from first treatment to first DXA scan was 8.9 years (s.d. 9.8, range –8.7 to 47.0). Patient characteristics did not

differ significantly between males and females, except for pituitary deficiencies which were more prevalent in males (Table 2). In males, there was a trend for higher frequency of TSH deficiency (47 (100%) vs 43 (90%), $P=0.06$) and for higher ACTH deficiency (43 (92%) vs 36 (77%), $P=0.05$). Sex hormone replacement therapy was used by 74 patients with hypogonadotropic hypogonadism (79% of males and premenopausal females). Use of sex hormone replacement therapy was significantly higher in males than females (94 vs 65%, $P=0.001$), also after postmenopausal women were excluded (96 vs 78%, $P=0.012$). Patients with CO craniopharyngioma (CO CP) had a longer follow-up (median 22 vs 16 years, $P<0.05$), higher frequency of radiotherapy in the past (65 vs 42%, $P=0.02$) and greater occurrence of epilepsy (22 vs 6%, $P=0.03$) compared with patients with adulthood-onset (AO) CP. A comparison of the included and excluded patients from the original

Table 2 Characteristics of our cohort of 95 Dutch and Swedish craniopharyngioma patients.

	All patients (n = 95)	Females (n = 48)	Males (n = 47)
Baseline characteristics			
Age at presentation (years) [†]	22 (3–62)	22 (4–62)	16 (3–62)
Childhood onset, n (%)	47 (50)	24 (50)	23 (49)
Adult onset, n (%)	48 (51)	24 (50)	24 (51)
Follow-up since presentation (years) [†]	19 (1–62)	20 (3–62)	17 (1–39)
Age at last follow-up (years) [†]	45 (16–78)	45 (17–77)	53 (16–78)
Tumor characteristics			
Location at presentation, n (%)			
Intrasellar	2 (2)	1 (2)	1 (2)
Suprasellar	47 (50)	25 (52)	22 (47)
Intra-/supra-sellar	39 (41)	21 (44)	18 (38)
No information available	7 (7)	1 (2)	6 (13)
Hydrocephalus, n (%)	20 (21)	12 (26)	8 (19)
Hypothalamic damage, n (%)	31 (34)	16 (34)	15 (34)
Craniopharyngioma treatment			
Neurosurgery, n (%)	93 (98)	46 (96)	47 (100)
Radiotherapy, n (%)	51 (54)	25 (52)	26 (55)
⁹⁰ Yttrium brachytherapy, n (%)	9 (10)	7 (15)	2 (4)
Recurrence, n (%)	33 (35)	18 (38)	14 (31)
Long-term health outcome			
Pituitary hormone deficiencies, n (%)			
GH	89 (95) [‡]	45 (96)	44 (94)
FSH/LH	85 (90) [§]	41 (85)	44 (94)
TSH	90 (95)	43 (90)	47 (100) [*]
ACTH	79 (84)	36 (77)	43 (92) ^{**}
AVP	65 (69)	34 (71)	31 (67)
Visual impairment, n (%)	72 (78) [¶]	37 (80)	35 (76)
Treatment for epilepsy, n (%)	6 (6)	3 (6)	4 (9)
Treatment for psychiatric illness, n (%)	12 (13)	6 (13)	6 (13)

[†]Median (range). [‡]Replacement therapy was used by 80 patients with growth hormone deficiency (91%). [§]Replacement therapy was used by 74 patients with hypogonadotropic hypogonadism (79% of males and premenopausal females); it was significantly higher in males than females (94 vs 65%, $P=0.001$), also after exclusion of postmenopausal women (96 vs 78%, $P=0.012$). ^{||}All patients were substituted with replacement therapy except for one patient, who was diagnosed with ACTH deficiency by metyraponetest but did not receive treatment later. [¶]Missing data for three subjects; 76% of the entire cohort. ^{*} $P=0.06$. ^{**} $P=0.05$. Mean hydrocortisone dose or equivalent was 20.9 ± 6.2 mg, range 5–50 (data available for $n=76$).

ACTH, adrenocorticotrophic hormone; AVP, arginine vasopressin or antidiuretic hormone; FSH/LH, follicle-stimulating hormone/luteinizing hormone; GH, growth hormone; n, number; TSH, thyroid-stimulating hormone.

cohort (6) is presented in Supplementary Table 1. Of 95 patients, 93 had two or more DXA scans available; at first and last DXA scan, respectively 66 and 74 patients had enough data available to evaluate MetS (BMI), 66 and 69 to evaluate MetS (BF%), and 61 and 67 patients to evaluate MetS (FMI).

