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PICTORIAL ESSAY

Brown adipose tissue ^{18}F-FDG uptake in pediatric PET/CT imaging

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Abstract Positron emission tomography (PET) using [F-18] 2-fluoro-2-deoxyglucose (FDG) fused with CT (^{18}F-FDG PET/CT) has been widely adopted in oncological imaging. However, it is known that benign lesions and other metabolically active tissues, such as brown adipose tissue (BAT), can accumulate ^{18}F-FDG, potentially resulting in false-positive interpretation. Previous studies have reported that ^{18}F-FDG uptake in BAT is more common in children than in adults. We illustrate BAT FDG uptake in various anatomical locations in children and adolescents. We also review what is known about the effects of patient-related physical attributes and environmental temperatures on BAT FDG uptake, and discuss methods used to reduce BAT FDG uptake on ^{18}F-FDG PET.

Keywords PET/CT · Brown adipose tissue · FDG uptake · False-positives · Children

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Introduction

Positron emission tomography (PET) using [F-18]2-fluoro-2-deoxyglucose (FDG) fused with CT (^{18}F-FDG PET/CT) has been widely adopted as a primary imaging modality in the evaluation of cancer patients [1–5]. However, a number of pitfalls are encountered in ^{18}F-FDG PET interpretation. For example, uptake in benign lesions and other metabolically active tissues, such as brown adipose tissue (BAT), can lead to false-positive interpretation and inaccurate disease staging [6–11]. Previous studies have reported that BAT FDG uptake is more common in children than in adults. The purpose of this article is to review: (1) prevalence, anatomical distribution and appearance of metabolically active BAT in children and adolescents; (2) effects of patient-related physical attributes (i.e. age, gender, body mass index) and environmental temperatures (i.e. outdoor ambient temperature, indoor room temperature) on BAT FDG uptake, and (3) strategies currently used to prevent BAT FDG uptake in ^{18}F-FDG PET.

Brown adipose tissue

Brown adipose tissue differs from white adipose tissue in histological appearance, function and anatomical distribution. BAT contains granular cytoplasm with multiple fat vacuoles within each adipocyte and is characterized by a high degree of

vascularity and mitochondrial density, which accounts for its characteristic brown color [12]. White adipose tissue serves as a site for lipid storage and insulation, whereas BAT serves as the primary site for non-shivering thermogenesis [13–15]. The presence of uncoupling protein 1 (UCP1), which is unique to BAT, enables non-shivering thermogenesis, which is particularly important during the initial decade of life [14, 16, 17]. Although the anatomical distribution of metabolically active BAT is relatively widespread in children, BAT regresses and becomes predictably concentrated in certain anatomical locations with increasing age [12, 15].

Anatomical distribution of BAT FDG Uptake

^{18}F-FDG uptake in BAT is driven by sympathetic release of norepinephrine, resulting in activation of β3 receptors [13]. Subsequent ^{18}F-FDG uptake through glucose transporter 1 (GLUT 1) and glucose transporter 4 (GLUT 4) [18, 19] is usually bilateral and symmetrical, although focal and asymmetrical uptake is not uncommon in some anatomical regions. BAT FDG uptake in children is most commonly seen in the neck and supraclavicular-axillary, mediastinal, paravertebral-intercostal, mediastinal, perinephric-suprarenal and upper abdominal wall regions (Fig. 1), more in some regions than others. Whenever possible ^{18}F-FDG PET images should be correlated with co-registered CT to improve anatomical localization and exclude underlying soft-tissue abnormality [10, 20].

Neck

Okuyama et al. [21] were the first to provide convincing evidence of BAT in the neck in their study of ^{123}I-metaiodobenzylguanidine distribution in children with neuroendocrine tumors. The classic distribution of BAT FDG uptake in the neck is bilateral and symmetrical and represents a series of discrete foci of BAT arranged in a curvilinear pattern [13] (Figs. 2 and 3). Often, BAT FDG uptake in the neck is seen in the posterior cervical region. In some patients, two foci of suboccipital uptake are seen on each side of the neck. In patients with prior intervention such as surgery or radiation affecting the neck or cervical sympathetic chain, uptake might be focal and asymmetrical (Fig. 4). Brown adipose tissue FDG uptake in the neck can obscure small pathological lesions. Furthermore, misregistration of PET and CT can complicate differentiation of uptake in neck nodes from BAT.

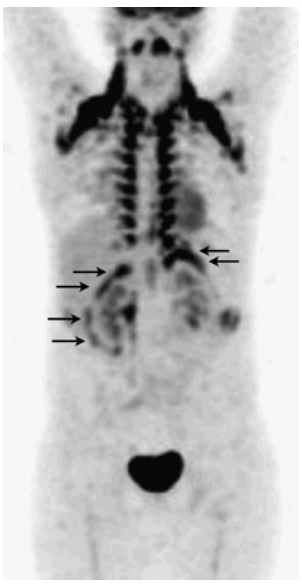


Fig. 1 Anterior maximum-intensity projection in a 13-year-old boy with BAT FDG uptake in the neck and supraclavicular-axillary, paravertebral-intercostal and mediastinal regions. It is relatively uncommon to see contiguous, curvilinear uptake around the lateral edges of the kidneys (*arrows*)

