Activation of brown adipose tissue in hypothyroidism

Constantin Lapa[a], Yoshifumi Maya[a,b], Martin Wagner[c,d], Paula Arias-Loza[e], Rudolf A. Werner[a], Ken Herrmann[a,f] and Takahiro Higuchi[a,d]

[a]Department of Nuclear Medicine, University Hospital Würzburg, Würzburg, Germany; [b]Research Centre, Nihon Medi-Physics Co Ltd, Chiba, Japan; [c]Institute of Clinical Epidemiology and Biometry, University of Würzburg, Würzburg, Germany; [d]Comprehensive Heart Failure Center, University Hospital Würzburg, Würzburg, Germany; [e]Department of Internal Medicine I, Division of Cardiology, University Hospital Würzburg, Würzburg, Germany; [f]Ahmanson Translational Imaging Division, Department of Molecular and Medical Pharmacology, David Geffen School of Medicine at UCLA, USA

ABSTRACT

Background Brown adipose tissue (BAT) attracts growing interest as a potential therapeutic target for obesity and diabetes. Hyperthyroidism is well-known to increase BAT activity, but the role of hypothyroidism is controversial. We aimed to investigate the association between different thyroid hormone (TH) states and BAT activity.

Methods FDG-PET studies were retrospectively evaluated in thyroid cancer patients after total thyroidectomy both at euthyroidism during TH replacement or at hypothyroidism after TH cessation. Serum TH levels were compared between patients with active BAT and control patients with non-active BAT matched for age, gender, and body mass index. Additionally, animal experiments with controls ($n = 5$) and hypothyroid rats ($n = 5$) were performed.

Results Out of 124 patients, 6 patients with active BAT were identified. These patients showed significantly higher thyroid-stimulating hormone (TSH) levels than matched controls ($P < 0.05$). In animal experiments, all hypothyroid animals showed BAT activation at room temperature (24 °C), whereas controls did not ($P < 0.001$). Increased BAT activity was also confirmed by increased expression of UCP-1 and D2.

Conclusions Increased BAT metabolism appears to be related with hypothyroidism, which might be the result of a feedback mechanism to maintain body temperature in a state of reduced basal thermogenesis. Future research needs to explore the underlying mechanistic and biological implications.

KEYWORDS

Brown adipose tissue; hypothyroidism; PET/CT; thyroid hormone; TSH

KEY MESSAGES

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Introduction

Until recently, brown adipose tissue (BAT) was considered to be present only in rodents, new-borns, and infants (1). However, functionally active regions of BAT have been identified in human adults and been shown to be inversely correlated with body mass index (2). BAT is primarily a thermogenic tissue that is highly innervated and vascularized and expresses the mitochondrial uncoupling protein 1 (UCP-1) (3). UCP-1 enables the release of energy as heat instead of storage as ATP molecules, a process which is called adaptive thermogenesis.

BAT has attracted a lot of attention as a potential target to combat obesity, and stimuli for its activation have been investigated (4–10). The role of the thyroid hormones (TH) has also been examined. Activation of BAT by overt hyperthyroidism or central administration of triiodothyronine (T3) has recently been demonstrated in both rodent and human studies (11–13). Additionally, the effect of thyroid hormone replacement therapy on BAT activity in a diabetic patient with a history of thyroid cancer was reported (14). In parallel, an effect of thyroid-stimulating hormone (TSH) itself or its receptor expression on rodent BAT has been suggested (12,15), but its role in humans is still controversial.

The aim of this study was to determine the potentially activating effects of various TH/TSH levels on BAT glucose utilization by analyzing positron emission tomography/computed tomography (PET/CT) scans of

CONTACT Constantin Lapa, MD lapa_c@ukw.de Department of Nuclear Medicine, University Hospital Würzburg, Oberdürrbacher Str. 6, 97080 Würzburg, Germany

thyroid cancer patients on and off thyroid hormone replacement therapy after total thyroidectomy. Also, a small animal model of hypothyroidism was employed to corroborate the human findings further.