The MetS and its components

Information on MetS (components) is presented in Tables 3 and 4. In 64 cases (78%), MetS components were evaluated within ± 1 year of the last DXA scan. In Supplementary Table 3, a comparison is made for patients where evaluation of MetS criteria was performed within 1 year or more than 1 year before or after DEXA scan. Patients evaluated within 1 year of DXA scan had a lower rate of obesity based on BF% at last DXA scan (46 vs 80%, $P=0.03$).

At last DXA scan, MetS defined by BMI, BF% and FMI occurred in 33 (45%), 35 (51%), and 34 (51%) subjects, respectively (Table 3). The frequency of MetS was comparable to our previous study of CP patients in which DXA scans were not used (P values for BMI, BF% and FMI respectively $P=0.45$, $P=0.25$, and $P=0.26$) (6), and were

at all rates higher than those in the general population ($P<0.001$). At last DXA scan, MetS is estimated to be (borderline) higher if defined by BF% or FMI vs BMI ($P=0.03$, $P=0.06$) in the current cohort. Subjects had an increased occurrence of obesity compared to the general population (range: 53–67% vs 30–31% depending on the definition, $P<0.05$) (Table 3). The occurrence of hypertension and low HDL cholesterol was higher than the general population, with frequencies of 40 ($P<0.001$) and 62% ($P<0.001$), respectively. Here MetS criteria took into account medication use. MetS was significantly more prevalent in obese compared to non-obese subjects if obesity was defined with BMI (62 vs 21%, $P=0.001$), BF% (55 vs 15%, $P=0.01$) and FMI (63 vs 25%, $P<0.01$). Visual deficits were also more prevalent in obese compared with non-obese patients with CP (if defined by increased BF% at first DXA scan 85 vs 59%, $P=0.01$; if defined by increased FMI at first DXA scan 90 vs 79%, $P<0.05$; if defined by high FMI at last DXA scan 90 vs 69%, $P=0.03$). Unexpectedly, there was no significant difference in hypothalamic damage between obese and non-obese subjects, but a trend was shown for some definitions (based on BMI at first DXA scan 41 vs 25%, $P=0.14$; at last DXA scan 44 vs 25%, $P=0.07$, based on BF% at first DXA scan 40 vs 29%,

Table 3 Metabolic syndrome and its components in patients with craniopharyngioma.

	All CP	Ref. CP	Norm. data	P	Dutch ($n=35$) vs Sweden ($n=60$)	P	Females ($n=48$) vs males ($n=47$)	P
MetS								
BMI	33 (45%)	20 (57%)	19%	<0.001	73 vs 37%	0.01	43 vs 46%	0.82
BF%	35 (51%)	20 (67%)	19%	<0.001	65 vs 46%	0.18	54 vs 46%	0.91
FMI	34 (51%)	19 (63%)	17%	<0.001	78 vs 47%	0.15	52 vs 50%	0.90
Metabolic components								
Obesity (FD)								
BMI	35 (43%)	16 (53%)	31%	<0.05	38 vs 45%	0.58	40 vs 46%	0.57
BF%	53 (64%)	21 (66%)	31%	<0.05	44 vs 72%	0.01	59 vs 69%	0.32
FMI	30 (47%)	17 (57%)	30%	<0.05	33 vs 49%	0.48	40 vs 53%	0.30
Obesity (LD)								
BMI	49 (57%)	29 (58%)	31%	<0.05	63 vs 54%	0.45	52 vs 61%	0.40
BF%	48 (75%)	18 (62%)	31%	<0.05	63 vs 80%	0.21	69 vs 81%	0.25
FMI	41 (59%)	22 (67%)	31%	<0.05	50 vs 60%	0.54	55 vs 62%	0.57
High glucose	52 (67%)	NA	NA	NA	75 vs 64%	0.36	53 vs 80%	0.01
High TGL	22 (29%)	NA	NA	NA	63 vs 20%	0.004	42 vs 18%	0.02
Low HDL	32 (41%)	4 (7%)*	7%	0.50	58 vs 36%	0.09	51 vs 31%	0.07
High BP	37 (46%)	12 (22%)**	32%	0.07	38 vs 48%	0.42	41 vs 50%	0.42

*For all adult patients HDL ≤ 0.9 mmol/L regardless of sex/medication to compare with reference data. If defined as in Table 1, low HDL occurs in 15 patients (40%) (higher than the normative data ($P<0.001$)). **Defined as blood pressure $>140/90$ mmHg, regardless of use of medication. If defined as in Table 1, it occurs in 24 patients (62%) (higher than normative data ($P<0.001$)). Respectively 74, 69 and 67 patients had enough data available to evaluate MetS (BMI), MetS (BF%) and MetS (FMI). The data set was not complete in all patients.