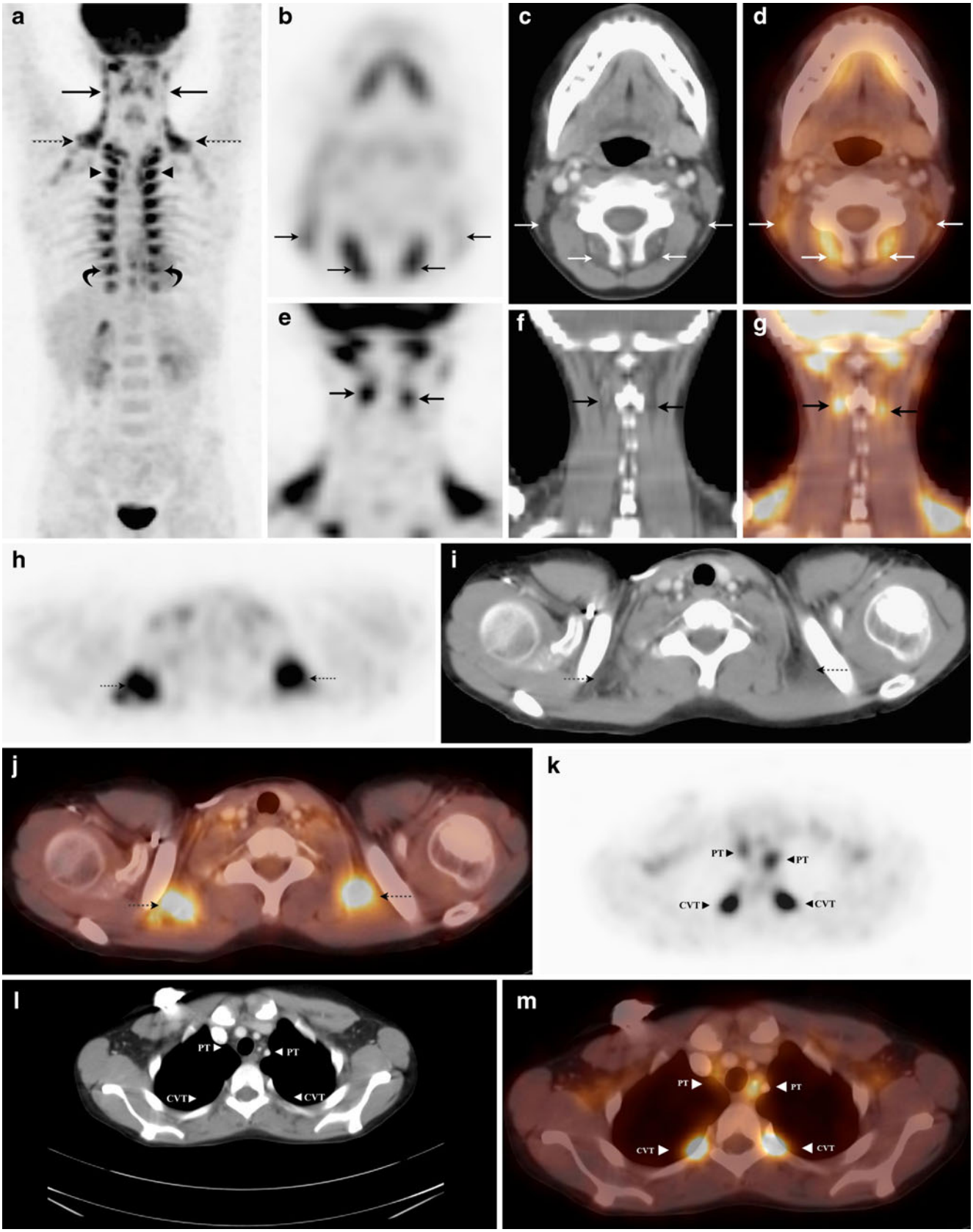
Supraclavicular-axillary region

In pediatric ^{18}F-FDG PET, BAT FDG uptake is most commonly found in the supraclavicular-axillary region [9]. FDG uptake in this area typically appears symmetrical and fusiform, extending contiguously from the inferior neck to the axillae (Figs. 2 and 3). As in the neck, uptake in the supraclavicular-axillary region can be markedly intense and can obscure small pathological lesions. During the era of ^{18}F-FDG PET-only imaging, fusiform uptake in the neck and supraclavicular regions had been attributed to muscle activity rather than BAT because physiological uptake in this region resolved after administration of benzodiazepine, a muscle relaxant and anxiolytic [22]. However, improved anatomical localization with the introduction of ^{18}F-FDG PET/CT has revealed that ^{18}F-FDG uptake in this area is in fact often attributable to BAT FDG uptake [9, 11].

Paravertebral-intercostal region

BAT FDG uptake in this region presents as bilateral, symmetrical foci in the intercostal spaces along the costovertebral junctions (Figs. 2, 5 and 6) [11, 23]. In cases with a high degree of BAT FDG uptake in this region,

