

Nuchal Skinfold Thickness: A Novel Parameter for Assessment of Body Composition in Childhood Craniopharyngioma

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Context: Hypothalamic obesity, cardiovascular disease (CVD), and relapse/progression have a major impact on prognosis in childhood-onset craniopharyngioma (CP). We analyzed nuchal skinfold thickness (NST) on magnetic resonance imaging performed for follow-up monitoring as a novel parameter for body composition (BC) and CVD in CP.

Objective: The objective of the study was to identify the association of NST with body mass index (BMI), waist to height ratio (WHtR), functional capacity, and blood pressure (BP) in CP and controls.

Design: This was a cross-sectional and longitudinal prospective study in CP patients.

Setting: The study was conducted at HIT-Endo, KRANIOPHARYNGEOM 2000/2007.

Patients: Participants included 94 CP patients and 75 controls.

Interventions: There were no interventions.

Main Outcome Measures: Association of NST with BC and BP in 43 CP and 43 controls was measured.

Results: NST correlated with BMI SD score (SDS; $r = 0.78$; $P < .001$; $n = 169$) and WHtR ($r = 0.85$; $P < .001$; $n = 86$) in the total cohort and CP patients (NST-BMI SDS: $r = 0.77$, $P < .001$, $n = 94$); NST-WHtR: $r = 0.835$, $P < .001$, $n = 43$) and controls (NST-BMI SDS: $r = 0.792$, $P < .001$, $n = 75$; NST-WHtR: $r = 0.671$, $P < .001$, $n = 43$). In CP, systolic BP correlated with NST ($r = 0.575$, $P < .001$), BMI SDS ($r = 0.434$, $P = .004$), and WHtR ($r = 0.386$, $P = .011$). Similar results were observed for diastolic BP in CP. In multivariate analyses, NST had a predictive value for hypertension in post-pubertal CP and controls (odds ratio 6.98, 95% confidence interval [1.65, 29.5], $P = .008$). During a longitudinal follow-up, changes in NST correlated with changes in BMI SDS ($P < .001$) and WHtR ($P = .01$) but not with changes in BP and functional capacity.

Conclusions: Because monitoring of magnetic resonance imaging and BC is essential for follow-up in CP, NST could serve as a novel and clinically relevant parameter for longitudinal assessment of BC and CVD risk in CP. (*J Clin Endocrinol Metab* 101: 4922–4930, 2016)

Childhood-onset craniopharyngiomas (CPs) are rare intracranial embryonal malformations of the sellar region (1). CPs show low-grade histological malignancy (World Health Organization grade I) and frequently affect hypothalamic and pituitary regions and the optic chiasm. Hypothalamic involvement and/or treatment-related lesions to the above structures result in impaired physical and social functionality (2) that includes severe neuroendocrine sequelae, mainly hypothalamic obesity, with major negative impact on quality of life in surviving patients (1–5). CP patients have a 3- to 19-fold higher cardiovascular mortality in comparison with the general population; women with CP have an even higher risk (6). The 20-year overall survival is impaired in patients with hypothalamic involvement of CP (2). Accordingly, regular monitoring by cranial magnetic resonance imaging (MRI) and assessment of body composition (BC) are essential parts of follow-up care (7).

Regional fat distribution rather than overall obesity has been recognized as important to understanding the link between obesity and cardiovascular disease (CVD). Visceral adipose tissue (VAT) is recognized as a unique, pathogenic fat depot, conferring metabolic risk above and beyond standard anthropometric measures, such as body mass index (BMI) and waist circumference (8). Individuals with large amounts of visceral fat are at an increased risk of insulin resistance, type 2 diabetes, and atherosclerosis (9, 10). However, VAT accounts for only modest correlations between cardiometabolic risk factors, suggesting that other mechanisms, or other fat depots, may also contribute to the development of CVD risk factors (8).

Upper-body sc fat, as estimated by neck circumference, may confer risk above and beyond visceral abdominal fat. Anatomically, upper-body sc fat is a unique fat depot located in a separate compartment compared with VAT. Systemic free fatty acid concentrations are primarily determined by upper-body sc fat, suggesting that this fat depot may play an important role in risk factor pathogenesis (11). Some studies have indicated that neck circumference may be an independent correlate of metabolic risk factors above and beyond BMI and waist circumference (12–15).

We report on nuchal skinfold thickness (NST) as measured on cranial MRI as a novel parameter for assessment of BC in long-term survivors of CP and the correlation of NST with blood pressure (BP) as a risk factor for CVD.