BF%, body fat percentage; BMI, body mass index; CP, craniopharyngioma; FD, first DXA scan (dual X-ray absorptiometry scan); FMI, fat mass index; HDL, high-density lipoprotein cholesterol; LD, last DXA scan; MetS, metabolic syndrome; n , number; NA, not available; Norm., normative; P , P -value; Ref. CP, referenced CP (all CP in the same age group as reference population); TGL, triglycerides; BP, blood pressure.

Baseline differences between Dutch and Swedish patients were age at presentation (median 16 vs 30 years; $P=0.021$), growth hormone replacement therapy (74 vs 92%, $P=0.018$), hypothalamic damage (59 vs 22%; $P=0.01$). MetS (component) definitions: see Table 1. MetS (components) are components evaluated at LD, except obesity (FD and LD).

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Table 4 Occurrence of the criteria for metabolic syndrome in craniopharyngioma patients at last DXA scan.

MetS	No criterion	One criterion	Two criteria	Three criteria	Four criteria	Five criteria	NA
MetS (BMI) (<i>n</i> (%))	6 (8)	13 (18)	19 (26)	15 (20)	10 (14)	4 (5)	7 (9)
MetS (BF%) (<i>n</i> (%))	4 (6)	9 (13)	16 (23)	15 (22)	5 (7)	1 (1)	19 (28)
MetS (FMI) (<i>n</i> (%))	5 (7)	11 (16)	16 (24)	18 (27)	5 (8)	4 (6)	8 (12)

MetS, metabolic syndrome; MetS (BMI), component of obesity defined with high BMI >30) or increased standardized deviation score (SDS); MetS (BF%), component of obesity defined with high fat percentage with limits defined according to sex and age, or by high SDS; MetS (FMI), component of obesity defined with increased FMI with limits defined according to sex and age or SDS; *n*, number; NA, not available (not all criteria are known).

The data set was not complete in all patients.

$P=0.31$; at last DXA scan 46 vs 32%, $P=0.23$, based on FMI at first DXA scan 43 vs 24%, $P=0.06$; at last DXA scan 46 vs 27%, $P=0.09$).

CO CP patients had a higher occurrence of obesity defined by BF% at last DXA scan (87 vs 59%, $P=0.03$) and a lower occurrence of the MetS component hypertension (31 vs 60%, $P<0.01$) than AO CP. The presence or absence of growth hormone replacement treatment in patients had no effect on MetS components.

Longitudinal change of metabolic parameters

The following numbers include only patients that have MetS (components) evaluated at both first and last DXA scan to evaluate possible longitudinal changes. There was no significant change in frequency of MetS of any definition during follow-up for MetS based on BMI from 31 (49%) to 25 (40%), $P=0.31$; for MetS based on BF% from 31 (53%) to 27 (47%), $P=0.52$; for MetS based on FMI from 32 (56%) to 27 (47%), $P=0.41$. Obesity frequencies defined by BMI showed a trend to increase between first and last visit (34 (44%) vs. 43 (56%), $P=0.06$), but obesity rates defined by BF% and FMI did not change (respectively from 42 (66%) to 44 (69%), $P=0.82$; from 27 (47%) to 32 (56%), $P=0.27$). Importantly, the number of patients with hypertension increased significantly (19 (26%) vs 34 (46%), $P=0.008$). However, the MetS component low HDL cholesterol did not change significantly (from 38 (54%) to 27 (39%), $P=0.09$). Neither was there a change in the components of high glucose (from 42 (62%) at first to 44 (65%) at last DXA scan, $P=0.84$) or low HDL cholesterol (from 38 (54%) to 27 (39%), $P=0.09$). The component high triglycerides decreased from 35 (51%) to 19 (28%) ($P=0.01$).