Methods

Subjects

We reviewed 234 PET/(CT) scans of 124 patients who had undergone total thyroidectomy due to thyroid cancer (range, 12–86 years; mean age, 58.3; 39% papillary thyroid cancer, 35% follicular, 18% medullary, 7% oncocytic/insular/poorly differentiated, 1% anaplastic) between March 2010 and September 2012. All patients presented during cancer follow-up. A total of 75 patients underwent imaging once, 23 were examined twice, and 9 subjects received three, and 10 patients four PET/(CT) scans. The remaining 7 subjects underwent five ($n = 2$), six ($n = 3$), and nine ($n = 2$) examinations, respectively.

All of the subjects enrolled were on TH replacement therapy (range, 1–348 months, mean, 76 months). At the time of examination, 26 of them (21%) had interrupted their thyroxine 4 weeks earlier and were studied off medication (mean prior duration of replacement therapy, 62 ± 42 months; range, 7–120 months). Nine had been injected two single doses of recombinant human TSH i.m. on two subsequent days prior to imaging (days −2 and −1) to allow for TSH-stimulated PET scans (day 0). The remaining patients were on TH replacement medication when undergoing imaging.

Gender distribution was equal (47% male), and mean BMI levels (26.1 kg/m^2) of the subjects were similar to the general population of Germany (25.7 kg/m^2; data from 2009). Outside temperatures at the day of examination were retrieved from the archives of the German Meteorological Service.

Laboratory tests

On the day of imaging, serum TSH and both free triiodothyronine (T3) and free thyroxine (T4) were measured in all patients. All analyses were performed in-house (University Hospital Würzburg, Department of Nuclear Medicine). For TSH, a fully automated immunoluminometric assay (ILMA; DPC Biermann Siemens, Bad Nauheim, Germany) was performed with a normal range of 0.3–4.0 mU/L. T3 and T4 were assessed using fully automated chemiluminescence immunoassays (LIA; DPC Biermann Siemens, Bad Nauheim, Germany). Normal ranges were 2.7–7.6 pmol/L for T3 and 11.0–23.0 pmol/L for T4 respectively.

Clinical FDG-PET/CT imaging

FDG was synthesized in-house with a 16 MeV Cyclotron (GE PETtrace 6; GE Healthcare, Milwaukee, WI, USA) using GE FASTlab methodology according to the manufacturer's instructions. Before use, radiochemicals were analyzed by high-performance liquid chromatography (HPLC) for radiochemical identity and purity. Acquisition of PET scans was performed according to the guidelines of the European Association of Nuclear Medicine (EANM). In brief, all patients fasted for at least 6 hours before images acquisition, and blood glucose levels were lower than 160 mg/dL. Subjects were studied in the morning, from 9 a.m. to 1 p.m., and stayed in a thermoneutral room (22–24 °C) for at least 30 minutes prior to FDG injection. A dose of 300 to 370 MBq of FDG was administered intravenously 60 minutes before scanning. During this period, all patients rested in a supine position at 22–24 °C. All patients experienced the room temperature as warm.

In 21 cases (9%), PET scans were acquired using a dedicated Siemens PET scanner (ECAT Exact 47, Siemens Medical Solutions, Erlangen, Germany) with a 16.2 cm axial field-of-view (FOV) and a 58.3 cm transaxial FOV. During the acquisition, transmission maps were acquired for attenuation correction using Ge-68 line sources.

Scanning time was 10 minutes per bed position. Scans were acquired from the top of the skull to the upper third part of the upper leg (usually seven bed positions). Subsequently the acquired dataset was reconstructed using a two-dimensional ordered subset expectation maximum algorithm with two iterations and eight subsets. Images were smoothed with a Gaussian filter assuming a full width at half maximum of 6.0 mm. Computed tomography of thorax and abdomen was available in 17/21 patients for anatomical correlation.