Patients and Methods

Patients

For this study, 94 patients with childhood-onset CP, recruited in the German CP registry and prospectively evaluated in the

multicenter trials HIT Endo and KRANIOPHARYNGEOM 2000/2007 (clinical trial numbers NCT00258453 and NCT01272622) were analyzed for height, weight, BMI, and NST during median long-term follow-up of 5 years (range 0.3–31 y) (16). The histological diagnosis of a CP was confirmed by reference assessment in all cases. Hypothalamic involvement of CP was assessed by MRI, computed tomography, and/or microscopic inspection during surgery. Hypothalamic involvement was defined as involvement of hypothalamic structures either by tumor growth into the hypothalamus or displacement of hypothalamic structures by the tumor (16). Seventy-five children and adolescents with normal findings in MRI served as controls. MRI was performed on controls for exclusion of intracranial pathologies, underlying headaches (50%) or unclear weight gain (50%).

In the subgroups of 43 of the 94 CP patients (46%) and 43 of the 75 controls (57%), associations between NST and BMI, waist-to-height ratio (WHtR), caliper-assessed skinfold thickness (abdominal, subscapular, biceps, triceps), and systolic and diastolic BP as risk factors for CVD could be assessed in cross-sectional analysis performed at the time of last follow-up visit. Parameters of BC, BP, functional capacity (Fertigkeitenskala Münster-Heidelberg [FMH] scores), and their association with NST could be analyzed during a prospective follow-up. NST, BMI SD score (SDS) (17), WHtR, FMH scores, and systolic/diastolic BP were assessed simultaneously in 28 patients at 83 postoperative follow-up visits with yearly intervals. Changes in parameters (δ) during yearly intervals were calculated ($n = 55$) and the correlations between δ NST and δ BMI SDS, δ NST and δ WHtR, δ BMI SDS and δ WHtR, δ NST and δ FMH scores, δ NST and δ systolic BP (millimeters of mercury), and δ NST and δ diastolic BP (millimeters of mercury) were analyzed.

The study was approved by the local standing committee on ethical practice, and written parental and/or patient consent was obtained in all cases.

Assessment of anthropometric parameters

Four skinfold measurements (triceps, biceps, subscapular, and abdominal) were taken on the right side of the body by a Harpenden caliper and recorded to the nearest 0.1 cm. NST was measured on T1-weighted cranial MRI scans of the midline performed on 1.5 Tesla scanners according to the following standardized assessment. First, a line was drawn crossing the two anatomically defined points: basion (anterior margin of the foramen magnum) and opisthion (posterior margin of the foramen magnum). The diameter of sc nuchal fat was measured over this line to the nearest 0.1 cm. NST was measured in triplicate by three independent persons and the arithmetic mean was used for analyses (see Figure 1). Interindividual reliability of the used arithmetic mean of NST was 0.982.

Waist circumference was measured midway between the lowest rib and the top of the iliac crest at the end of gentle expiration. Circumferences were measured over the naked skin and noted to the nearest 0.1 cm. Infants were measured in the supine position. Height was measured using a stadiometer. The median of three height measurements is shown as SDS according to the references of Prader et al (18). Patients were weighed on calibrated mechanical or electronic step scales, wearing underwear only. BC and the degree of obesity were evaluated by calculating the BMI SDS according to the references of Rolland-Cachera et al (17). Pubertal stage was assessed according to Tanner stages (19).

Systolic and diastolic BP was measured in millimeters mercury and recorded using an automatic sphygmomanometer in seated position after resting for 15 minutes.

Functional capacity assessment

The German daily life ability scale FMH was used for self-assessment of functional capacity (20). The FMH measures the capability for routine actions, with 56 items such as can walk without aid or earns money. It was normalized with 971 persons (45.5% female), ages between 0 and 102 years, resulting in age-dependent percentiles. The average time for answering the FMH questionnaire was 4.5 minutes in first-time users.

Statistical analyses

Statistical analysis was performed with SPSS 23 for Windows (IBM Corp) and R version 3.2.5. Groups were compared using a Student's *t* test for normally distributed data, the Mann-Whitney *U* test for nonnormal data, and Fisher's exact tests for categorical variables. The normality assumption was verified graphically. Correlation was calculated with the Pearson correlation coefficient; difference between two dependent correlations was analyzed using the Williams's test. In case of longitudinal data, a correlation coefficient for repeated observations was calculated (21). Univariate and multivariate logistic regressions were applied. A stepwise selection process was used, keeping only variables with $P \leq .05$ in the final model. Results of logistic regression are presented as odds ratios and corresponding 95% confidence intervals. The local significance level was set to $P = .05$. Nevertheless, all inferential statistics are intended to be exploratory (hypotheses generating), not confirmatory, and are interpreted accordingly. Therefore, no adjustment for multiple testing was applied.