Fig. 2 Anterior maximum-intensity projection in a 12-year-old boy. **a** ▶ There is BAT FDG uptake in the neck (*arrows*) and supraclavicular-axillary region (*dotted arrows*). Symmetrical FDG uptake in the neck is shown on axial PET (**b**), CT (**c**) and PET/CT (**d**) images. Note that the medial arrows point to neck BAT surrounded by muscle, as shown on coronal PET (**e**), CT (**f**) and PET/CT (**g**) images. BAT FDG uptake in the supraclavicular region is shown on axial PET (**h**), CT (**i**) and PET/CT (**j**) images. The upper mediastinum (*arrowheads*) on the maximum-intensity projection image, with uptake in the costovertebral junction (*CVT*) and paratracheal regions (*PT*), is shown on axial PET (**k**), CT (**l**), and PET/CT (**m**) images. The lower mediastinum (*curved arrows)* on the maximum-intensity projection, with uptake around the azygous vein (*AZ*), hemiazygous vein (*HA*), and costovertebral junction (*CVT*), is shown on axial PET (**n**), CT (**o**), and PET/CT (**p**) images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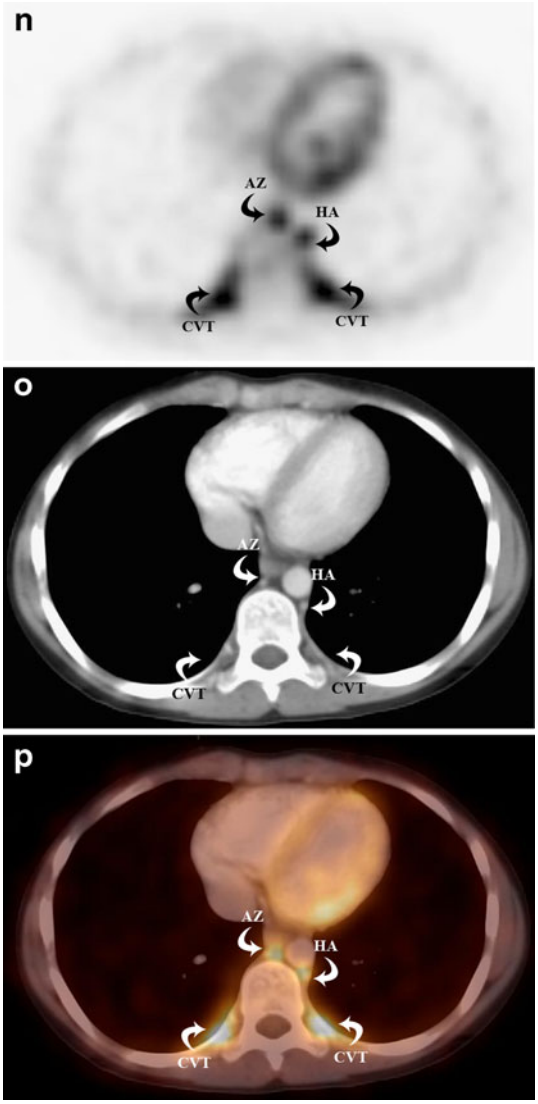

Fig. 2 (continued)

uptake is readily identifiable using coronal images. Special attention should be focused on differentiating BAT FDG uptake in this region from skeletal or paraspinal lesions.

Mediastinum

BAT FDG uptake in the mediastinum is often seen in the paratracheal, paraesophageal and perivascular regions (Figs. 2, 3 and 6) and might also be evident in the pericardial region. Most often, BAT FDG uptake is seen between and surrounding intrathoracic blood vessels such as the azygos and hemiazygos veins (Fig. 2), great vessels in the upper mediastinum (Fig. 2), and aorta (Fig. 6). Typically, BAT FDG uptake in the mediastinum appears as relatively symmetrical, rounded foci of activity (Fig. 2). However, unlike the neck, asymmetrical uptake is not uncommon (Fig. 3).

Mediastinal BAT uptake is almost always seen in conjunction with BAT FDG uptake in the neck and/or supraclavicular-axillary regions. However, Truong et al. [10] reported five patients with isolated mediastinal BAT FDG uptake. Focal BAT FDG uptake in the mediastinum can be easily misinterpreted as malignancy. Therefore, careful correlation of metabolic activity on ^{18}F-FDG PET with anatomy on CT is highly recommended [10].

Perinephric-suprarenal region

BAT FDG uptake in this region presents as focal activity adjacent to the upper pole of the kidney, or curvilinear activity surrounding the lateral aspect of the kidneys (Fig. 7). Increased suprarenal BAT FDG uptake can mimic an adrenal neoplasm [8]. ^{18}F-FDG PET/CT fusion images can be used for precise localization and to exclude abnormal adrenal mass.

Abdominal wall

Based on our experience, BAT FDG uptake in the abdominal wall presents as focal or linear activity deep to the midline linea alba, which separates the left and right rectus sheaths (Figs. 6 and 7).

Physical traits affecting BAT FDG uptake

Age

BAT FDG uptake is more common in children and adolescents than in adults [10, 11]. Truong et al. [10] reported mediastinal brown fat uptake in 1.3% of adults compared with 50% of children, and Yeung et al. [11] showed that metabolically active BAT uptake in the neck is significantly more prevalent in children (15%) than in adults (1.9%). Furthermore, Gelfand et al. [24] reported that BAT FDG uptake is seen more frequently in adolescents (>10 y) than younger children.