In the remaining 213 cases (91%), hybrid PET/CT imaging was performed on an integrated PET/CT scanner (Siemens Biograph® mCT 64, Siemens, Knoxville, TN, USA) consisting of a lutetium oxyorthosilicate (LSO) full-ring PET and a 64-slice spiral CT. Transmission data were acquired using a contrast-enhanced or low-dose CT (80 mAs or 30 mAs, 120 kV, a 512×512 matrix, a 5-mm slice thickness, an increment of 30 mm/s, a rotation time of 0.5 s, and a pitch index of 0.8) extending from the base of the skull, or the vertex, to the proximal thighs. Consecutively, PET emission data were acquired in three-dimensional mode with a 200×200 matrix with 2-min emission time per bed position. After decay and scatter correction, PET data were reconstructed iteratively with attenuation correction using a dedicated software (HD. PET, Siemens Esoft). Standardized uptake values (SUV) were determined by

assigning spherical volumes of interest of 1.0 cm diameter around foci of activated brown fat, and maximum SUVs (SUV_{max}) were then calculated.

Interpretation and statistical analysis of clinical FDG-PET imaging

All images were reviewed by two experienced nuclear medicine physicians. Participants were considered BAT-positive if symmetrical FDG uptake in cervical, supraclavicular, and paravertebral regions was higher than mediastinal blood pool. CT scans—available in 230/234 cases—were used to confirm localization to adipose tissue (density of −250 to −50 Hounsfield units). To investigate the association of TSH, T3, and T4 levels with BAT, a case–control design was used. Per BAT-positive patient ('case') up to four BAT-negative patients ('control'; in $n = 2$ cases, only three controls were available per patient, thus summing up to $n = 22$ control patients) (Figure 1) were selected, matched for gender, age (±13 y) and BMI (±5 kg/m^2). BAT-negative patients could serve as a control only once, regardless of the available number of scans. Temperature at the day of examination was calculated as the mean of the lowest and highest temperature observed for that day at the City of Würzburg. Univariate associations (considering previous matching) of the respective variables with the probability of BAT-positive versus negative are displayed as odds ratios (OR) with respective 95% confidence intervals (CI), as derived from exact conditional logistic regression. Statistical analyses were performed with SAS 9.2, while the macro %match was used to match cases and controls.

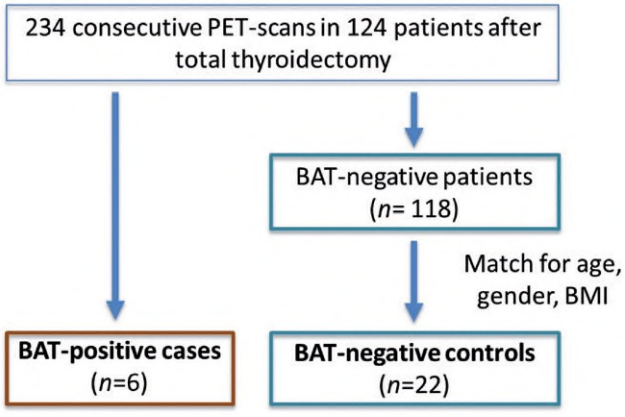

Figure 1. Flow chart of clinical study in thyroid cancer patients. A total of 234 consecutive FDG-PET scans of 124 thyroid cancer patients were reviewed for BAT activity. Participants were considered BAT-positive if symmetrical FDG uptake in cervical, supraclavicular, and paravertebral regions was higher than mediastinal blood pool. CT scans were used to confirm localization to adipose tissue. To investigate the association of TSH, T3, and T4 levels with BAT, a case-control design was used. Per BAT-positive patient ('case') up to 4 BAT-negative patients ('control'; in $n = 2$ cases, only 3 controls were available per patient, thus summing up to $n = 22$ control patients) were selected, matched for gender, age, and BMI. BAT-negative patients could serve as a control only once, regardless of the available number of scans. BAT = brown adipose tissue; BMI = body mass index; PET/CT = positron emission tomography/computed tomography.

