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An International Survey Investigating the Incidence and Management of Brown Fat Uptake on ^{18}F-FDG PET/CT at Children's Hospitals and Interventions for Mitigation

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Brown fat can present challenges in patients with cancer who undergo ^{18}F-FDG PET scans. Uptake of ^{18}F-FDG by brown fat can obscure or appear similar to active oncologic lesions, causing clinical challenges in PET interpretation. Small, retrospective studies have reported environmental and pharmacologic interventions for suppressing brown fat uptake on PET; however, there is no clear consensus on best practices. We sought to characterize practice patterns for strategies to mitigate brown fat uptake of ^{18}F-FDG during PET scanning. **Methods:** A survey was developed and distributed via e-mail LISTSERV to members of the Children's Oncology Group diagnostic imaging committee, the Society for Nuclear Medicine and Molecular Imaging pediatric imaging council, and the Society of Chiefs of Radiology at Children's Hospitals between April 2022 and February 2023. Responses were stored anonymously in REDCap, aggregated, and summarized using descriptive statistics. **Results:** Fifty-five complete responses were submitted: 51 (93%) faculty and fellow-level physicians, 2 (4%) technologists, and 2 (4%) respondents not reporting their rank. There were 43 unique institutions represented, including 5 (12%) outside the United States. Thirty-eight of 41 (93%) institutions that responded on environmental interventions reported using warm blankets in the infusion and scanning rooms. Less than a third (n = 13, 30%) of institutions reported use of a pharmacologic intervention, with propranolol (n = 5, 38%) being most common, followed by fentanyl (n = 4, 31%), diazepam (n = 2, 15%), and diazepam plus propranolol (n = 2, 15%). Selection criteria for pharmacologic intervention varied, with the most common criterion being brown fat uptake on a prior scan (n = 6, 45%). **Conclusion:** Clinical practices to mitigate brown fat uptake on pediatric ^{18}F-FDG PET vary widely. Simple environmental interventions including warm blankets or increasing the temperature of the injection and scanning rooms were not universally reported. Less than a third of institutions use pharmacologic agents for brown fat mitigation.

Key Words: brown adipose tissue; fentanyl; pediatric PET; pediatric oncology

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The American Cancer Society predicted that by the end of 2022 there would be an estimated 15,950 pediatric and adolescent patients diagnosed with cancer (*1*). For many cancer types, imaging with ^{18}F-FDG PET/CT plays a key role in the initial workup and in measuring the response to therapy (*1*,*2*). The significant increase in the availability of ^{18}F-FDG PET/CT (PET) over the last 2 decades has led to PET imaging's being deemed the standard of care for diagnostic and surveillance imaging of oncology patients (*3*–*8*). PET detects malignancy because of the relative overreliance of cancer cells on glucose for metabolism in comparison to surrounding tissues (*4*). Malignant tissues have more glucose transporters 1 and 4 on the cell surface than do other tissues (*9*,*10*). This results in a relative concentration of ^{18}F-FDG in malignant cells. Inside the cell, ^{18}F-FDG emits photons that are detected by the PET camera. An overlay with a CT scan can help localize active or malignant tissues (*9*,*10*). Other metabolically active tissues, including brown fat, blood, heart, and brain, also have increased glucose transporters to support their metabolic activity and have relatively greater uptake of ^{18}F-FDG, potentially leading to difficulty in discerning malignant tissue on the basis of uptake alone (*4*,*10*–*14*).

Brown fat plays an important role in thermoregulation, particularly in children and adolescents (*15*,*16*). Because of the metabolic activity of brown fat, it appears avid on ^{18}F-FDG PET, potentially mimicking or obscuring tumor (*4*,*9*,*13*,*17*). Brown fat is commonly found in the neck, mediastinum, and supraclavicular areas, which can present challenges for disease workup and response-to-therapy evaluations (Fig. 1) (*9*,*12*–*14*,*17*,*18*). This is particularly challenging in pediatric lymphomas, for which the common sites of disease overlap with the anatomic distribution of brown fat (*2*,*4*,*5*,*9*). Inability to discern malignancy from normal tissue can lead to situations in which oncologists must consider invasive biopsies of suggestive ^{18}F-FDG–avid foci. In contrast, adequate brown fat mitigation increases the specificity and sensitivity of ^{18}F-FDG PET (*12*–*14*,*16*,*19*–*24*).