Gender

In adults, BAT FDG uptake is more common in women than in men [9, 11, 23, 25]. Cypess et al. [25] reported BAT FDG uptake in 7.5% of women versus 3.1% of men. Similarly, Truong et al. [10], Yeung et al. [11], and Cohade et al. [9] reported a greater prevalence of BAT FDG uptake in females. Results from rodent studies suggest that this gender difference is explained by relatively larger size and higher density of cristae within BAT mitochondria of females, resulting in greater glucose utilization and higher thermogenic capacity [26]. However, Gelfand et al. [24]

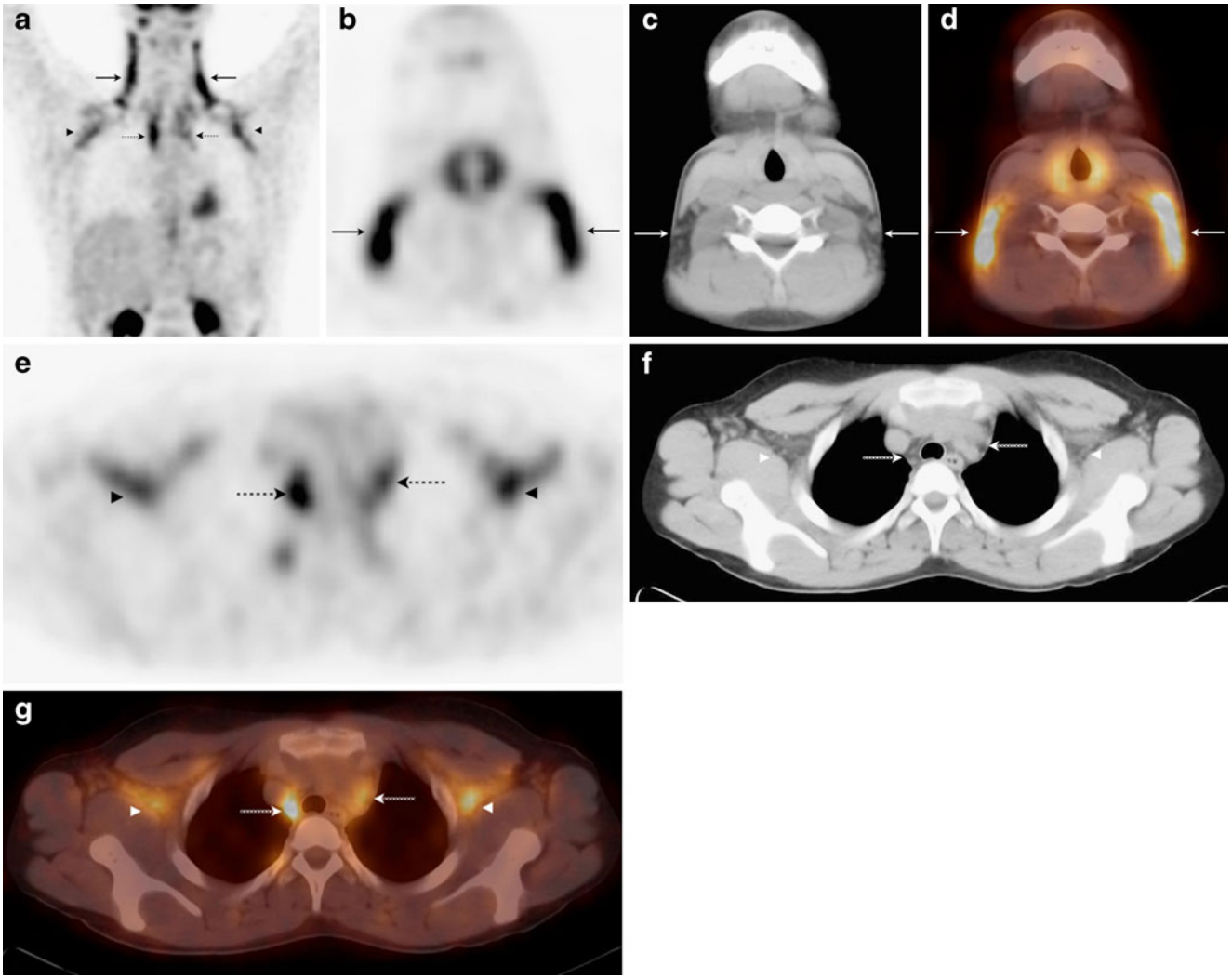

Fig. 3 Coronal PET in a 13-year-old boy with BAT FDG uptake in multiple anatomical locations, including the neck (*arrows*), asymmetrical uptake in the mediastinum (*dotted arrows*), and uptake in the supraclavicular-axillary region (*arrowheads*) (**a**). Uptake in the neck is seen on axial PET (**b**), CT (**c**) and PET/CT (**d**) images. Uptake in the mediastinum (*dotted arrows*) and supraclavicular-axillary regions (*arrowheads*) is shown on PET (**e**), CT (**f**), and PET/CT (**g**) images

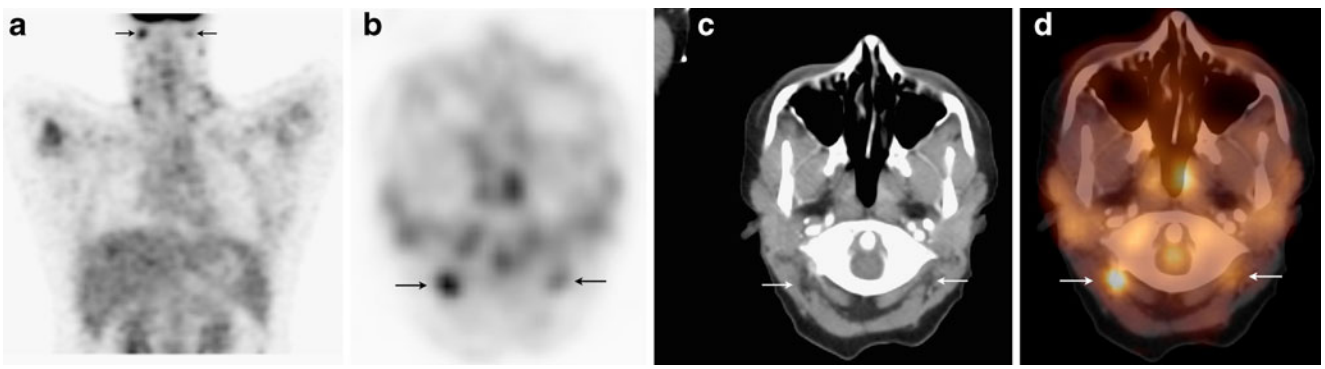

Fig. 4 Coronal PET in a 15 year-old girl with BAT FDG uptake in the neck (*arrows*) (**a**). Asymmetric uptake in the upper neck is shown on PET (**b**), CT (**c**), and PET/CT (**d**) images. Note that there is a small degree of misregistration as seen in the axial images