Animal experiments with a rat model of hypothyroidism

Wistar rats weighing 250–280 g (Charles River, Wilmington, MA, USA) were housed at the animal facility at the Center of Experimental and Molecular Medicine (ZEMM) of the University of Würzburg. Animals received water and food ad libitum and were housed in filter-top cages at ambient temperature with a light/dark cycle of 12/12 h. Pathogen status was assessed according to FELASA B protocol on a regular basis. Rats were randomized into vehicle control and treatment groups ($n = 5$ each; group sizes corresponded to the biometrical calculations provided in the relevant animal license). The latter received methimazole (20 mg/kg/day) in their drinking water for 4 weeks. Subsequently, blood was drawn to check for hypothyroidism.

Animal FDG-PET imaging and ex vivo tissue analysis

After 4 weeks of medication, all animals underwent FDG-PET scans at three different ambient temperatures (10 °C, 24 °C, and 32 °C; achieved by custom-made temperature-control chamber) utilizing a dedicated small animal PET scanner (Inveon; Siemens Medical Solutions, Erlangen, Germany). After overnight fasting (>8 hours), animals were kept in the respective ambient temperature for 2 hours prior to PET. FDG (20–30 MBq) was administrated intraperitoneally 1 hour before imaging. Under general anesthesia with 2% isoflurane, static PET acquisition was performed for 10 min. Data were reconstructed using ordered subset expectation maximization algorithm without attenuation correction. Tracer uptake in BAT as percentage injected dose per tissue volume (%ID/mL) was determined by assigning spherical volumes of interest around foci at interscapular BAT.

After completion of all PET studies, with imaging at room temperature (24 °C) being the last study, the animals were euthanized for *ex vivo* BAT tissue analysis. RNA was extracted from BAT samples using the RNeasy kit (Qiagen, Valencia, CA, USA), quantified with a NanoDrop spectrophotometer using a high-capacity cDNA reverse transcription kit (Applied Biosystems, Foster City, CA, USA). Genes of interest (D2 and UCP-1) were

measured by quantitative RT-PCR (Bio-Rad iCycler iQ Real-Time PCR Detection System; Bio-Rad Laboratories Hercules, CA, USA) using the TaqMan® Gene Expression Master Mix (Life Technologies, Carlsbad, CA, USA). Primers were purchased from Life Technologies (Carlsbad, CA, USA). Relative gene expression levels were calculated and compared with glyceraldehyde-3-phosphate dehydrogenase (GAPDH) as internal control.

All data are presented as mean ± standard deviation. Normality of data was confirmed by the Kolmogorov–Smirnov test, and equality of variances was tested with the Brown–Forsythe test. Multiple group comparison was performed by one-way ANOVA, followed by the Tukey test. Differences between the means was considered statistically significant when $P < 0.05$.

Study approval

The retrospective human study was approved by the institutional review board of Würzburg University (approval number 36/13) and did not involve any additional procedures or blood tests. All patients gave written informed consent to FDG-PET/CT imaging for the purpose of restaging and assessment of disease activity. All research was conducted according to the principles set forth by the Declaration of Helsinki.

Animal studies were performed in agreement with the Guide for Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996) and in compliance with the German law on the protection of animals (license 55.2-2531.01-78/13).

Results

FDG-PET imaging in patients after total thyroidectomy

On retrospective visual analysis of 124 patients with post-total thyroidectomy FDG-PET scans, 6 patients (4.8%) showed focal increased FDG uptake in cervical, supraclavicular, and paraspinal depots consistent with active BAT (Figure 2; Supplementary Figure 1, available online). All BAT-positive patients (6/6) were female; 4/6 had stopped TH replacement therapy 4 weeks prior to the PET scan and presented therefore with overt biochemical hypothyroidism, 1/6 had previously received injections of recombinant TSH, and 1/6 patient undergoing imaging was still on TSH-suppressing thyroxine therapy. In comparison with the controls matched for sex, BMI, and age ($n = 22$) (Table I), BAT-positive patients had higher serum TSH levels (128.0 versus 0.45 mU/L) which also appeared to be statistically significant in conditional regression analysis (OR 1.40, $P = 0.02$) (Table II). Of note, none of the positive subjects or controls was on potentially BAT-influencing medications (including beta-blockers, catecholamines, or anti-depressants).