Results

Ninety-four (55 females, 39 males) of 576 patients (286 females, 290 males) with childhood-onset CP recruited in the German Childhood Craniopharyngioma Registry with longitudinal follow-up in the trials HIT Endo and KRANIOPHARYNGEOM 2000/2007 were included in our study. A total 482 childhood-onset CP patients were excluded because one or more of the following inclusion criteria were not fulfilled: sagittal MRI of sufficient quality for assessment of NST (Figure 1) and height and weight for assessment of BMI measured within 3 months before or after the time point of MRI. Seventy-five children and adolescents (30 females, 45 males) with normal findings in MRI fulfilled the above-mentioned inclusion criteria served as controls. In a cross-sectional study on 43 CP patients (27 females, 16 males) and 43 controls (23 females, 20 males), NST could be analyzed in relation to BMI, WHtR, caliper-assessed skinfold thickness, and systolic and diastolic BP at the time of last postoperative follow-up visit (Table 1). In the longitudinal prospective part of our study, conventional parameters of BC, BP, and

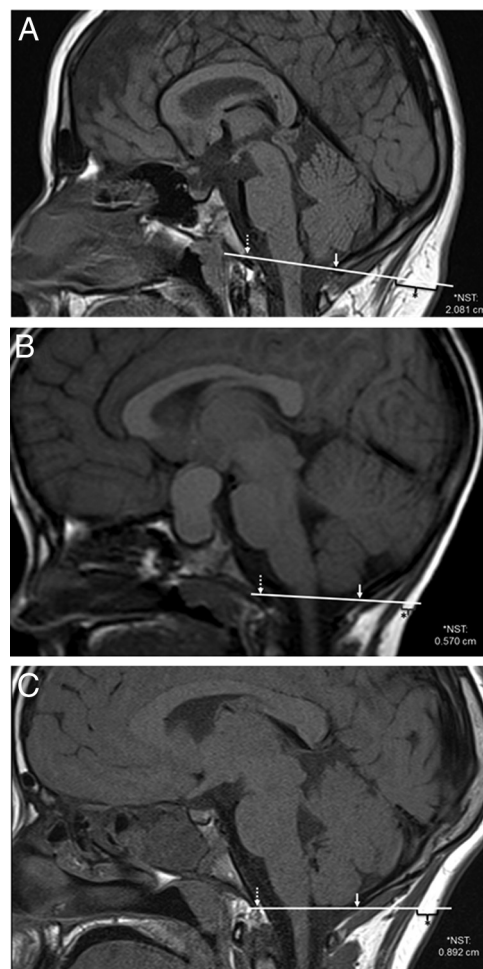


Figure 1. NST was measured on T1-weighted sagittal cranial MRI of the midline according to the following standardized assessment: first, a line was drawn crossing the two anatomically defined points: basion (anterior margin of the foramen magnum, indicated by hatched line arrow) and opisthion (posterior margin of the foramen magnum, indicated by solid line arrow). The diameter of sc nuchal fat was measured over this line to the nearest 0.1 cm. Panel A shows NST in a CP patient with severe obesity due to hypothalamic involvement (hypothalamic involvement grade II [2], BMI +8.91 SD). Panel B shows NST in a CP patient with reduced BMI due to diencephalic syndrome (hypothalamic involvement grade I [2], BMI –2.63 SD [17]). Panel C shows NST in a healthy, normal-weight control (BMI +1.82 SD).

their association with NST could be analyzed in 28 patients at 83 postoperative follow-up visits with yearly intervals.

Cross-sectional study on NST, BC, and CVD

Childhood-onset CP patients were older (median age 16.4 y, range 4.0–39.4 y) and presented with higher BMI SDS (median BMI +2.05 SD, range –4.41 to +15.43 SD) at the time of our study when compared with controls (median age 10.2 y, range 2.9–18.4 y; median BMI +0.80 SD, range –2.4 to +12.2 SD) (Table 1). NST correlated positively with BMI SDS ($r = 0.78$; $P < .001$; $n = 169$) and WHtR ($r = 0.85$; $P < .001$; $n = 86$) in the total cohort and in the subgroups of CP patients (NST-BMI SDS: $r = 0.77$,