Agreement between anthropometric measurements and DXA scan for MetS and obesity

A Cohen's kappa measurement of agreement was performed with MetS and obesity (Supplementary

Table 4). Almost perfect agreements were found between MetS evaluated by BMI and either MetS evaluated by BF% (Kappa 0.82, $P<0.001$) or MetS evaluated by FMI (Kappa 0.85, $P<0.001$). MetS was evaluated incorrectly by BMI compared to BF% in six patients (9%) and FMI in five patients (7%) (Table 5). At last DXA scan, the estimated occurrence of MetS was lower when evaluated by BMI as compared to BF% and FMI (respectively 42 vs 52% ($P=0.03$), 43 vs 51% ($P=0.06$)). This was not the case for the first DXA scan (respectively 49 vs 54%, $P=0.38$; 48 vs 53%, $P=0.25$), suggesting the difference in estimation of MetS becomes less accurate as patients become older.

In Fig. 1, BMI was set out vs BF% and FMI to illustrate discordances in the evaluation of obesity. The occurrence of obesity was lower if assessed by BMI when compared with obesity assessed by BF% (43 vs 65%, $P<0.001$ at first DXA scan, 58 vs 74%, $P=0.03$ at last DXA scan) but not when compared to FMI (41% vs 47%, $P=0.22$ at first DXA scan; 57 vs 58%, $P=1.00$ at last DXA scan). At last DXA scan, obesity estimations are discordant if BMI is compared to BF% (18 patients (29%)) and FMI (9 patients (13%)) at last DXA scan (see Table 6 for concordance of obesity measures).

A Bland–Altman plot and analysis (42) was performed for BMI SDS with BF% and FMI SDS (Fig. 2 and Supplementary Table 5). An upward trend is seen in the difference of the average for BMI/BF% SDS at first and last DXA scan (Fig. 2). Differences outside the 95% agreement interval are observed, especially at the lower and higher averages, suggesting discrepancies occur mostly in the upper and lower end of the ranges. This effect was not observed for FMI.

Determinants for occurrence of obesity and MetS and its components in patients with craniopharyngioma

Results of the univariable and multivariable logistic regression analyses on explanatory factors for MetS and its components at last DXA scan are shown in

Table 5 Concordance of metabolic syndrome for definitions of the criterion of BMI, body fat percentage (BF%) and fat mass index (FMI) at first and last DXA scan in craniopharyngioma patients.

	BMI, n (%)			
	First DXA scan		Last DXA scan	
	Non-MetS	MetS	Non-MetS	MetS
BF%, n (%)				
Non-MetS	28 (44)	1 (2)	32 (49)	0 (0)
MetS	4 (6)	30 (49)	6 (9)	28 (42)
FMI, n (%)				
Non-MetS	29 (48)	0 (0)	33 (49)	0 (0)
MetS	3 (5)	29 (48)	5 (7)	29 (43)

Non-MetS represent subjects without the presence of metabolic syndrome, MetS with the presence of metabolic syndrome. The bold numbers and percentages are discordances of the different definitions. Metabolic syndrome is underestimated in 9% for BF% and 8% for FMI compared to BMI. The numbers may not add up to 100% due to rounding issues. The data set was not complete in all patients. n, number.

Supplementary Table 6. Explanatory factors in univariable models for MetS (BMI, BF% and FMI) were age at last DXA scan, recurrence or progression, hydrocephalus and visual impairment. These factors remained significant in multivariable analysis in one of the models with the

exception of visual impairment. The explanation of the models was limited (Nagelkerke's R^2 0.15–0.29). The dose of glucocorticoid replacement was not a significant contributor (data not shown).

Type II diabetes mellitus and cardio- and cerebrovascular morbidity

Eleven patients with CP (12%) had diabetes mellitus of which one had type I diabetes mellitus. The frequency of T2D was higher in patients with CP compared with normative data (14% in subjects with the same age category as the normative data, vs 6% in normative data; $P < 0.05$), but there was no difference in incidence between obese and non-obese CP patients. Myocardial infarctions occurred in four patients with CP (4%) with a median onset at 58 years of age (range 39–75). Nine subjects (10%) had experienced cerebrovascular accidents with a median age of onset of 41 years (range 16–66) and with a median of 8 years since first presentation of CP (range 0–25).