Animal experiments in a rat model of hypothyroidism

Treatment with methimazole resulted in overt hypothyroidism in all animals with TSH levels >14 mU/L (mean ± SD, 16.7 ± 3.0 versus 0.4 ± 0.2 in controls) and non-detectable TH levels. At room temperature (24 °C), all hypothyroid rats showed significantly increased FDG

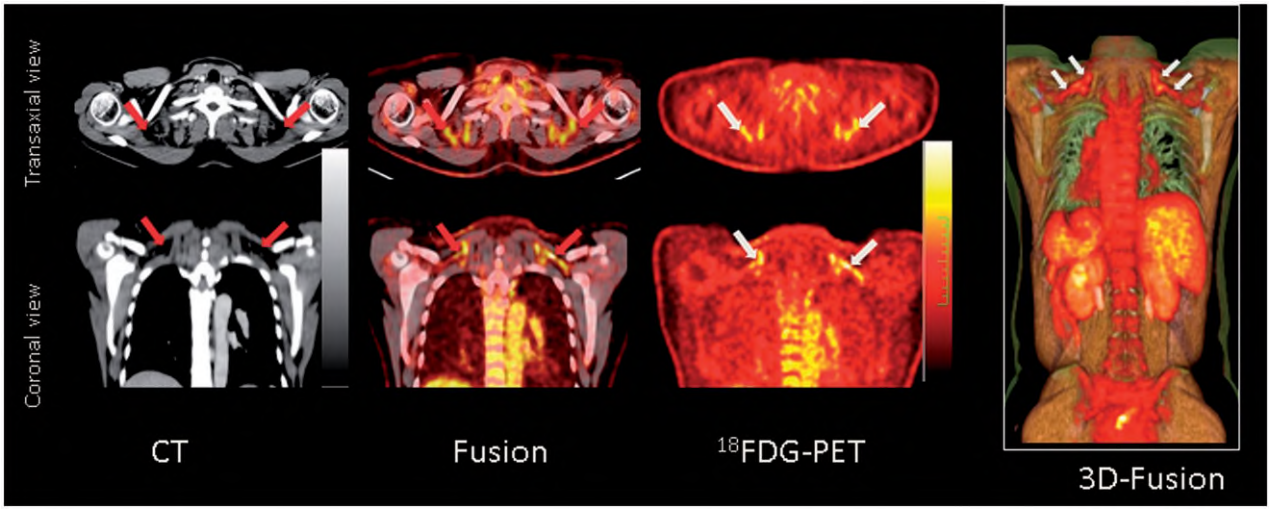

Figure 2. Activated brown adipose tissue in a patient with low TH levels and a history of thyroid cancer. A 43-year-old woman with a history of papillary thyroid cancer presenting during short-term profound hypothyroidism (TSH, 168 mU/L) while off all thyroid hormone treatment as part of restaging with whole-body ^{131}I-imaging. Due to elevated thyroglobulin levels and an unremarkable ^{131}I-scan, FDG-PET/CT was performed, revealing metabolically active brown adipose tissue in the supraclavicular regions (arrows).

uptake at interscapular BAT indicating increased BAT metabolism, whereas none of the control animals did (mean, 0.40 ± 0.14%ID/mL versus 0.13 ± 0.02%ID/mL, $P < 0.05$) (Figure 2). Increased BAT activity was also confirmed by increased gene expression of UCP-1 and D2, markers of thermogenesis in BAT (4.5-fold and 35-fold expression in comparison to controls, respectively, $P < 0.05$). Exposure to higher temperatures (32 °C) effectively diminished FDG uptake in hypothyroid rats (mean, 0.15 ± 0.01%ID/mL versus 0.40 ± 0.14%ID/mL at 24 °C, $P < 0.01$). Furthermore, exposure to lower temperatures (10 °C) significantly induced FDG uptake in the controls (mean, 0.32 ± 0.10%ID/mL versus 0.13 ± 0.02%ID/mL at 24 °C, $P < 0.001$), whereas it could not further increase tracer accumulation in the hypothyroid rats (mean, 0.39 ± 0.13%ID/mL versus 0.40 ± 0.14%ID/mL at 24 °C, P = ns) (Figure 3).