Over the past 20 y, preliminary pilot studies have investigated various pharmacologic and nonpharmacologic interventions

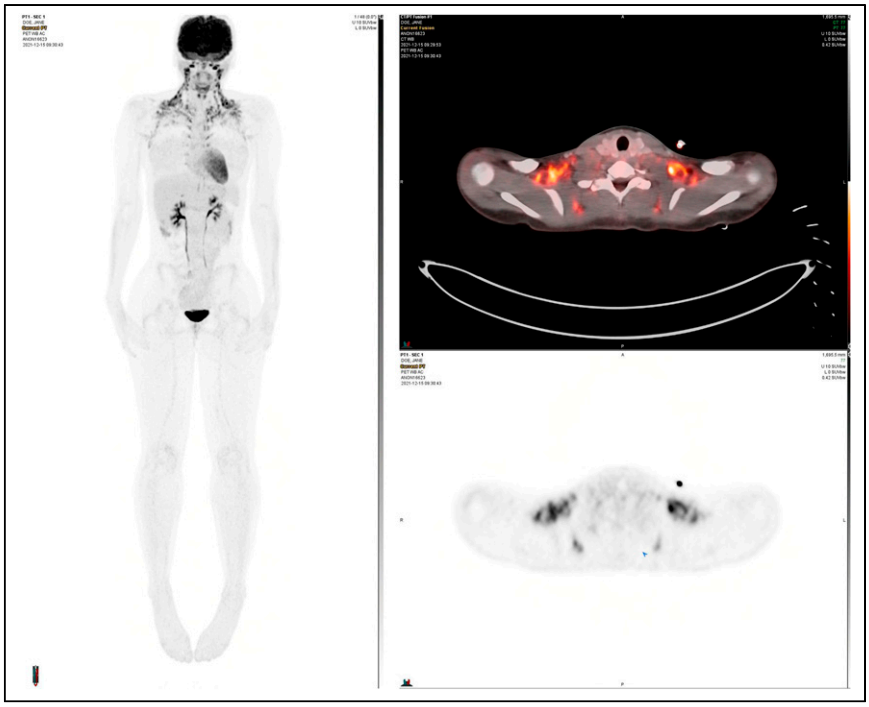

FIGURE 1. ^{18}F-FDG PET images of 16-y-old girl with stage IVb classic Hodgkin lymphoma who had imaging done at end of planned chemotherapy. Extensive cervical brown fat is present bilaterally. Within, several nodular areas show increased uptake. On review of fused PET/CT images, areas were determined to likely represent brown fat uptake. All images are fused PET/CT images. Coronal plane on left and two images on right are axial. Image credit Justin Sims, MD.

with potential to suppress brown fat, and these have shown varying levels of success (*19*,*21*–*25*). Currently, there is not a universally adopted standard for the interventions that should be used. Studies on adults and children differ widely on the evidence supporting which pharmacologic interventions are chosen, and a paucity of data exists supporting the safety, feasibility, and efficacy of such interventions (*21*,*23*,*25*–*28*). Warming rooms and the use of warm blankets have been found to be beneficial for reducing brown fat uptake, but we hypothesize that clinical practice varies (*8*,*16*,*20*,*22*). Our objective was to evaluate the clinical practices of pediatric nuclear medicine physicians to mitigate brown fat uptake in pediatric and young adult patients undergoing ^{18}F-FDG PET.

MATERIALS AND METHODS

We conducted an international survey developed by both pediatric oncologists and pediatric nuclear medicine practitioners evaluating clinical practices to mitigate brown fat uptake. The survey was distributed via email LISTSERV (L-Soft international, Inc.) to the Society of Nuclear Medicine and Molecular Imaging pediatric imaging counsel, the Children's Oncology Group diagnostic imaging committee, and the Society of Chiefs of Radiology at Children's Hospitals. The survey was available from April 2022 to February 2023. Questions ascertained respondents' specialty, frequency of reading pediatric PET scans, and details regarding brown fat mitigation at their institution. Respondents were asked about environmental factors controlled at their institution, such as increased room temperature and use of warm blankets, and whether their institution used pharmacologic interventions to suppress brown fat (fentanyl, propranolol, diazepam, or other). Those using pharmacologic interventions were surveyed on their criteria for use, which agents they use, and what dose they use. Survey responses were stored securely in a REDCap database (*29*). A full list of survey questions is available in the supplemental materials (available at http://jnm.snmjournals.org). The respondents were anonymous; however, the institution name was requested so that multiple responses from a single institution could be collated. Survey results were compiled and analyzed, and descriptive statistics are presented as percentages, median, and range. This project was approved by the institutional review board at Riley Hospital for Children, and the requirement for informed consent was waived.

RESULTS

The data generated during the current study are available from the corresponding author on reasonable request.