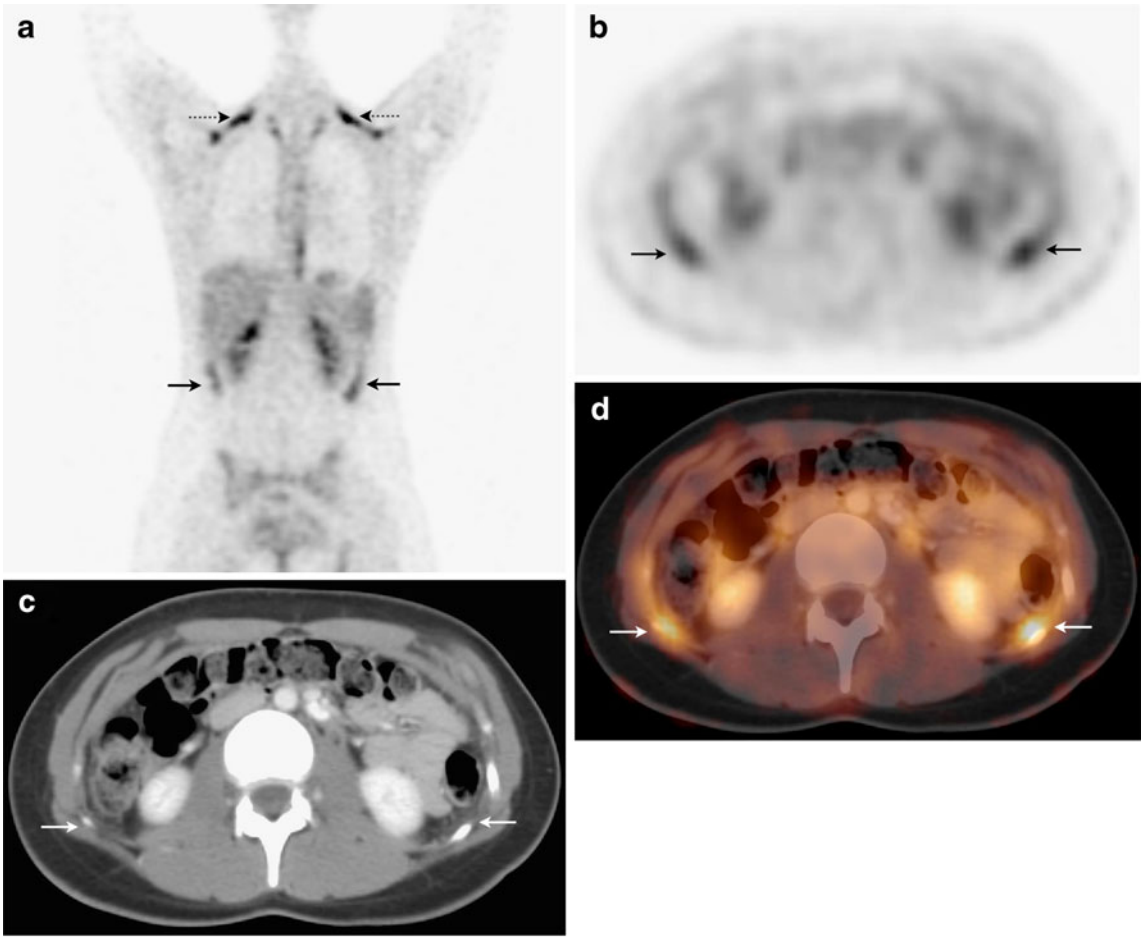

Fig. 5 Coronal PET in a 17-year-old girl with BAT FDG uptake in the lower intercostal (*arrows*) and supraclavicular-axillary (*dotted arrows*) regions (**a**). Uptake in the lower intercostal region is shown on axial PET (**b**), CT (**c**) and PET/CT (**d**) images

observed that the prevalence of BAT FDG uptake in children did not differ between boys and girls, although there was a greater incidence of BAT FDG uptake in adolescents attributed largely to adolescent girls [24]. It would be valuable for future studies with larger pediatric populations to investigate whether there exists a gender difference when children and adolescent subgroups are considered separately.

Body mass and body mass index

In adult studies, Cypess et al. [25] and Rodriguez-Cuenca et al. [26] each reported an inverse correlation between BAT FDG uptake and body mass index (BMI). However, other studies have failed to reproduce these findings in age- and gender-matched control groups [9–11]. The effect of body mass and BMI in children has not been well-evaluated. Often, increasing body mass is accompanied by advancing age. In addition, since absolute BMI might be a less accurate predictor of body fat in children than in adults [27], future studies in children might benefit by using BMI percentile instead of absolute BMI.