Table 1. Characteristics of Craniopharyngioma Patients and Healthy Controls

Patients Characteristics	Craniopharyngioma	Normal Controls	P Value
Total group, n	94	75	
Gender, females/males	55/39	30/45	.017
Age at diagnosis, y	8.29 (1.30–21.28)	–	–
Follow-up time, y	5.03 (0.22–30.90)	–	–
Hypothalamic involvement, n	44 (47%)	–	–
Gross total resection, n	19 (20%)		
Age at study, y	16.40 (4.00–39.40)	10.20 (2.86–18.41)	<.001
BMI at study (SDS) (17)	2.05 (–4.41 to 15.43)	0.80 (–2.42 to 12.20)	.005
Height at study (SDS) (18)	–0.46 (–4.90 to 4.69)	–1.35 (–5.54 to 4.66)	.053
Nuchal skinfold, cm	0.99 (0.47–2.76)	0.66 (0.34–2.22)	<.001
Subgroups, n	43	43	
Gender, females/males	27/16	23/20	.51
Age at study, y	18.70 (5.67–35.24)	10.50 (3.29–18.41)	<.001
Pubertal stage (Tanner) (19)	I: 12; II: 0; III: 2; IV: 29	I: 27; II: 5; III: 2; IV: 9	<.001
BMI at study (SDS) (17)	4.22 (–1.10 to 15.43)	1.03 (–2.41 to 11.97)	<.001
Height at study (SDS) (18)	0.05 (–3.39 to 4.69)	–0.55 (–3.99 to 4.66)	.59
Waist circumference, cm	107.0 (51.0–175.0)	75.0 (50.0–127.0)	.001
WHtR	0.59 (0.38–0.93)	0.47 (0.35–0.66)	<.001
Nuchal skinfold, cm	1.17 (0.52–2.76)	0.73 (0.36–1.76)	<.001
Skinfolds, cm, abdominal	3.90 (0.22–6.00)	1.50 (0.30–5.30)	<.001
Subscapular	3.50 (0.19–6.50)	1.20 (0.30–4.80)	<.001
Biceps	2.50 (0.50–5.90)	1.10 (0.30–2.80)	<.001
Triceps	3.10 (0.70–6.30)	1.70 (0.30–4.30)	<.001
RR systolic BP, mm Hg	123 (94–176)	118 (94–153)	.043
RR diastolic BP, mm Hg	77 (59–143)	72 (50–106)	.005

Characteristics of 94 patients with childhood-onset CP recruited in HIT Endo and KRANIOPHARYNGEOM 2000/2007 and 75 controls, who were analyzed for NST assessed on MRI, height SDS (18), and BMI SDS (17), and the subgroups of 43 CP patients and 43 controls who could be analyzed based on complete data sets for NST, BMI SDS (17); WHtR; caliper-measured skinfold thickness (abdominal, subscapular, biceps, triceps); and systolic and diastolic BP. Shown are median and range if not otherwise specified.

$P < .001$, $n = 94$); NST-WHtR: $r = 0.835$, $P < .001$, $n = 43$) and controls (NST-BMI SDS: $r = 0.792$, $P < .001$, $n = 75$; NST-WHtR: $r = 0.671$, $P < .001$, $n = 43$) (Figure 2). Comparing these correlations, both NST and BMI SDS showed high correlation with WHtR in CP patients (Wilcoxon's test: $P = .58$).

In the subgroups of 43 CP patients and 43 controls, associations between NST, WHtR, caliper-assessed skinfold thickness (abdominal, subscapular, biceps, triceps), BMI, and BP could be analyzed (Table 1). Also in the subgroups, NST correlated with BMI SDS and WHtR in the 43 CP patients ($r = 0.808$, $P < .001$; $r = 0.835$, $P < .001$) and 43 controls ($r = 0.813$, $P < .001$; $r = 0.671$, $P < .001$) (Figure 3).

Comparing NST with caliper-measured skinfold thickness, subscapular and abdominal skinfold thickness had highest correlation with NST both in CP patients (subscapular: $r = 0.802$, $P < .001$; abdominal: $r = 0.71$, $P < .001$) and controls (subscapular: $r = 0.724$, $P < .001$; abdominal: $r = 0.730$, $P < .001$) (Supplemental Figure 1).

In 43 CP patients, systolic BP correlated with NST ($r = 0.575$, $P < .001$) (Figure 4), BMI SDS ($r = 0.434$, $P =$

$.004$), and WHtR ($r = 0.386$, $P = .011$). Similar results were observed for diastolic BP in CP patients, showing that diastolic BP correlated with NST ($r = 0.565$, $P < .001$), BMI SDS ($r = 0.516$, $P < .001$), and WHtR ($r = 0.434$, $P = .004$). The correlation between NST and systolic BP was higher ($P = .015$) than the correlation between WHtR and systolic BP, whereas the levels of correlations were similar between NST and systolic BP and BMI SDS and systolic BP ($P = .09$). In 43 controls, diastolic BP only correlated with NST ($r = 0.320$, $P = .037$) (Figure 4). Correlations between diastolic BP and BMI SDS and WHtR and between systolic BP and NST, BMI SDS, and WHtR did not reach statistical significance in controls.