Discussion

To our knowledge, this is one of the first reports demonstrating an association between BAT activity and hypothyroidism in humans. BAT-positive patients with increased glucose utilization in BAT visualized by FDG-PET had significantly higher TSH serum levels than BAT-negative controls matched for sex, BMI, and age. Our study is consistent with a recent case report on an adolescent presenting with profound primary hypothyroidism and active BAT (16). Furthermore, our findings were supported by a rat model of hypothyroidism demonstrating increased FDG-uptake in BAT at room temperature compared with euthyroid control animals.

An increasing body of literature supports a significant role of serum TH in BAT metabolism. One of the early reports by Silva et al. demonstrated that both cold exposure and sympathetic activation could induce hyperactivation of type II iodothyronine 5′-deiodinase (17). Furthermore, a positive effect of TH on GDP binding, uncoupling protein-1 expression, and cAMP-inducible type II deiodinase has been reported (18,19). Thus until now, little is known about the effects of TH in human BAT, considering the significant differences in

Table II. Analysis of BAT-positive cases ($n = 6$) versus BAT-negative controls ($n = 22$) for influence of various factors on the likelihood of BAT activity.

Variable	Exact conditional logistic regression	
	OR (95% CI)	*P*
Duration of disease (per month)	0.99 (0.98; 1.01)	0.41
Season		
Spring versus winter	1.39 (0.04; ∞)	0.84
Summer versus winter	2.72 (0.14; ∞)	0.51
Fall versus winter	5.40 (0.41; ∞)	0.21
Temp (per °C)	1.15 (0.98; 1.41)	0.09
TSH (per log mU/L)	1.40 (1.06; 2.10)	0.02[a]
T4 (per log pmol/L)	0.33 (0.09; 1.20)	0.10
T3 (per log pmol/L)	0.23 (0.03; 1.42)	0.12
T4 medication (per μg/day)	0.99 (0.97; 1.01)	0.23
Duration of T4 medication (per month)	0.99 (0.98; 1.01)	0.35
Glucose (per mg/dL)	0.94 (0.80; 1.05)	0.36

[a]In exact conditional logistic regression, only TSH levels are a significant predictor of BAT activity.
T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

Table I. Characteristics of BAT-positive patients and their matched controls.

	BAT-positive ($n = 6$)	BAT-negative ($n = 22$)
Female gender, %	100%	100%
Age [y], median (range)	41.0 (31.0; 63.0)	49.5 (21; 64)
BMI [kg/m^2], median (range)	22.3 (21.0; 27.3)	24.9 (17.2; 31.2)
Disease, *n* (%)		
FTC	1 (16.7)	6 (27.3)
Insular CA	0	1 (4.6)
MTC	0	6 (27.3)
PTC	5 (83.3)	7 (31.8)
Oncocytic CA	0	1 (4.6)
Poorly differentiated CA	0	1 (4.6)
Duration of disease [mo], median (range)	72.8 (7.3; 121.8)	84.4 (1.5; 205.3)
Season, *n* (%)		
Spring	1 (16.7)	7 (31.8)
Summer	2 (33.3)	4 (18.2)
Fall	3 (50.0)	5 (22.7)
Winter	0	6 (27.3)
Temperature [°C], median (range)	18.05 (7.65; 23.05)	10.8 (−11.3; 23.05)
TSH [mU/L], median (range)	128.0 (0.02; 260.0)	0.45 (0.01; 96.0)
T4 [pmol/L], median (range)	3.9 (3.9; 27.6)	18.0 (3.9; 28.4)
T3 [pmol/L], median (range)	3.0 (1.5; 7.1)	5.2 (1.8; 8.4)
T4 medication [μg/d], median (range)	75.0 (0; 150)	150 (0; 225)
Duration of T4 medication [mo], median (range)	66.0 (7.0; 120.0)	84.0 (2.0; 204.0)
Glucose levels [mg/dL], median (range)	75.0 (65.0; 86.0)	76.5 (64.0; 100.0)
Diabetes mellitus, *n* (%)	0	0