Effect of environmental temperature on BAT FDG uptake

Outdoor temperature

Cold-induced thermogenesis in BAT is driven by sympathetic release of norepinephrine, resulting in activation of β receptors [13, 18, 19]. It is believed that increased glucose transporter activity during thermogenesis is responsible for increased BAT FDG uptake on PET following cold exposure [18] (Fig. 6). In a study of 1,017 patients, Cohade et al. [28] reported that the prevalence of ^{18}F-FDG uptake in supraclavicular BAT in adults increased during the winter months (January to March) compared to the rest of the year. The prevalence of BAT FDG uptake was also higher during the winter

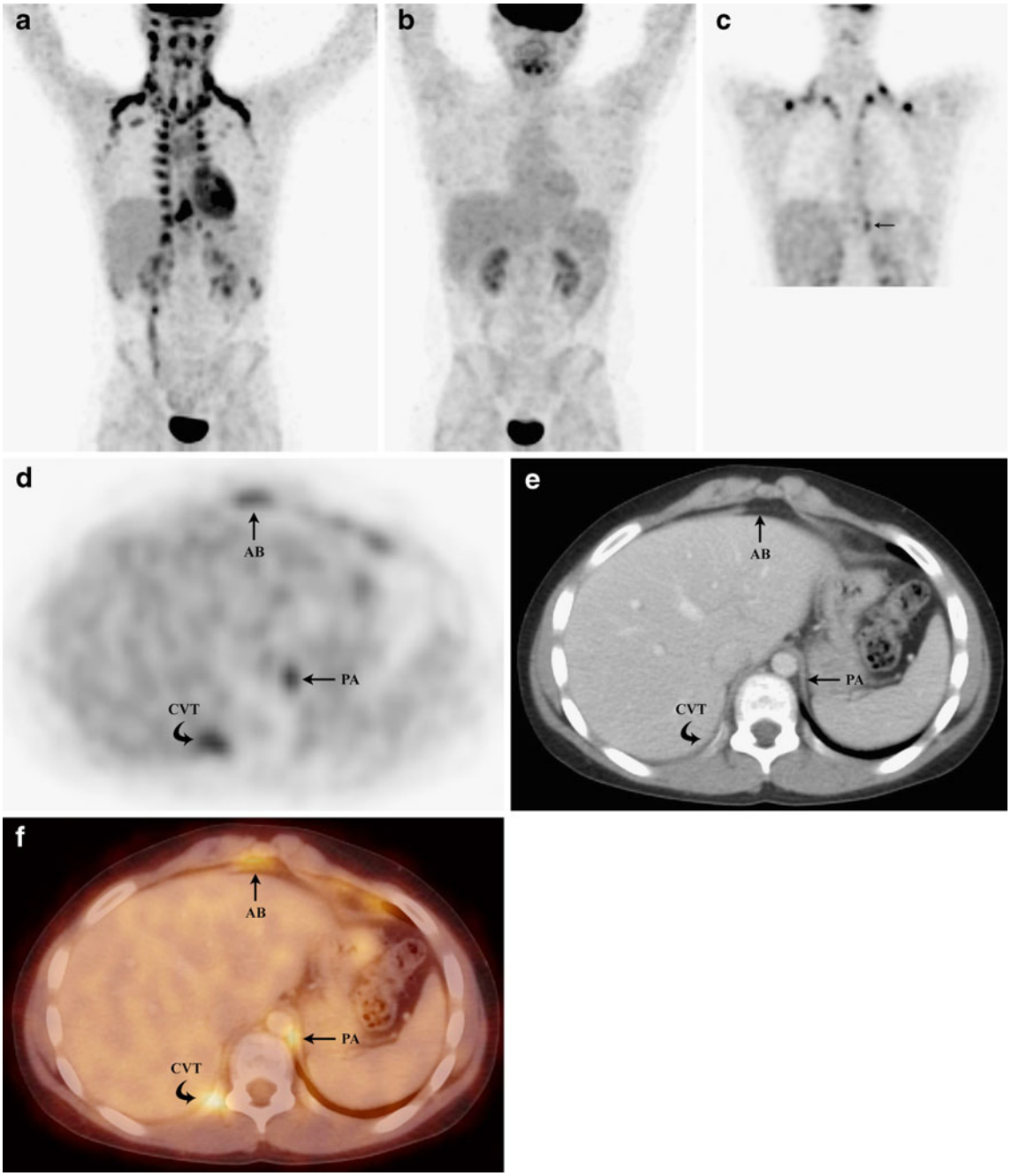

Fig. 6 Anterior maximum-intensity projections of a 13-year-old boy show the effect of cold (**a**) and warm (**b**) outdoor temperature on ^{18}F-FDG PET performed during the winter and the preceding summer (7 months apart), respectively. Coronal PET (**c**) of the boy obtained during the winter shows BAT FDG uptake in the periaortic region (*arrow*). Also note the uptake in the supraclavicular region. Uptake is seen in the paraaortic (*arrow*, *PA*), anterior abdominal (*arrow, AB*) and costovertebral (*curved arrow, CVT*) regions on axial PET (**d**), CT (**e**) and PET/CT (**f**) images

months for the subset of children in that study, although differences did not reach statistical significance because of the relatively small pediatric sample size (n=21) [28]. Cohade et al. [28] hypothesized that even if there is an acute response in BAT activity because of cold exposure, a prolonged period of cold exposure might be necessary to elicit increased BAT FDG uptake on PET, as evidenced by a delay of up to 2 months between cold exposure and increased BAT FDG uptake on PET [28]. However, findings from other studies do not support the necessity of prolonged cold exposure in this regard. In a study of 1,159 patients, including 22 children, Kim et al. [29] reported changes in BAT FDG uptake within days of cold exposure and found that the relationship between BAT

