Inverse association between brown adipose tissue activation and white adipose tissue accumulation in successfully treated pediatric malignancy[1–4]

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ABSTRACT

Background: Although the accumulation of white adipose tissue (WAT) is a risk factor for disease, brown adipose tissue (BAT) has been suggested to have a protective role against obesity.

Objective: We studied whether changes in BAT were related to changes in the amounts of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) in children treated for malignancy.

Design: We examined the effect of BAT activity on weight, SAT, and VAT in 32 pediatric patients with cancer whose positron emission tomography–computed tomography (PET-CT) scans at diagnosis showed no BAT activity. Changes in weight, SAT, and VAT from diagnosis to remission for children with metabolically active BAT at disease-free follow-up (BAT+) were compared with those in children without visualized BAT when free of disease (BAT−).

Results: Follow-up PET-CT studies (4.7 ± 2.4 mo later) after successful treatment of the cancer showed BAT+ in 19 patients but no active BAT (BAT−) in 13 patients. BAT+ patients, in comparison with BAT− patients, gained significantly less weight (3.3 ± 6.6% compared with 11.0 ± 11.6%; $P = 0.02$) and had significantly less SAT (18.2 ± 26.5% compared with 67.4 ± 71.7%; $P = 0.01$) and VAT (22.6 ± 33.5% compared with 131.6 ± 171.8%; $P = 0.01$) during treatment. Multiple regression analysis indicated that the inverse relations between BAT activation and measures of weight, SAT, and VAT persisted even after age, glucocorticoid treatment, and the season when the PET-CT scans were obtained were accounted for.

Conclusion: The activation of BAT in pediatric patients undergoing treatment of malignancy is associated with significantly less adipose accumulation. This trial was registered at clinicaltrials.gov as NCT01517581. *Am J Clin Nutr* 2012;95:1144–9.

INTRODUCTION

White and brown adipocytes differ in their expression of hormones, cytokines, and inflammatory factors and modulate different biological functions (1–3). Although white adipose tissue (WAT)[5] serves as the primary site of energy storage, brown adipose tissue (BAT) instead metabolizes fat to produce heat and regulate body temperature (4–7). Available information from cross-sectional studies in patients undergoing positron emission tomography–computed tomography (PET-CT) examinations suggests that WAT and BAT are inversely related (4, 5, 8–10). Lean subjects exhibit greater BAT activity than do obese subjects, and several studies have observed a negative relation between body mass or body fat and the degree of metabolically active BAT (4, 5, 8–12). Additional support of the link between weight and BAT comes from animal studies that reported that a reduced amount or function of BAT led to obesity, insulin resistance, and dyslipidemia (13–15), whereas an increased amount or function protected against weight gain and its comorbidities (16–18).

Although BAT is likely present in all humans (19), the low prevalence of BAT depiction in adults and in elderly subjects has hindered longitudinal assessments of the relation between BAT activity and WAT. Under typical imaging conditions, BAT is detected more frequently in children and teenagers than in adults with malignancy (20–23). Because most children with cancer have significantly shorter treatment courses and greater survival rates than do adult patients (24), by selecting pediatric patients we have the ability to examine the relation of repeated measures of body composition and BAT. In this study, we longitudinally examined the relations between BAT activity and changes in weight and the amounts of subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), and abdominal muscle in children successfully treated for pediatric cancer.

SUBJECTS AND METHODS

Study subjects

Study subjects were patients seen regularly in the division of Hematology and Oncology at the Children's Hospital Los Angeles from October 2008 to September 2011. This study was

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[5] Abbreviations used: BAT, brown adipose tissue; BAT−, without metabolically active brown adipose tissue at disease-free follow-up; BAT+, with metabolically active brown adipose tissue at disease-free follow-up; BSA, body surface area; CT, computed tomography; HU, Hounsfield units; PET, positron emission tomography; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; WAT, white adipose tissue.