Fifty-five (11%) of a potential 490 responses were received. Forty-three unique institutions were represented, with most respondents being from the United States (n = 38, 88%), followed by Australia (n = 3, 7%) and Canada (n = 2, 5%). The demographic characteristics of the survey respondents are summarized in Table 1.

TABLE 1
Respondent Characteristics

Characteristic	Data
Level of training (n = 55)	
Radiologist/nuclear medicine faculty	50 (91)
Radiologist/nuclear medicine fellow	1 (2)
Technician	2 (4)
No response	2 (4)
Faculty/fellows: frequency of reading ^{18}F-FDG PET imaging for pediatric patients (n = 51)	
Daily	16 (31)
Twice weekly	16 (31)
Once weekly	11 (22)
A few images per month	6 (12)
Rarely	2 (4)
Unique institutions represented (n = 43)	
United States	38 (88)
Canada	2 (5)
Australia	3 (7)

Data are counts followed by percentages in parentheses. Percentages may not add up to 100 because of rounding.

TABLE 2
Estimated Frequency of Observed Brown Fat and Use of Interventions to Mitigate Brown Fat Uptake of ^{18}F-FDG

Parameter	Institutions using pharmacologic interventions, n = 13 (30%)	Institutions not using pharmacologic intervention, n = 30 (70%)
Temperature of injection room (n = 43)		
<21°C (<70°F)	2 (15)	3 (10)
21.1°C–22.2°C (70°F–72°F)	4 (31)	6 (20)
22.7°C–23.3°C (73°F–74°F)	1 (8)	2 (7)
23.9°C–24.4°C (75°F–76°F)	2 (15)	3 (10)
25°C–25.5°C (77°F–78°F)	1 (8)	0
>25.5°C (>78°F)	0	4 (13)
Do not know	3 (23)	12 (40)
Use of warm blankets (n = 41)*		
Yes	38 (93)	
No		3 (7)

*No reply for 2 institutions.
Data are counts followed by percentages in parentheses. Percentages may not add up to 100 because of rounding.

Thirteen of 43 institutions (30%) reported using pharmacologic interventions to suppress brown fat activity. Most sites (n = 37, 84%) reported using warm blankets, with 2 of the 43 sites not answering this question. There was variability in room temperature, with 44% (n = 12) of institutions maintaining uptake-room temperatures of <21.1°C–23.3°C (<70°F–74°F) and 33% (n = 9) of institutions maintaining temperatures of 23.8°C to >25.5°C (75°F to >78°F) (Table 2).

Among the 13 institutions using at least one pharmacologic agent for brown fat mitigation (Table 3), propranolol (n = 5, 38%) and fentanyl (n = 4, 31%) were used most frequently. A history of metabolically active brown fat on a prior examination was the most common criterion for pharmacologic intervention (n = 6; 45%). Of institutions administering a pharmacologic intervention, 62% (n = 8) were administered by nursing staff within radiology or nuclear medicine and 23% (n = 3) were self-administered by the patient. Two sites were not aware of how medications were administered. Only a subset of institutions (n = 13, 30%) reported doses of medications used for brown fat mitigation. Doses of diazepam reported at 2 institutions were 0.8 mg/kg or a flat dose of 1 mg orally for all patients. Doses of propranolol reported at 2 institutions were 1 mg/kg or a sliding scale up to a maximum dose of 40 mg for 70 kg patients. Fentanyl was used at 4 institutions. At two, the dose ranged from 1 μg/kg for patients weighing less than 25 kg to 0.75 μg/kg for patients weighing more than 25 kg, with a maximum of 50 μg. At another, the dose was 1 μg/kg

TABLE 3
Pharmacologic Interventions for Brown Fat Mitigation

Parameter	Data
Criteria for pharmacologic intervention (n = 13)	
History of brown fat on previous scan	6 (45)
Every patient	2 (15)
Age > 8 y	1 (8)
Age < 25 y	1 (8)
Lymphoma patients; history of brown fat; outside temperature 18.3°C (<65°F)	1 (8)
Diazepam for all patients; propranolol added for patients < 10 y	1 (8)
Only if previous brown fat limited scan interpretation	1 (8)
Specific pharmacologic interventions (n = 13)	
Propranolol	5 (38)
Fentanyl	4 (31)
Diazepam	2 (15)
Diazepam with or without propranolol if needed	2 (15)
Who administers the medication (n = 13)	
Patient	3 (23)
Nursing staff within radiology	8 (62)
Do not know	2 (15)

Data are counts followed by percentages in parentheses. Percentages may not add up to 100 because of rounding.

up to a maximum of 50 μg. The fourth institution did not indicate its preferred dosing of fentanyl.