In multivariate analyses, we analyzed which anthropometric parameter (NST, WHtR, BMI SDS, abdominal, subscapular, biceps, and triceps skinfold thickness) had an independent impact on systolic and diastolic BP as a risk factor for CVD in 43 CP patients and 43 controls. Systolic and diastolic BP in all CP patients and controls were classified as hypertensive or normotensive BP according to a study on WHtR and elevated BP (22). When

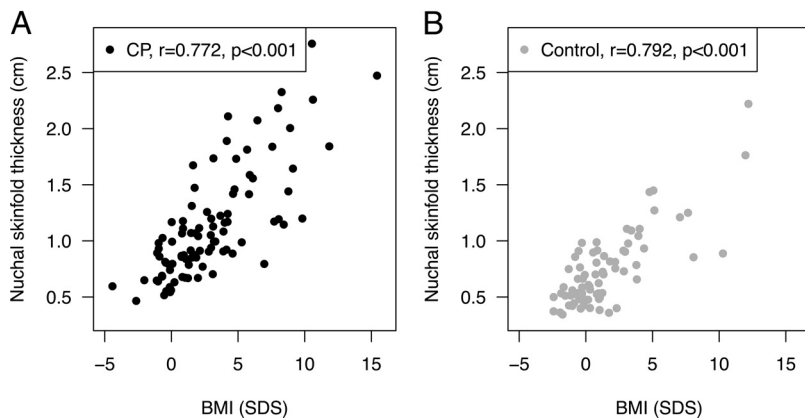


Figure 2. Correlations between NST as measured on cranial MRI and BMI SDS (17) in 94 patients with childhood-onset craniopharyngioma recruited in HIT Endo and KRANIOPHARYNGEOM 2000/2007 (A) and 75 controls (B).

analyzing the total subgroup of 86, no risk factor for hypertension could be identified (data not shown). However, when limiting the analyses to patients in post-pubertal Tanner (19) stage 4 or greater (n = 26 normal BP, n = 11 hypertensive BP), a noticeable increase in risk of hypertension could be observed in univariate analyses for NST, BMI SDS, WHtR, triceps, and subscapular skinfold thickness. When entering all anthropometric parameters in a multivariate logistic regression analysis and performing stepwise selection, only NST remained in the final model, showing an almost 7-fold increase of risk of hypertension per centimeter NST (odds ratios 6.98, 95% confidence interval [1.65, 29.5], *P* = .008). Obviously this analysis is strongly limited by the small sample size.

Forty-four of 94 CP patients (47%) presented with hypothalamic involvement of CP (Table 1). Hypothalamic involvement was significantly associated with obesity in CP. Patients with hypothalamic involvement presented with higher BMI (median BMI +3.07 SD, range -4.41 to +11.85 SD, *P* = .06), higher NST (median NST 1.09 cm,

range 0.47–2.76 cm, *P* = .008), and higher WHtR (median WHtR 0.65, range: 0.43–0.91, *P* = .014), when compared with CP without hypothalamic involvement (median BMI +1.51 SD, range -1.10 to +15.43 SD; median NST 0.90 cm, range 0.52–2.47 cm; median WHtR 0.56, range 0.38–0.93).

We also analyzed other subgroups of CP with special characteristics. Nineteen of 94 CP patients (20%) were treated by radical surgical resection resulting in reference-confirmed complete tumor removal. After such gross-total

resection patients presented with higher BMI SDS (median BMI +4.86 SD, range -1.06 to +10.54 SD) and NST (median 1.22 cm, range 0.55–2.76 cm) when compared with patients after incomplete resection (median BMI +1.72 SD, range -4.41 to +15.43 SD; median NST 0.94 cm, range 0.47–2.47 cm) (*P* = .004; *P* = .034).

A subgroup of three patients presented with a BMI less than -2 SD at the time of diagnosis (-2.63 SD, -2.05 SD, -3.00 SD) and a diencephalic syndrome according to previously published criteria (23). In all patients with diencephalic syndrome, low BMI SDS was associated with low NST (NST 0.471 at BMI -2.63 SD; NST 0.644 at BMI -2.05 SD; NST 0.616 at BMI -4.41 SD). All patients increased their BMI to the upper normal range during follow-up. Longitudinal data on NST development during follow-up were not available in these patients with diencephalic syndrome.

Six patients (14%), operated exclusively via transsphe-noidal approach, presented with lower (*P* < .001) BMI