BMI = body mass index; CA = carcinoma; FTC = follicular thyroid carcinoma; MTC = medullary thyroid carcinoma; PTC = papillary thyroid carcinoma; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

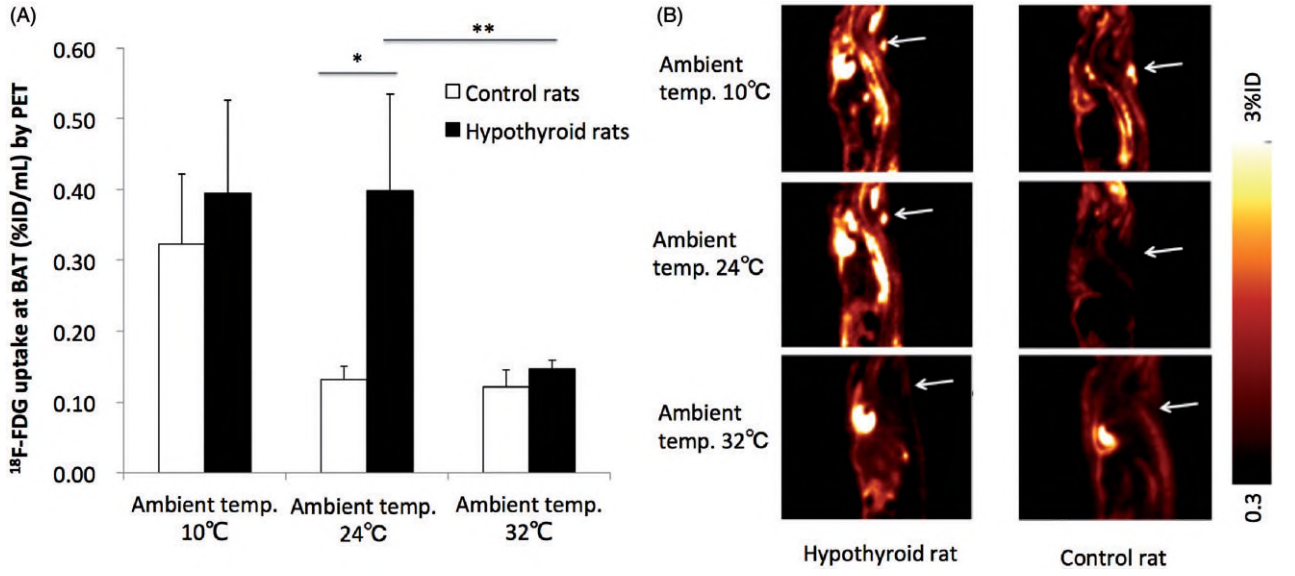

Figure 3. Brown adipose tissue (BAT) activity in hypothyroid rats and euthyroid control rats at different ambient temperatures. At room temperature (24 °C), hypothyroid rats display significantly increased FDG uptake in interscapular BAT depots (mean, 0.40 ± 0.14%ID/mL versus 0.13 ± 0.02%ID/mL, * $P < 0.05$; arrows). Exposure to 32 °C effectively diminishes FDG uptake (mean, 0.15 ± 0.01%ID/mL versus 0.40 ± 0.14%ID/mL at 24 °C, ** $P < 0.01$; arrows). Exposure to lower temperatures (10 °C) induces FDG uptake in the control rats (mean, 0.32 ± 0.10%ID/mL versus 0.13 ± 0.02%ID/mL at 24 °C, *** $P < 0.001$), whereas FDG uptake in the hypothyroid rats cannot be further increased (mean, 0.39 ± 0.13%ID/mL versus 0.40 ± 0.14%ID/mL at 24 °C, $P =$ ns).