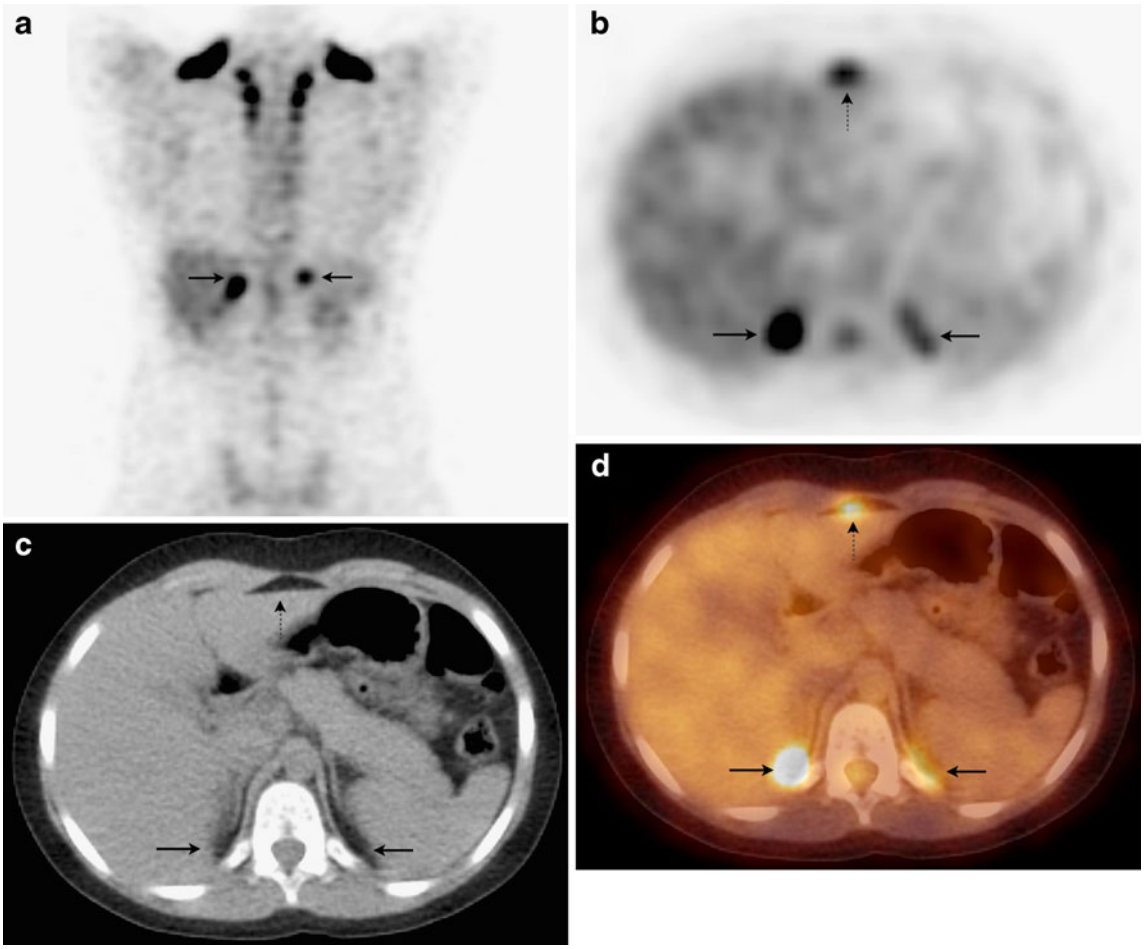

Fig. 7 Suprarrenal (*arrows*) and abdominal wall (*dotted arrows*) BAT FDG uptake in a 9-year-old boy. **a** Coronal PET. **b** Axial PET. **c** CT. **d** PET/CT

FDG uptake and outdoor temperature was most significant when correlated with short-term averages in temperature (i.e. <7 days). Furthermore, animal studies have reported acute changes in BAT activity within minutes of changes in environmental temperature [14]. The relationship between outdoor temperature and BAT FDG uptake remains to be thoroughly investigated in children.

Indoor temperature

It has been shown that increasing indoor room temperature can significantly reduce BAT FDG uptake in children [30] (Fig. 8). Zukotynski et al. [30] reported that the incidence of BAT FDG uptake decreased from 27% to 9% after increasing the indoor temperature from 21°C to 24°C and maintaining children in the warmed environment for 30 min prior to and 1 h after intravenous tracer administration. Passively or actively warming patients prior to and after the injection of ^{18}F-FDG might be a safe non-pharmacological approach to prevent BAT FDG uptake in children [31].

Note that indoor temperatures must also be controlled during the summer in order to minimize BAT FDG uptake. Bar-Sever et al. [32] suggested that uncomfortably cool air conditioning might have caused BAT FDG uptake despite year-round warm climates. Gelfand et al. [24] also alluded to variations in indoor temperature as a potential confounding influence in their study, which did not report a relationship between outdoor temperature and BAT FDG uptake.