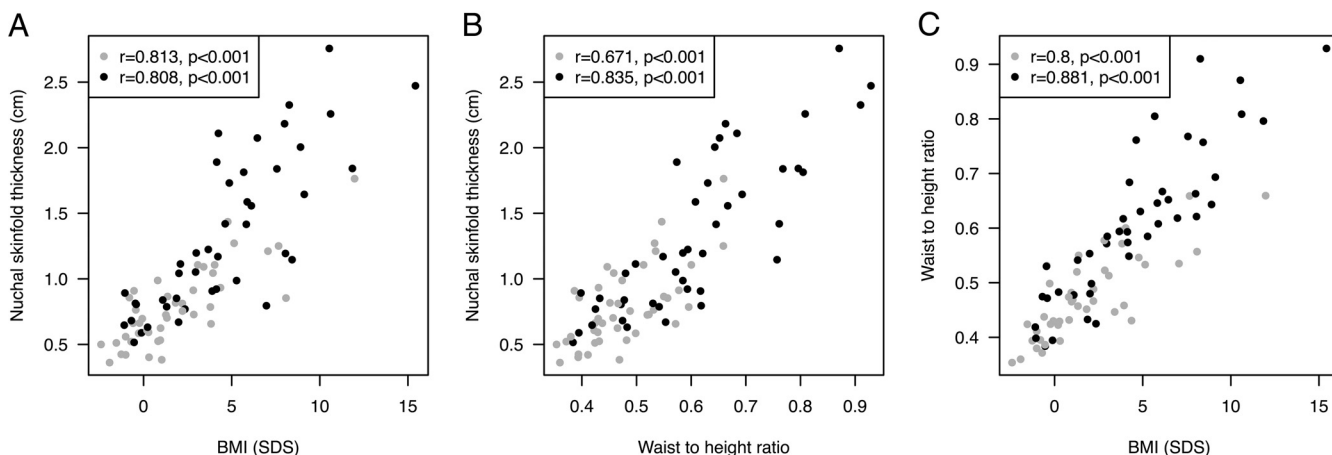


Figure 3. Correlations between NST as measured on cranial MRI and BMI SDS (17) (A), NST and WHtR (B), WHtR and BMI SDS (20) (C) in 43 patients with childhood-onset craniopharyngioma (black dots) recruited in HIT Endo and KRANIOPHARYNGEOM 2000/2007 and 43 controls (gray dots). *r* = Pearson correlation coefficient.

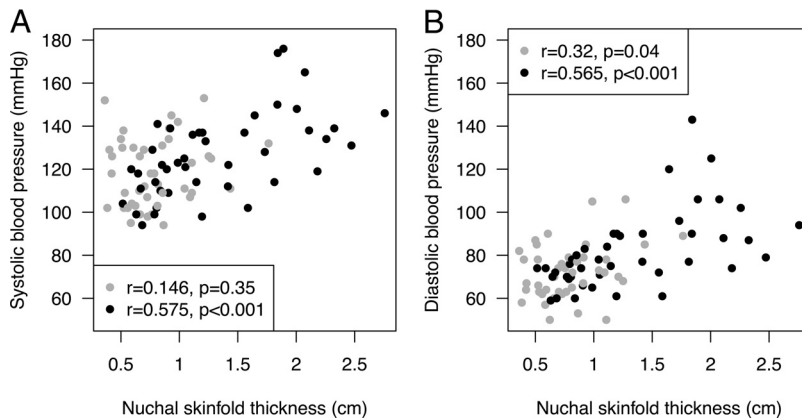


Figure 4. Correlations between NST as measured on cranial MRI and systolic (A) and diastolic (B) BP (millimeters of mercury) in 43 patients with childhood-onset craniopharyngioma (black dots) recruited in HIT Endo and KRANIOPHARYNGEOM 2000/2007 and 43 controls (gray dots). r = Pearson correlation coefficient.

SDS (median BMI -0.57 SDS, range -1.10 to $+1.31$ SDS) at last visit (median follow-up 4.9 y, range 1.7–10.9 y) and lower ($P = .001$) NST (median NST 0.73 cm, range 0.59–0.89 cm) when compared with patients ($n = 36$) treated via transcranial approach (median BMI $+5.07$ SDS, range -0.53 to $+15.43$ SDS; median NST 1.32 cm, range 0.52–2.76 cm, median follow-up 10.2 y, range 0.1–27.6 y). NST was closely correlated with BMI SDS also in this subgroup of patients treated via a transphenoidal approach.

Prospective longitudinal study on NST, BC, and CVD

During longitudinal follow-up, changes in NST were significantly associated with changes in BMI SDS ($r = 0.703$; $P < .001$) and WHtR ($r = 0.562$; $P = .01$) (Figure 5). However, changes in NST during follow-up were not associated with changes in systolic and diastolic BP and functional capacity (FMH scale) as a measure of quality of life (Figure 5). Correlations between changes in NST and changes in caliper-measured skinfold thickness did not reach statistical significance (Supplemental Figure 2). One patient suffering from severe obesity (BMI 6.0 SDS) was treated by bariatric surgery (gastric sleeve resection) and experienced a severe decrease in BMI SDS of -6 SD during 14 months after bariatric surgery, which was associated with a 1.0-cm reduction of NST.