adipose tissues between rodents and humans. It is important to test the possible extrapolation of the animal model results to human patients (20). *In-vitro* analysis of multipotent cells isolated from human adipose tissue demonstrated that T3 increases uncoupling protein-1 expression and oxygen consumption rate in human adipose-derived stem cells (21). In the present study, we found a positive association between hypothyroid conditions and metabolically active BAT in humans. These results were quite unexpected, since most of the rodent studies focus on TH as a stimulus of BAT metabolism. Most recently, studies by Endo et al. demonstrated that not only TH but also TSH might stimulate uncoupling protein-1 expression in murine BAT to prevent a further decrease in body temperature in hypothyroid mice (15). The compensatory mechanism located at BAT is also suggested in hypothyroid mice exhibiting a strong metabolic response to sustain normal daily energy expenditure (22,23). Our results derived from the clinical study are in line with our findings in a small animal model of induced hypothyroidism which also indicate a compensatory function of maximum BAT activation in hypothyroid rats to maintain body temperature. The precise mechanisms involved in our human findings are not known, but one of the potential explanations might be that compensatory high TSH levels induce uncoupling protein-1 expression resulting in BAT activation in analogy to the results of the small animal setting.

Active brown adipose tissue was found most frequently in younger female patients with lower BMI, a finding also in line with already published data (24). In contrast to previous studies, however, we did not observe any correlation of BAT activity with the season of the scan (2). This might be explained by the fact that temperature differences in Germany for the time of interest were rather modest. In addition, all patients remained in a warm waiting area before FDG injection and during rest prior to imaging itself. BAT activity was found in approximately 5% of subjects which is in the reported range of patients in unstimulated states (24). The amount of exogenous thyroid hormone was not a predictor of activated brown fat. Nor did the duration of thyroid hormone intake have any influence. Neither a period of thyroxine medication as short as 4 weeks nor a duration of more than 25 years proved to be predictors of brown fat activity.

This study has several limitations. First, the human study is retrospective in design. Additionally, due to the variety of different patients with different thyroid hormone states, the study population is rather complex. Therefore, in the multifactorial process of BAT regulation, a controlled, prospective approach would be warranted to gain full insight in the correlation of BAT activity and thyroid states. Unfortunately, catecholamine levels were not available in the patients. As hypothyroidism activates the sympathetic nervous system, a potentially confounding influence of increased

sympathetic stimulation on BAT activity cannot be fully excluded. The use of oral contraceptives in female participants is unknown.

Only 6 patients presented with metabolically active brown adipose tissue. Given the small number of cases ($n = 6$) and controls ($n = 22$), the interpretation and generalizability of the observed findings are limited, and conclusions need to be drawn with caution. However, though based on a considerably limited number of observations, our results are one of the first illustrations of compensatory BAT activation in human beings as a response to high TSH levels due to overt hypothyroidism. In analogy to the small animal model, BAT might be activated to maintain body temperature in a state of reduced basal thermogenesis. In contrast, supraphysiologic intake of thyroid hormone with TSH suppression might not be effective to stimulate BAT metabolism. In more than 100 thyroid cancer patients on and off thyroid hormone replacement therapy, we could not demonstrate any activating effect of pure TH intake. In the present study, only one patient on TH replacement therapy (with suppressed TSH and peripheral euthyroidism) presented with active BAT. A recent case study reported on the beneficial effects of TH replacement therapy on BAT activity in a patient with thyroid cancer (14). Potentially (fluctuations in) T3 levels in those patients were adequate to modify BAT. However, the influence of other factors like the ambient temperature cannot be fully excluded.

Interestingly, most of the patients who received rTSH (8/9) did not demonstrate active BAT despite high TSH levels. Potentially, the short-term TSH elevation induced by the two single rTSH injections is not as effective as sustained intrinsic high TSH levels induced by genuine hypothyroidism regarding BAT modification.

In brief, increased BAT metabolism can be observed in hypothyroidism and might be the result of a feedback mechanism to maintain body temperature in a state of reduced basal thermogenesis. Future research needs to explore the underlying mechanistic and biological implications, which may serve as a hint for approaching novel BAT-targeted treatments of obesity.

Declaration of interest

Y.M. is an employee of Nihon Medi-Physics Co. Ltd, Chiba, Japan. All other authors report no conflicts of interest.

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Supplementary material available online
Supplementary Figure 1