Current methods to reduce BAT FDG uptake

Pharmacological approaches

As mentioned previously, heat production by BAT is stimulated by norepinephrine released from the sympathetic nervous system in response to cold temperatures [14]. β1, β2 and predominantly β3 receptors are expressed in BAT and stimulated by norepinephrine [14]. Various drugs including opiates and benzodiazepines are known to block

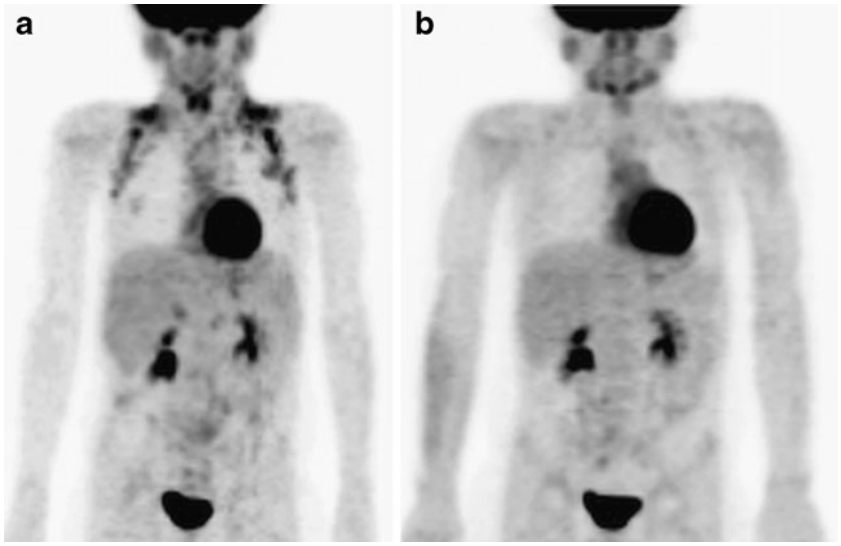

Fig. 8 Anterior maximum-intensity projections in a 9-year-old boy show the effect of warming on BAT FDG uptake. Raising indoor room temperature from 21°C (**a**) to 24°C (**b**) resulted in a substantial decrease in BAT FDG uptake in these images, which were obtained 11 months apart

these receptors, thereby reducing BAT FDG uptake [24]. Barrington and Maisey [22] demonstrated that oral diazepam given before the uptake period can reduce or suppress neck and paravertebral BAT FDG uptake in adults. Furthermore, Parysow et al. [33] showed that a low dose of 20 mg of oral propranolol given 60 min prior to ^{18}F-FDG administration can reduce BAT FDG uptake in adults. In children, Gelfand et al. [24] showed that intravenous fentanyl (0.75–1.0 μg/kg up to a maximum dose of 50 μg given 10 min prior to ^{18}F-FDG injection with appropriate monitoring) can significantly reduce BAT FDG uptake. However, Gelfand et al. [24] reported that low-dose diazepam did not reduce BAT FDG uptake. Similarly, in a randomized control trial, Sturkenboom et al. [34] reported that low-dose diazepam did not significantly suppress BAT FDG uptake in adults.

Diet

Recently, Williams and Kolodny [35] reported significantly decreased BAT FDG uptake and blood glucose levels when using a high-fat diet protocol. Patients were instructed to eat a high-fat and low-carbohydrate diet the night before and the morning of the ^{18}F-FDG PET study [35]. The effect of this high-fat diet on BAT uptake is likely related to fatty-acid loading, which elicits thermogenesis without significant glucose metabolism [35]. However, the effect of the high-fat diet on tumor FDG uptake has not been fully explored [35].

Warming

As discussed earlier, warming children prior to and after the injection of ^{18}F-FDG is a safe non-pharmacological approach to prevent BAT FDG uptake [31]. Note that patient warming should begin at least 30 min prior to FDG injection; warming after the FDG injection will not suppress BAT FDG uptake. However, in addition to adjusting room temperature, wrapping patients in heated or non-heated blankets during scanning, and asking patients to dress warmly and avoid cold environments on the day of the ^{18}F-FDG PET might further minimize the incidence of metabolically active BAT FDG uptake.

Conclusion

Compared to adults, metabolically active BAT is more common in pediatric imaging. While the anatomical distribution of BAT is relatively widespread during the first decade of life, BAT becomes concentrated in certain anatomical regions with increasing age. Although ^{18}F-FDG uptake in metabolically active BAT is typically bilateral and symmetrical, uptake that is focal and asymmetrical is not uncommon in certain locations. Careful attention to anatomical location on CT is needed to avoid misinterpretation, potentially leading to false-positive results on oncological studies. The use of combined ^{18}F-FDG PET/CT can improve diagnostic accuracy by helping to rule out abnormality.

Although adult studies suggest that BAT FDG uptake is influenced by physical traits such as age, gender and BMI, these relationships are less clear in children and further research in the pediatric population is needed. However, based on pediatric studies that have been published, in order to minimize BAT FDG uptake, exposure to cold temperatures should be limited prior to ^{18}F-FDG PET, and patients should be warmed before and during the uptake phase prior to imaging. At the Society for Pediatric Radiology Annual Meeting, which took place in Boston,

MA, in April 2010, an informal survey was conducted by Dr. S.T. Treves to assess the methods currently employed in reducing BAT FDG uptake (personal communication). The survey included nine pediatric institutions in North America and suggested that the most commonly used methods for preventing brown fat FDG uptake were room temperature control (8 of 9) and warm blankets (7 of 9). Medications were used at 3 of 9 institutions. Overall, the use of the techniques reviewed in this article might significantly reduce BAT FDG uptake, enabling more efficient and accurate image interpretation.

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