Discussion

According to the World Health Organization definition, metabolic syndrome consists of insulin resistance and at least two other risk factors from high BP, hypertriglyceridemia, low high-density lipoprotein cholesterol, increased BMI, and microalbuminuria. Metabolic syndrome can cause CVD and onset of type 2 diabetes in

childhood. Children with obesity have a higher risk of developing metabolic syndrome, caused by their higher amount of fat tissue compared with normal-weight children (24–26). It is important to differentiate between two types of fat tissue: VAT (intraabdominal) and sc adipose tissue (27). VAT is an important risk factor for metabolic syndrome and has a higher correlation with the risk of CVD than sc adipose tissue and total adipose tissue.

MRI of the body is the golden standard to measure the different adipose tissue compartments of the body, but MRI is an expensive method to perform for this use alone. Several studies have analyzed the use of anthropometric parameters in predicting the risk of metabolic syndrome and cardiovascular risk factors. In a study of adults in which the visceral adipose tissue on MRI was used as the reference model, the waist circumference had a higher correlation with VAT in comparison with BMI, which seemed to be more correlated with the total adipose tissue (28). A study of adolescents in which anthropometric parameters were compared with MRI showed the same results, although the value of the waist circumference differed among different age groups (29). A study of Koren et al (30) showed that the BMI Z-score and the sagittal abdominal diameter, which measures the abdominal thickness at waist level in supine position, were both better predictors of visceral adiposity tissue in adolescents compared with BMI, waist circumference, or waist-to-hip ratio. Although in adults the waist-to-hip ratio is associated with cardiovascular events and diabetes, this relationship is less clear in children, probably due to developmental changes in body fat distribution during growth (31, 32).

Several studies have documented that the ratio of waist circumference to height (WHtR) is superior to waist circumference and BMI to predict cardiovascular risk factors (33–36). In a study of German adolescents, WHtR correlated strongly with BMI SDS, and both parameters had a predictive value for the BP (21). A benefit of the WHtR measurement is that, according to their study, the parameter does not need to be adjusted for age: in every age category, a cut of value of 0.5 can be used. This makes this parameter usable for comparison in children at different ages (21, 37).

Preis et al (12) and da Silva et al (38) reported on neck circumference as a novel measure of cardiometabolic risk. Preis et al (12) observed that neck circumference was cor-

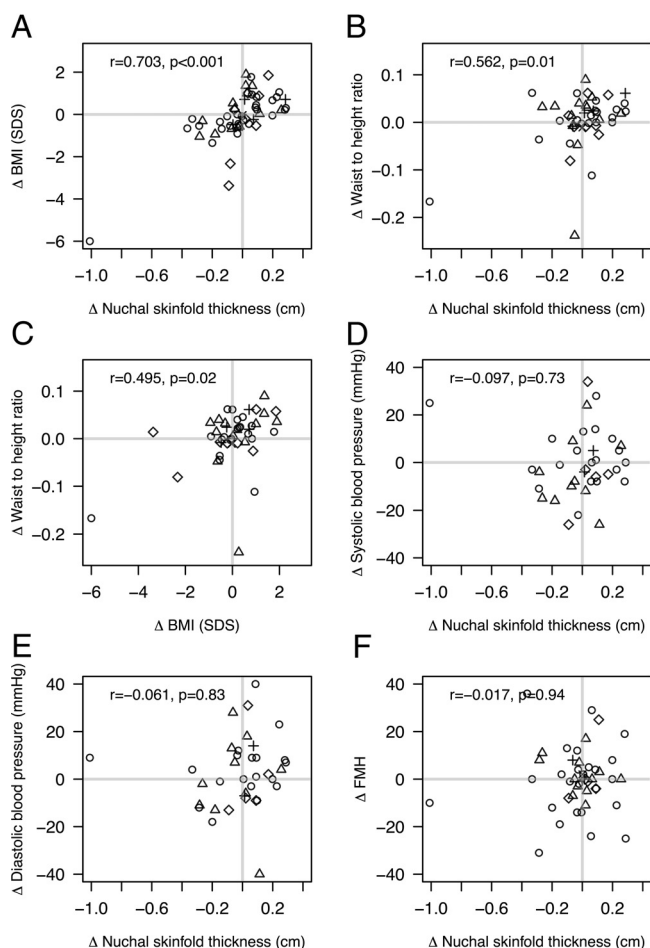


Figure 5. NST, BMI SDS (17), WHtR, systolic/diastolic BP, and functional capacity were assessed simultaneously in 28 patients at 83 postoperative follow-up visits with yearly intervals. Changes in parameters of BC, BP, and functional capacity (δ) during longitudinal follow-up at yearly intervals were calculated ($n = 55$). Depicted are the correlations between δ NST and δ BMI SDS (A), δ NST and δ WHtR (B), δ BMI SDS and δ WHtR (C), δ NST and δ systolic BP (millimeters of mercury) (D), δ NST and δ diastolic BP (millimeters of mercury) (E), and δ NST and δ FMH percentile (ability scale FMH) (F). \circ , δ between visits 1 and 2; \triangle , δ between visit 2 and 3; \diamond , Pearson correlation coefficient; \diamond , between visit 3 and 4; $+$, δ between visits 4 and 5; \times , δ between visits 5 and 6.