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compliant with the Health Insurance Portability and Accountability Act, and the investigational protocol was approved by the Institutional Review Board for clinical investigations at the Children's Hospital Los Angeles; informed consent was waived because all imaging was performed for clinical purposes. Eligibility criteria for this study included children ≤18 y of age who *1*) had PET-CT scans with evidence of malignant disease but no metabolically active BAT at diagnosis and *2*) were disease free within 1 y of diagnosis. With the use of this approach, we studied 32 pediatric patients (6.8–18.5 y of age); 28 patients had lymphoma (20 patients with Hodgkin, 4 patients with B cell, 3 patients with Burkitt, and 1 patient with anaplastic large cell lymphoma), 1 patient had acute lymphoblastic leukemia, 1 patient had melanoma, 1 patient had medullablastoma, and 1 patient had rhabdomyosarcoma. Of the 32 patients, 14 patients (all with lymphoma) were treated with glucocorticoids as part of their treatment regimen.

Outcome measures

Age, height, and weight measures were determined at the time of each PET-CT examination. The BMI-for-age percentile was calculated via the CDC's BMI-for-age growth chart calculator by using age, sex, and height and weight measurements (http://apps.nccd.cdc.gov/dnpabmi/Calculator.aspx). Body surface area (BSA) calculations were made by using the Dubois and Dubois formula as follows:

$$\text{BSA}\left(\text{m}^2\right) = 0.007184 \times \left\{[\text{height (cm)}]^{0.725}\right\} \times \left\{[\text{weight (kg)}]^{0.425}\right\} \quad (1)$$

PET-CT scans were performed with a Gemini system (GXL Release 3.3; Philips Healthcare) in patients after 12 h of fasting. Patients were injected with fluorodeoxyglucose between 2.4 and 13.6 mCi, depending on body weight (0.14 mCi/kg) (22). The radiotracer was administered immediately after the serum glucose concentration was measured. PET scans were not performed if the glucose concentration was >200 mg/dL. All studies were performed after intravenous and oral contrast (meglumine diatrizoate; Gastrografin, Bristol-Myers Squibb) enhancement as set forth by the PET-CT protocol of the imaging department of the Children's Hospital Los Angeles. No muscle relaxants or additional agents were administered, and all patients were indoors at room temperature (22°C) for ≥2 h before the examination. Hospital gowns were worn during the radiologic study as well as for the 2 h immediately before the study. The total acquisition time for each study was 1 h. The axial in-plane spatial resolutions for PET and CT slices were 4 and 1.17 mm, respectively, and slice thicknesses were 4 and 5 mm, respectively.

All PET-CT examinations were reviewed independently by 2 radiologists to determine the presence or absence of metabolically active BAT. A patient was considered to have BAT when both radiologists diagnosed its presence. Studies with discrepant assessments were reevaluated by both radiologists together to arrive at a consensus. Subjects were categorized into 2 groups (BAT+ and BAT−) on the basis of the presence or absence of metabolically active BAT at disease-free follow-up examinations.

Measures of SAT, VAT, and abdominal musculature were obtained from the CT component at baseline and follow-up. Abdominal adipose tissue and muscle volumes were measured semiquantitatively on the basis of CT Hounsfield units (HU) by using an offline computer workstation running SliceOmatic image segmentation software (Tomovision Inc) (25). In brief, measurements of SAT and VAT were obtained by measuring all voxels with negative HU values (with exclusion of air in the bowel) in a 2.5-cm section at the level of the umbilicus (26). For the purposes of this study, SAT was defined as the volume (in cm^3) of adipose tissue located between the skin and rectus muscles, the external oblique muscles, lumbar quadrate muscles, and the erector muscles of the spine, whereas VAT was defined as the intraabdominal adipose tissue surrounded by the rectus muscles, the oblique muscles, the lumbar quadrate muscle, the psoas muscles, and the vertebral body at the same site. At the same locations and from the same CT images, the volume of abdominal musculature (rectus muscles, oblique muscles, lumbar quadrate muscles, psoas muscles, and erector muscles of the spine) was determined by measuring all voxels with positive HU values (with exclusion of bone, viscera, vessels, and bowel) (27). CVs for CT measures of SAT, VAT, and abdominal musculature have been reported to be between 1.5% and 3.5% (28).