Discussion

This is the first study to assess the value of body composition measured by DXA scan in evaluating MetS in CP survivors. A discordancy in evaluation of MetS occurs in 9% of the cases if BMI is used as opposed to BF%. Moreover, the occurrence of obesity was estimated 22% higher if measured by BF% compared to BMI. Since obesity itself is a predictor of cardiovascular disease (43), this suggests that DXA scan can be of great value in certain cases. In the Rotterdam/Gothenborg cohort, a standardized incidence ratio of 4.9 for cerebrovascular accidents was observed (5). The risk of T2D was approximately doubled in CP patients compared to the general population. The long-term care of patients with CP should include cardiovascular risk management. Figure 2 suggests that discrepancy is most evident in the extremes, the very thin and very fat CP patients. Despite these results, the agreement between methods for MetS is good, as evaluated by Cohen's kappa. In clinical practice, confirmation by DXA scan will not be of added value if obesity is obviously apparent from BMI. Although discordance is not as impressive as found in childhood cancer patients (22), obesity evaluation is discordant in one out of five patients and MetS evaluation is discordant in one out of ten if BMI is used instead of BF%. Therefore, our recommendation is to decide on a case-by-case basis if a DXA scan should be performed.

Figure 1

BMI vs body fat percentage (BF%) and fat mass index (FMI) at first (AC) and last (BD) DXA scan in craniopharyngioma patients. Obesity based on BF% or FMI are bordered by the blue vertical line for males and by the red vertical line for females on the X-axis. The purple horizontal line borders obesity based on BMI. Female and male patients in the right lower quadrant are considered obese by fat percentage/FMI, but not by BMI.

Table 6 Concordance and definition of obesity with BMI, body fat percentage (BF%) and fat mass index (FMI) at first and last DXA scan in craniopharyngioma patients.

	BMI, n (%)			
	At first DXA scan		At last DXA scan	
	Non-obese	Obese	Non-obese	Obese
BF%, n (%)				
Non-obese	26 (34)	1 (1)	12 (19)	4 (7)
Obese	18 (23)	32 (42)	14 (23)	32 (52)
FMI, n (%)				
Non-obese	33 (52)	1 (2)	25 (36)	4 (6)
Obese	5 (8)	25 (39)	5 (7)	35 (51)

The bold numbers and percentages are discordances of the different definitions. At last DXA scan, obesity is underestimated in 23% of the cases if defined by BF% in comparison to BMI; for FMI this percentage is much lower. The numbers may not add up to 100% due to rounding issues. The data set was not complete in all patients.

n, number.

The risk of a decreased BMD should also be taken into account when deciding if a DXA scan should be included in the patients' management.

There was a striking sex-dependent difference in MetS components: while men had an increased risk of having the high glucose component, women were more likely to

have high triglycerides (Table 3). This disparity may be explained by the higher risk for men to develop T2D (44), and estrogen replacement therapy raising triglycerides in women (45). Still, this effect should be limited: premenopausal females seem to be undertreated with gonadal replacement therapy, as they receive significantly less frequently replacement treatment compared with men. Being female has been shown to positively correlate with MetS (46), but in our cohort, the MetS rate was equal between genders. Female sex was a protective factor for high glucose and a risk factor for high triglycerides and low HDL.

To determine factors that influence MetS and obesity, a logistic regression model was established. Age is a main predictor for all definitions of MetS (based on BMI, BF% and FMI; Supplementary Table 6) as the prevalence of MetS increases with age (47). Another important predictor for MetS (BF%) is visual impairment, which is in line with the findings of the previous study of Wijnen *et al.* (6), who studied a larger cohort. To our knowledge, the only other study investigating MetS (components) in CP patients, is Tosta *et al.* (46), who found that BMI SDS at diagnosis positively influenced the presence of the MetS post-treatment. Radiation was expected to be a factor involved, as this is a risk factor in developing the MetS and obesity in cancer survivors (48), but it was not found to be so in our study. Although hypothalamic damage was expected to be a significant contributor, it was only borderline significant for two definitions of MetS (MetS (BMI) and MetS (BF%); Supplementary Table 6). Our cohort may have been underpowered to define hypothalamic damage and radiation therapy as a significant predictors. Although the hypothalamus plays a major role in weight maintenance, it has been shown that patients develop morbid obesity under hypothalamus-sparing operative strategies (49),

Figure 2

Bland-Altman plots. Plot (A) and (B) present data on the first DXA scan; plot (C) and (D) of the last DXA scan. Respectively, on the X-axis the average, and on the Y-axis the difference is expressed of BMI standardized deviation scores (SDS) and body fat percentage SDS (AC) or fat mass index SDS (BD). An upward trend is seen in the difference of the average for BF% at first and last DXA scan (AC). The difference in SDS of BMI and BF% seems larger at the end of the ranges, since the differences are observed outside the 95% agreement interval. These suggested discrepancies appear mostly in the upper and lower end of the ranges. For the difference of the average for FMI, the upward trend is not obviously shown.

suggesting that obesity is multifactorial. Hydrocephalus (50) is associated with obesity, so finding this as a significant contributor for MetS was not unexpected.