DISCUSSION

We sought to examine practices used by pediatric nuclear medicine physicians aimed at mitigating brown fat uptake in ^{18}F-FDG PET scanning of children and young adults. Our survey demonstrated a wide range of approaches to brown fat mitigation. Most respondents reported use of warming blankets, and about one third of the institutions used a pharmacologic intervention. There was variability in the specific pharmacologic intervention implemented—with propranolol and fentanyl being most common—as well as variability in dose. The criteria for using pharmacologic interventions were highly variable, with little overlap among institutions.

Brown fat can be seen in people of all ages, with a previously reported incidence of 34%–51% in children and adolescents with cancer (*9*,*12*,*14*,*20*–*26*,*28*). Limiting the confounding effect of brown fat is imperative, as current pediatric and adolescent protocols using immunotherapies rely more heavily on disease response evaluations at critical time points in therapy (*7*,*12*,*30*). Uptake of ^{18}F-FDG by brown fat in and around previous sites of disease may confound the response determination. Although knowing the common anatomic location and using a CT overlay can help in some cases, medial or midline uptake in the mediastinum or cases in which brown fat is not symmetric are more challenging (*13*). Paidisetty et al. showed several cases of less common locations of brown fat uptake, including paratracheal and axillary (*31*). Further, the fact that nodal disease may be lost in the surrounding brown fat can be troublesome in baseline imaging (*31*). If confounding ^{18}F-FDG–avid brown fat precludes accurate assessment, patients may undergo additional imaging or potentially receive additional therapy (*31*).

Previous single-site studies have examined environmental approaches to reducing brown fat uptake of ^{18}F-FDG (*8*,*14*,*21*–*26*,*28*). One study of 300 adults found that instructing patients to dress warmly for their commute to the appointment and application of a 50°C (122°F) warming blanket decreased the incidence of brown fat uptake from 15% to 3% (*32*). This study also demonstrated that younger patients were more likely to demonstrate brown fat uptake ($P < 0.001$), reflecting the known higher incidence of brown fat in children.

Control of the uptake environment and the imaging environment is one of the most feasible ways to limit brown fat uptake. Despite literature demonstrating that temperatures greater than 23.3°C (75°F) were associated with significantly less brown fat uptake of ^{18}F-FDG (*8*,*22*), most institutions responding to our survey indicated that they maintain their uptake rooms at temperatures of less than 23.3°C (75°F). In addition to increased room temperatures, warm blankets have also been shown to be an effective intervention to reduce brown fat uptake. Specifically, Huston et al. showed that warm blankets were associated with a 45% decrease in visible brown fat (*33*). Most respondents (84%) did report use of warm blankets during radiopharmaceutical injection.

Studies investigating brown fat mitigation by pharmacologic intervention have been retrospective and single-center and have focused primarily on the use of propranolol. Propranolol is believed to be effective because of its blockade of brown fat's β_3 adrenergic activation that occurs with exposure to cold (*34*). The largest, most recent study (in 2020) demonstrated the effectiveness of propranolol for brown fat mitigation in 471 pediatric oncology patients (*26*). That study reported a significant decrease in brown fat uptake from 35%–44% to 15% with propranolol pretreatment but did not see a significant effect with preinjection warming alone (*26*). Two smaller studies (from 2007) on adults investigated 11 and 26 patients who had visible brown fat on an initial PET scan. These patients were subsequently rescanned days later with propranolol pretreatment and demonstrated significant reductions in visible brown fat (*25*,*28*). These studies are limited by use of vastly different doses of propranolol (20 and 80 mg) and variability in the timing of the doses given (120 and 60 min before tracer injection) (*25*,*28*).

There have been several other small trials of propranolol but with very different propranolol doses (*24*–*28*). Furthermore, studies using oral propranolol have had widely ranging timings of administration—from 30 min to 2 h before tracer injection (*24*–*28*).

The body of literature supporting the use of fentanyl for brown fat mitigation is smaller than that for propranolol, with only one single-site retrospective study supporting its use (*21*). That study of 69 pediatric patients demonstrated a reduction in the incidence of brown fat uptake in the fentanyl group versus the untreated group (incidence of 7% vs. 26%, $P = 0.0039$) (*21*). Several opioid-class medications including fentanyl have demonstrated activity in reducing anesthesia-induced shivering. The short onset and duration of action of fentanyl make it theoretically ideal for use in brown fat mitigation (*21*,*35*–*37*). Although Gelfand et al. showed fentanyl to be superior to low-dose and medium-dose diazepam for brown fat mitigation, there have been no trials comparing fentanyl with propranolol and no prospective trials regarding its use (*21*). Lastly, there has been no investigation or discussion in the literature of the feasibility or potential health care burden of fentanyl administration, which may require nursing support.