Statistical analyses

Statistical analyses were performed with Statview software (version 5.0.1; SAS Institute) by using unpaired *t* tests, chi-square tests, and simple and multiple linear regression analyses. The goodness-of-fit for regression models was evaluated with the postestimation procedures of STATA software (version 8 StataCorp). All models presented passed the following goodness-of-fit criteria: residuals appeared to be random and no strong influence or leverage points were present, on the basis of both a graphical and distribution evaluation. All values are expressed as means ± 1 SD, except when otherwise indicated.

RESULTS

The age, anthropometric characteristics, and CT measures of SAT, VAT, and abdominal musculature of the 32 patients at diagnosis are shown in **Table 1.** As shown in **Table 2**, 19 patients (13 boys and 6 girls) had metabolically active BAT when they were free of disease (BAT+), whereas 13 patients (7 boys and 6 girls) remained without visible BAT activity at follow-up (BAT−).

Sex did not influence the incidence of BAT depiction (in 65% of boys compared with 50% of girls; $P = 0.70$). The time interval between the initial diagnosis and disease-free PET-CT scans was 4.7 ± 2.4 mo and was similar for BAT+ and BAT− patients (4.8 ± 2.6 compared with 4.6 ± 2.1 mo; $P = 0.82$). There was also no difference in BAT depiction between patients treated

TABLE 1
Characteristics of 32 pediatric cancer patients at diagnosis[1]

	All (n = 32)	Males (n = 20)	Females (n = 12)
Age (y)	13.8 ± 3.6	14.6 ± 3.0	12.6 ± 4.2
Weight (kg)	58.7 ± 20.8	62.1 ± 18.7	53.0 ± 23.6
Height (cm)	158.5 ± 19.9	165.6 ± 17.7	146.6 ± 18.0
BMI-for-age percentile	69.0 ± 29.4	63.2 ± 32.1	78.7 ± 22.3
BSA (m^2)	1.6 ± 0.4	1.7 ± 0.3	1.4 ± 0.4
SAT (cm^3)	465 ± 320	414 ± 313	550 ± 328
VAT (cm^3)	70.9 ± 48.9	72.8 ± 49.7	67.7 ± 49.5
Muscle (cm^3)	284 ± 93.4	315 ± 88.1	233 ± 81.4

[1] All values are means ± SDs. BSA, body surface area; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

TABLE 2
Characteristics of BAT+ and BAT− pediatric cancer patients at disease-free follow-up[1]

	All (n = 32)			Males (n = 20)			Females (n = 12)		
	BAT+ (n = 19)	BAT− (n = 13)	P	BAT+ (n = 13)	BAT− (n = 7)	P	BAT+ (n = 6)	BAT− (n = 6)	P
Age (y)	15.0 ± 3.6	13.1 ± 3.4	0.16	15.1 ± 3.5	14.6 ± 2.1	0.73	14.7 ± 4.1	11.4 ± 4.0	0.20
Weight (kg)	65.4 ± 21.9	56.5 ± 18.6	0.24	68.0 ± 22.0	58.8 ± 10.8	0.32	59.9 ± 22.6	53.8 ± 26.0	0.67
Height (cm)	164.4 ± 19.6	151.6 ± 17.9	0.07	170.5 ± 18.7	159.0 ± 12.8	0.17	151.2 ± 15.3	142.9 ± 20.2	0.44
BMI-for-age percentile	70.6 ± 29.1	76.9 ± 33.6	0.57	64.3 ± 32.3	68.2 ± 41.1	0.82	84.3 ± 14.9	87.2 ± 20.9	0.79
BSA (m^2)	1.71 ± 0.4	1.5 ± 0.3	0.07	1.8 ± 0.4	1.6 ± 0.2	0.12	1.5 ± 0.4	1.4 ± 0.4	0.53
SAT (cm^3)	547 ± 329	596 ± 338	0.69	473 ± 314	521 ± 289	0.74	709 ± 329	684 ± 397	0.91
VAT (cm^3)	91.2 ± 57.0	89.2 ± 32.0	0.92	81.3 ± 52.8	91.3 ± 31.9	0.64	112.8 ± 64.9	86.8 ± 34.9	0.41
Muscle (cm^3)	322 ± 97.3	251 ± 80.2	0.036	349 ± 101	284 ± 66.0	0.14	264 ± 62.8	211 ± 82.6	0.24