Predictors of poor outcomes are visual deterioration (51), hydrocephalus and multiple operations due to tumor recurrence (5, 52). Recurrence or progression was a key predictor in all definitions. All predictors could be a sign of advanced brain disease and may be interrelated. On the other hand, no interaction was found while establishing the model. Advanced brain disease is likely to influence aspects of lifestyle such as physical activity.

There are some limitations in this study. Several factors contribute to a possible selection bias: there are size and weight limitations of DXA scanners (53), the study was performed in referral centers, and the decision to perform a DXA scan was made by clinical judgment of the physicians, which is why only a subset of our previously studied cohort was assessed (6). MetS criteria were evaluated within a window spanning 3 years either side of the last DXA scan. This period was chosen since earlier studies have shown that BMI change is central to other correlated features in the MetS (54) and BMI was stable for 3 years in a group of childhood cancer survivors (22). Also, in a group of over 5000 French subjects, MetS was found to be stable over a period of 3 years (55). Furthermore, any DXA scanner was accepted, even though it is known that the DXA scan has a considerable intra-individual variability (56) and results may differ between machines; it would have been ideal to cross-calibrate all scanners (57). To cope with this, we used age- and sex-matched s.d. scores. The DXA scan is still considered to be the method of preference when BMI and adiposity are considered discordant (21, 25). For evaluation of obesity by BMI, a cutoff of $\geq 30 \text{ kg/m}^2$ for reasons of conformity with our earlier study (6) and by the WHO guidelines (58), as well as to avoid overdiagnosis. However, we realize that cutoffs used for the waist circumference according to the International Diabetes Federation (IDF) values were closer to matching a BMI of 25 kg/m^2 in males. The IDF definition notes that, if BMI $> 30 \text{ kg/m}^2$, central obesity can be assumed and waist circumference does not need to be measured (27). This remains however a topic of discussion. Since we were unable to retrieve information on waist circumference and to avoid overdiagnosing as well as to be able to make comparisons with our previous research, we decided to use a cutoff level of $> 30 \text{ kg/m}^2$ for BMI.

Since the availability of literature is extremely limited on the topic, the data we present here are still highly important for clinicians in considering the use of DXA scans in long-term follow-up, despite its limitations. It is

the only study in patients with CP that compares body composition measures vs BMI for evaluation of obesity and the MetS as well as contains longitudinal follow-up.

In conclusion, patients with CP are at high risk of obesity and MetS. Obesity and MetS are underestimated if measured by BMI. Moreover, age, visual impairment and recurrence or progression are predictors of MetS or its components. This study is single in its existence providing evidence that DXA scan measured BF% is a better alternative for evaluation of obesity and MetS in certain patients with CP, especially those in the upper and lower range of BMI or BF%. The cost-effectiveness of performing DXA-scans remains to be determined before general clinical use in CP survivors can be recommended.

Supplementary data

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-19-0181>.

Declaration of interest

Gudmundur Johannsson is on the editorial board of EJE. Gudmundur Johannsson was not involved in the review or editorial process for this paper, on which he/she is listed as an author. The other authors have nothing to disclose.

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Author contribution statement

Selveta S van Santen collected the data, conceived and designed the analysis, performed the analysis and wrote the paper. Daniel S Olsson collected the data, critically reviewed the paper and helped shape the research. Casper Hammarstrand collected the data. Mark Wijnen collected the data and critically reviewed the paper. Marry M van den Heuvel-Eibrink critically reviewed the paper. Aart J van der Lely critically reviewed the paper. Gudmundur Johannsson critically reviewed the paper and helped shape the research. Joseph A M J L Janssen critically reviewed the paper and helped shape the research. Sebastian J C M M Neggers conceived the presented idea, developed the theory, contributed data, conceived and designed the analysis, critically reviewed the paper and helped shape the research.

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