The literature regarding the use of diazepam for brown fat mitigation is mixed. Initial retrospective pilot data from 6 women found that mitigation was effective in decreasing physiologic skeletal muscle uptake on PET (*38*). Cousins et al. suggested there may be some confusion between brown fat and skeletal muscle uptake, suggesting diazepam may have an effect on brown fat, but later trials found no effect (*21*,*23*). Given this lack of evidence to support use of diazepam for brown fat mitigation, and the absence of evidence to support the use of multiple agents, it was surprising to see respondents

to our survey indicating use of diazepam as a single agent and in combination with propranolol.

Pharmacologic interventions are not without patient risk, particularly in pediatric oncology patients who may be on several other medications, increasing the risk for polypharmacy interactions. No large prospective studies have reported the safety profile of any pharmacologic intervention in brown fat mitigation. Propranolol does have a history of longstanding use for treatment of infantile hemangiomas. In patients being treated for hemangiomas, some hospitals require inpatient treatment on initiation of propranolol because of concerns about hypoglycemia, bradycardia, and hypotension associated with its use, though there have been recent studies supporting its initiation in outpatients (*39*). Propranolol is the only drug with prospective data on its use as a pretreatment for ^{18}F-FDG PET. The study followed 10 patients between the ages of 14 and 24 y who received a weight-based dose of propranolol (maximum, 20 mg). None of the patients reported any signs or symptoms of hypoglycemia, bradycardia, or hypotension (*27*). However, the dose was half that used in the largest retrospective propranolol study, which did not comment on any adverse events (*26*). With several doses in use, consensus on the optimal dose has not been achieved. For fentanyl, there is extensive literature showing safety in its use for sedation and analgesia. Doses reported in the brown fat mitigation study were only 25% of the low dose suggested in the package insert (*40*). There has not been a formal pilot safety study investigating the frequency of side effects, such as hypoxia or hypotension, in this dose range in pediatric oncology. Larger prospective trials may help uncover the incidence of adverse events with pharmacologic interventions in this population.

At this time, there is not enough literature to discern which techniques for brown fat mitigation are most efficacious and safe, hence the wide variability in practice patterns reported in our survey and the need for additional research. In addition, resources are different across hospitals. Although the evidence is mixed, all of us authoring this article are currently using fentanyl for brown fat mitigation because of the demonstrated effect on brown fat, minimal impact on time spent in the radiology department, and control of medication timing. Fentanyl is administered in the department; we are not reliant on families to obtain the medication before the scan or to remember to take the medication at the correct time. Furthermore, all patients are kept in a warmed room with warm blankets before scanning.

Limitations are inherent in clinical research, particularly with surveys. As with all surveys, we were limited by a low response rate in this highly niche population of pediatric nuclear medicine familiar with PET imaging. Despite our best efforts to recruit participants from the email LISTSERV of several radiology and nuclear medicine groups, the response rate was 11%. Pediatric nuclear medicine is a small field, such that there are fewer practitioners than in adult nuclear medicine or general radiology, resulting in a falsely low response rate due to unfamiliarity with pediatric PET. Despite these limitations, this survey demonstrated the high level of variance regarding brown fat mitigation in both environmental and pharmacologic interventions at pediatric hospitals.

CONCLUSION

Our survey of pediatric nuclear medicine physicians demonstrates a wide range of clinical practice regarding brown fat mitigation for ^{18}F-FDG PET at major children's hospitals. This finding may, in part, reflect the varying and limited literature on this topic specific to pediatrics. Further prospective, randomized controlled trials comparing propranolol and fentanyl, with safety monitoring and cost analyses, would build a consensus for the optimal strategy to mitigate brown fat uptake. Because many trials look to augment therapy on the basis of response to prior treatment, it is critical to minimize brown fat interference effectively and safely for our pediatric and adolescent patients with cancer.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: What are the current clinical practices regarding brown fat mitigation at children's hospitals?

PERTINENT FINDINGS: This international survey of 43 children's hospitals found that many use prewarming with blankets for pediatric patients undergoing ^{18}F-FDG PET/CT, whereas 38% of hospitals maintain their rooms at the recommended temperature and 30% use pharmacologic interventions for brown fat mitigation. Criteria for interventions varied widely among institutions.

IMPLICATIONS FOR PATIENT CARE: Despite several papers showing efficacy for environmental and pharmacologic interventions, clinical practice regarding brown fat mitigation varies. This survey demonstrates the need for larger studies in this area.

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