[1] All values are means ± SDs. P values were obtained by using unpaired t tests. BAT−, subjects without metabolically active brown adipose tissue at disease-free follow-up; BAT+, subjects with metabolically active brown adipose tissue at disease-free follow-up; BSA, body surface area; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

with or without glucocorticoids (57% compared with 61%; P = 0.82). In contrast, there was a tendency for more occurrences of BAT+ during the winter months, which, for the purpose of this study, were November, December, and January, than during the remaining months (82% compared with 48%; P = 0.06).

There were no significant differences in the age, anthropometric measures, or CT values of SAT and VAT between BAT+ and BAT− groups at follow-up; this was true regardless of whether all subjects were analyzed together or whether boys and girls were analyzed separately (Table 2). When all children were analyzed together, values for abdominal muscle were greater in BAT+ subjects.

Percentage gains in weight, SAT, and VAT were significantly greater in BAT− subjects than in BAT+ subjects (**Figure 1**). This was true for all subjects together and when boys were analyzed separately (Figure 1, A and B). Although the percentage gains in weight, SAT, and VAT also were greater in girls without BAT, these changes were not significant (Figure 1C). The greatest difference in adiposity between BAT+ and BAT− subjects was observed in the VAT depot. Changes in visceral adiposity for each patient are shown in **Figure 2**. There was no difference in the percentage change in abdominal musculature between BAT groups (4.7% in BAT+ patients compared with 3.5% in BAT− patients; P = 0.77).

Compared with the 18 patients whose treatment regimen did not include glucocorticoid therapy, the 14 patients treated with glucocorticoids did not have significant gains in weight (8 ± 12.4% compared with 5 ± 6.7%; P = 0.28), SAT (58 ± 66% compared with 23 ± 40%; P = 0.07), or VAT (101 ± 155% compared with 40 ± 85%; P = 0.16). However, in patients treated with glucocorticoids, gains in VAT were significantly greater in BAT− patients than in BAT+ patients (202 ± 200% compared with 26 ± 30%; P = 0.029). Multiple linear regression analyses indicated that BAT depiction had a negative association with the percentage change in weight, SAT, and VAT independent of age, season, and whether or not the patients were treated with glucocorticoids (**Table 3**).

DISCUSSION

We studied the effect of BAT activation on the weight and measures of adiposity in children successfully treated for malignancy whose PET-CT scan at diagnosis showed no evidence of BAT function. Children and teenagers who had evidence of BAT activity at follow-up PET-CT studies gained significantly less weight and had significantly less subcutaneous and visceral adiposity than did those who remained without BAT activity when disease free. On average, increases in weight and SAT were 3 times greater, and increases in VAT were 6 times greater, in patients who did not show any BAT activity compared with patients who had metabolically active BAT. In accordance with previous investigations, we showed that BAT becomes more metabolically activated during the winter months (21, 29), even in patients living in sunny California (23). Consistent with the need for nonshivering thermogenesis, BAT activity is greater in colder weather (30). This was even seen over narrow temperature ranges, as in previous studies that reported BAT depiction in nearly all PET-CT examinations of young men when obtained at 16°C (31) but in only one-half of young men when obtained at 19°C (32). However, the effect of BAT activity on changes in weight, SAT, or VAT persisted even after age, glucocorticoid treatment, and season were accounted for. Altogether, the findings of this longitudinal study provide strong evidence that the metabolic activation of BAT is inversely related to changes in adiposity.