related with VAT and BMI. After further adjustment for VAT, they found that neck circumference was positively associated with systolic and diastolic BP and other risk factors for CVD. As a limitation of their study, the authors stated that neck circumference serves only as a proxy for upper-body sc fat without radiographic quantification of this fat depot (12).

Prognosis and morbidity in long-term survivors of CP are frequently impaired by hypothalamic obesity due to tumor and/or treatment related hypothalamic lesions and high relapse and recurrence rates (1–5). CP patients have a 3- to 19-fold higher cardiovascular mortality in comparison with the general population (6). Accordingly, regular monitoring by cranial MRI and assessment of BC are essential parts of their follow-up care (3, 39). Despite sev-

eral studies on the causes of the hypothalamic obesity and many therapeutic approaches, no effective therapeutic strategy for treating hypothalamic obesity has been found thus far.

In our study, cranial MRI performed during follow-up monitoring was used to measure and analyze NST as a novel parameter for assessment of BC. The associations between NST and other parameters of BC (skinfold thickness, BMI, WHtR) and BP as cardiometabolic risk factors were analyzed in long-term survivors of CP and controls. In cross-sectional analyses, NST correlated with BC at the last follow-up visit and NST was strongly associated with WHtR as a parameter of VAT. Patients with hypothalamic involvement presented with higher NST. However, ranges of NST showed a large overlap when compared between patients with and without hypothalamic involvement, indicating that BC might be a more specific indicator of hypothalamic obesity than hypothalamic imaging. We also found that NST independently contributed to hypertension as a cardiometabolic risk factor in postpubertal ages. The high predictive value of NST for BC and diastolic BP as CVD risk factor when compared with conventional parameters was also confirmed in controls. However, for systolic BP, this could not be confirmed in controls, which might be related to the different BMI distribution in CP vs controls.

In longitudinal analyses, the strong association between changes in NST and changes in BMI SDS and WHtR could be confirmed. On the other hand, changes in NST were not correlated significantly with changes in BP, caliper-measured skinfold thickness, and functional capacity. We speculate that this could be explained due to short 12-month intervals of measurement not appropriate for the development of clinical relevant changes in functional capacity and BP.

Recent research has focused extensively on BC and CVD risk. Emphasis has been placed on whether an individual has an upper-body or lower-body fat distribution and what proportion of fat is stored in visceral vs sc fat depots. Typically, central obesity, particularly high levels of upper-body visceral fat, is associated with adverse metabolic outcomes such as insulin resistance, diabetes, hypertension, and elevated triglycerides, whereas individuals with lower-body obesity tend to have lower levels of these adverse metabolic outcomes (40). Our study supports the concept that NST could serve as a standardized and easily measurable proxy of body composition and presumably upper-body sc fat, which has been reported as a novel, discrete, and pathogenic fat depot. Furthermore, our study supports previous reports (2, 3) that hypothalamic involvement has major impact on the development of obesity in long-term survivors of childhood-onset CP.

Strengths and limitations

Our pilot study adds to the current literature on obesity by showing for the first time that NST is correlated with BC (BMI SDS, WHtR). NST is easily measurable based on the reported standardized procedure with high interindividual reliability of assessment. We were able to compare NST with parameters for BC in a large, well-defined cohort of CP patients. One of the limitations of our study is that, due to the frequency of existing eating disorders in our cohort of CP patients, fasting blood samples for the assessment of other risk factors for CVD such as lipids were not available in these patients. Other measures of visceral adiposity (ie, abdominal MRI, dual energy X-ray absorptiometry, impedance studies) as well as normative data, for example by age, sex, and ethnicity, and neuropsychological and lipid status could not be analyzed in our pilot study but will be part of the study protocol of the next prospective trial performed in the German Craniopharyngioma Registry.

Conclusions

In conclusion, we do not recommend MRI-based assessment of NST as a routine clinical tool in all obese patients. However, because MRI monitoring is an essential part of follow-up for early detection of recurrence in CP, measurement of NST could serve as a clinically relevant, easily determinable, and standardized parameter for the assessment of BC in light of the high association of abdominal fat mass and its potential predictive value for risk of hypertension and CVD in CP patients. This is particularly relevant for CP patients with hypothalamic involvement of CP, who are at special risk for severe obesity and hypertensive BP.

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