Approximately one-half of the patients in our cohort were treated with high doses of glucocorticoids as part of the treatment protocol. However, we showed that BAT activity was not influenced by glucocorticoid treatment. Previous data on the influence of glucocorticoids on BAT were primarily based on animal studies and were conflicting. Although some studies suggested that glucocorticoids enhance the metabolic activity of BAT (33), other studies reported an inactivating effect of the glucocorticoid system on BAT, with brown adipocytes that became more lipid filled and white adipocyte-like (34, 35). Other studies showed no effect on BAT mass in rats, despite a marked reduction in visceral WAT after adrenalectomy (36).

Glucocorticoids are known to promote central adiposity (37), and as expected, glucocorticoid-treated patients gained more visceral adiposity than did patients who were not treated with glucocorticoids. It should be noted that in glucocorticoid-treated patients, those who showed no BAT activity gained significantly more visceral adiposity than did those with metabolically active BAT when disease free. Although both glucocorticoid treatment and BAT activity had competing effects on the accumulation of VAT, only BAT function was a significant predictor of gains in VAT. This observation was consistent with available cross-sectional data

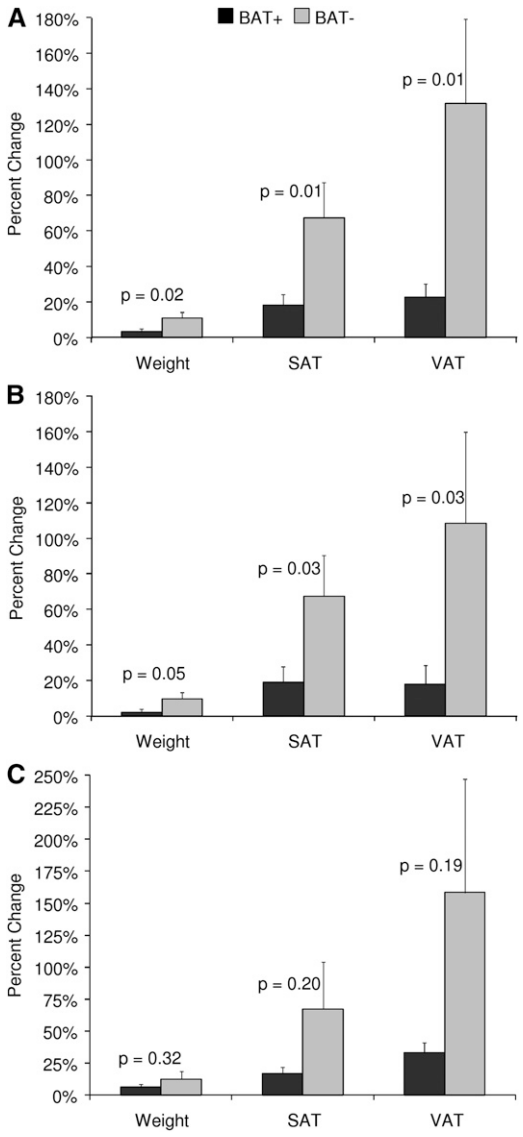

FIGURE 1. Mean (±SEM) percentage changes in weight, SAT, and VAT in 32 pediatric cancer patients with respect to BAT depiction at disease-free follow-up (BAT+, n = 19; BAT−, n = 13) (A), 20 male pediatric cancer patients with respect to BAT depiction at disease-free follow-up (BAT+, n = 13; BAT−, n = 7) (B), and 12 female pediatric cancer patients with respect to BAT depiction at disease-free follow-up (BAT+, n = 6; BAT−, n = 6) (C). P values were obtained by using unpaired t tests. BAT, brown adipose tissue; BAT−, subjects without metabolically active brown adipose tissue at disease-free follow-up; BAT+, subjects with metabolically active brown adipose tissue at disease-free follow-up; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

that suggested that measures of central adiposity, even more than BMI, are inversely correlated with the amount of BAT (5, 38).

Although the basis for the negative relation observed between BAT and WAT has yet to be fully defined, it is likely the reflection of greater energy dissipation and increased energy expenditure associated with BAT activity. BAT contains a unique protein, uncoupling protein 1, which uncouples oxidative phosphorylation and releases energy stored in the mitochondria as heat (7, 8, 39, 40). BAT activity positively correlates with resting metabolic rate (9), and Virtanen et al (40) have estimated that ~63 g BAT could combust the energy equivalent of 4.1 kg WAT over 1 y. Additional support for the link between BAT and energy balance comes from observations that showed that BAT thermogenesis protected against diet-induced weight gains in animals lacking BAT (41–44). However, it is also possible that WAT suppresses BAT function. WAT is known to produce cytokines and chemokines, such as TNF-α, IL-6, and monocyte chemoattractant protein 1, that induce inflammation (45–48) and could potentially have cytotoxic effects on BAT. Indeed, high concentrations of TNF-α have been shown to induce apoptotic degeneration of brown adipocytes (49). Studies are needed to determine the direction of causality between BAT activity and WAT accumulation.

Regardless of the mechanisms that account for the reciprocal relation between BAT and WAT, these 2 adipose tissues differ in structure, function, and lineage, as evidenced by their differing gene-expression profiles; thus, WAT is akin to macrophages, but BAT resembles muscle (50–52). We recently observed that children with metabolically active BAT had significantly greater muscle volume than did those without identifiable BAT (23), and that large increases in the amount of BAT, such as that of skeletal muscle, occur during puberty (53, 54). These clinical observations were consistent with data from cell cultures that indicated that brown adipocytes and myocytes may derive from a common lineage in the paraxial mesoderm (55, 56). Although, in the current study, we observed that subjects with visualized BAT had greater musculature than did those without visualized BAT, we did not find differences in the percentage of change in muscle between groups. The degree to which our results were confounded by the effect of disease severity, inactivity, and glucocorticoid therapy on muscle mass is unknown.

The factors behind the occurrence of metabolically active BAT after treatment of cancer are unknown, and few studies have previously examined the relation between BAT and malignancy. We recently observed an inverse association between the presence of metabolically active BAT and the presence of tumors in children with lymphoma (57), and the possibility exists that malignancy suppresses BAT function. Patients with malignant lymphomas have high circulating concentrations of TNF-α (30, 49, 58, 59). The apoptotic degeneration of brown adipocytes has been reported to be mediated by the p55 TNF-α receptor subtype (58), and its deletion has been shown to increase thermogenesis with an associated increase of uncoupling protein 1 in BAT (30, 49, 58, 59). However, it is unknown whether disease influences

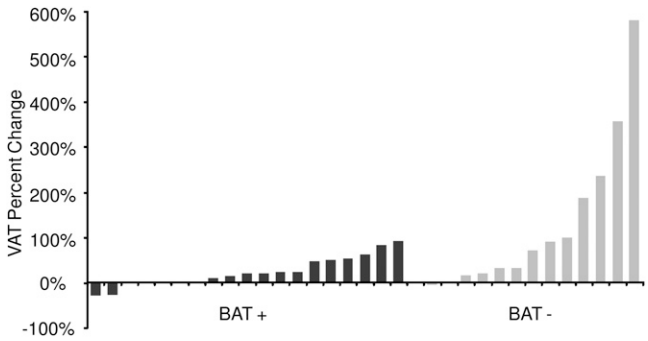

FIGURE 2. Percentage changes in VAT in 32 pediatric cancer patients with respect to BAT depiction at disease-free follow-up. BAT, brown adipose tissue; BAT−, subjects without metabolically active brown adipose tissue at disease-free follow-up; BAT+, subjects with metabolically active brown adipose tissue at disease-free follow-up; VAT, visceral adipose tissue.

TABLE 3
Multiple regression models for the prediction of percentage change in weight, SAT, and VAT in 32 pediatric cancer patients at disease-free follow-up[1]

	B	σ	β	*P*
Percentage change in weight				
$BAT^{+/-}$	−0.074	0.033	−0.385	0.033
Age	−0.009	0.005	−0.334	0.057
$Glucocorticoids^{+/-}$	0.028	0.032	0.147	0.387
Season[2]	0.045	0.034	0.226	0.198
Percentage change in SAT				
$BAT^{+/-}$	−0.527	0.189	−0.480	0.010
Age	−0.014	0.026	−0.091	0.593
$Glucocorticoids^{+/-}$	0.351	0.182	0.323	0.064
Season[2]	0.233	0.195	0.205	0.243
Percentage change in VAT				
$BAT^{+/-}$	−1.110	0.432	−0.452	0.016
Age	−0.056	0.059	−0.163	0.353
$Glucocorticoids^{+/-}$	0.566	0.417	0.233	0.186
Season[2]	0.452	0.446	0.178	0.320

[1] *B*, unstandardized coefficient; $BAT^{+/-}$, presence or absence of metabolically active brown adipose tissue at disease-free follow-up; $glucocorticoids^{+/-}$, presence or absence of glucocorticoids in treatment regimen; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; β, standardized coefficient; σ, SE of unstandardized coefficient.

[2] Winter (November, December, and January) compared with other seasons.

BAT status after treatment, and additional studies are needed to determine the mechanisms that control BAT activation after disease treatment.

To decrease the potential for confounding bias, we purposely chose to study children with visible tumors but no visualization of BAT on the initial PET-CT scans. Shorter treatment periods, higher cure rates, and greater BAT prevalence in pediatric patients when compared with adults strengthened the value of our cohort. The use of sophisticated imaging technology, the evaluation of both white adipose depots, and the longitudinal assessments were additional strengths of the study.

This study had several notable limitations. It was based on the analysis of PET-CT examinations, and BAT depiction was used as the sole measure of BAT. However, the validity of this outcome measure was supported by recent histologic data from Lee et al (19) that indicated that the amount of BAT was related to its activity and showed a greater abundance of brown fat in BAT-positive than in BAT-negative PET studies. Moreover, our data were based on retrospective examinations of children treated for malignancy, and we could not control for the potential effects of the severity of disease, treatment regimen, diet, or physical activity on BAT activity. By selecting patients with disease-free PET-CT scans within 12 mo of diagnosis, the confounders associated with not recruiting healthy subjects were somewhat minimized. Unfortunately, no technique is currently available for safe prospective examinations of BAT in pediatric populations. Radiation exposure from PET-CT imaging precludes such studies in normal, healthy subjects.

In conclusion, the adipose organ is not homogenous but composed of brown and white adipocytes that, paradoxically, have contrasting implications for metabolic health, with WAT serving as a risk factor for disease and with BAT suggested as having a protective role. Previous evidence that suggested an inverse association between BAT and WAT was based on cross-sectional data that showed that BAT activity correlates inversely with BMI in adult and pediatric populations (4, 5, 8–11, 38). Our longitudinal study provides additional evidence in support of the notion that BAT activity prevents weight gain and the accumulation of subcutaneous and, more strikingly, visceral adiposity. Such findings underscore the potential importance of metabolic activity of BAT in the regulation of body weight, which may be harnessed for the treatment of obesity (39, 60, 61).

The authors' responsibilities were as follows—VG and CHF: designed the research; VG and FG: conducted the research; JSC, MLS, and FJD: analyzed the data; VG, JSC, MLS, and HHH: wrote the manuscript; VG: had primary responsibility for the final content of the manuscript; and all authors: participated intellectually and practically in this work, including in the conception, design, and conduct of the experiment, participated in data interpretation, and read and approved the final manuscript. None of the authors had a conflict of interest.

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