Original Investigation

Correlation of Brown Adipose Tissue with Other Body Fat Compartments and Patient Characteristics: A Retrospective Analysis in a Large Patient Cohort Using PET/CT

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Rationale and Objectives: The objective of this study was to assess the relationship of brown adipose tissue (BAT) activity with different fat compartments of the body, body mass index (BMI), outdoor temperature, thyroid-stimulating hormone (TSH) levels, blood glucose, age, and sex in a large patient population using F-18-fluordesoxyglucose positron emission tomography-computer tomography (FDG-PET/CT) scans obtained under thermoneutral conditions.

Materials and Methods: FDG-PET/CT scans of 4852 patients were retrospectively analyzed for BAT activity. The volumes of the different fat compartments visceral adipose tissue (VAT), subcutaneous adipose tissue (SCAT), and liver fat, were assessed by computed tomography. Age, sex, TSH levels, blood glucose levels, BMI, primary disease, and the outdoor temperature were determined. Multiple linear regression analyses were performed to identify independent relationships between the parameters.

Results: The VAT, SCAT, and liver fat content were lower in BAT-positive patients than in BAT-negative patients (each $P < 0.0001$). BAT-positive patients had a lower BMI ($P < 0.0001$) and were more often female ($P < 0.0001$), younger ($P < 0.0001$), and had higher TSH levels ($P = 0.0002$), whereas the outdoor temperature and the blood glucose level were not different compared to BAT-negative patients. Age, sex, VAT, and SCAT were independent factors related to BAT.

Conclusions: Age, sex, and VAT are the most important determinants of BAT activity under thermoneutral conditions. VAT reflects the association between BAT activity and body fat mass more clearly than BMI. The strength of the association between VAT and BAT decreases during aging in men, but increases in women. This may indicate a different importance of BAT activity for obesity in men and in women.

Key Words: PET/CT; brown adipose tissue; body fat.

INTRODUCTION

Brown adipose tissue (BAT) is exclusively found in mammals and generates heat to protect animals from hypothermia (1). For a long time, it was thought that BAT is present in humans only in newborns, until it was found to be present also in about 5%–10% of adults under thermoneutral conditions (2–5). BAT activity is increased upon cold activation (6–8). However, whereas cold-activated BAT was found in approximately 50% of younger subjects, it was merely found in 10% of older people (9).

BAT has the function of nonshivering thermogenesis. Being activated by the sympathetic nervous system, BAT has a high glucose and fatty acid consumption (10,11). This increase in BAT-associated expenditure is thought to have positive effects on body fat mass (12). In agreement with this notion, BAT mass and activity are negatively associated with the body mass index (BMI), the total fat mass, and the mass of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SCAT) (6,8,9,13). In particular, the body fat compartment VAT is related to obesity-related disorders (14). In addition, increased BAT mass and activity are thought to be associated with improved glucose and lipid metabolism (15–17). Consequently, activation of BAT

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is accompanied by increased insulin sensitivity and diminished glucose levels, although this association is not confirmed consistently in published data (2,13,15,18). Interestingly, although cold exposure can strongly induce BAT activity and cold-induced thermogenesis in young adults, the effects on body fat mass are small (19). Furthermore, it is not realistic that cold exposure will become a widely applied tool to treat obesity and its metabolic consequences in the clinical setting. This raises the question as to what extent BAT mass and activity associate with different body compartments, liver fat (LF) content, and glucose levels under thermoneutral conditions. As further regulators, thyroid hormones have been shown to induce BAT activity in mice and in men (20,21).

Therefore, the aim of our study was to analyze the relationship between BAT and body fat distribution measured by VAT, SCAT mass, and LF content in a large population of nononcological and oncological patients in a clinical routine setup using F-18-fluordesoxyglucose positron emission tomography-computer tomography (FDG-PET/CT). Furthermore, the association of BAT with the outdoor temperature, thyroid-stimulating hormone (TSH), blood glucose, BMI, age, and sex was assessed. Additionally, the patients were divided into subgroups regarding age and sex, and the strengths of these relationships in the subgroups were compared in detail.

MATERIALS AND METHODS

Patients

Data of a total of 4852 patients who underwent clinically indicated FDG-PET/CT scans between August 2004 and July 2009 at our institution, located in Germany, in the temperate climate zone, were evaluated concerning the presence of active BAT. The patient collective included pediatric patients in a small percentage. Definition criteria for the presence of active BAT were areas in PET scans with symmetric paravertebral, nuchal, supra- or infraclavicular FDG uptake, a maximum standardized uptake value (SUV) above 2, and a density of fat in computed tomography (CT) at the localization of the FDG uptake (−250 to −50 HU) (5). Two BAT-negative control patients were matched to each BAT-positive scan according to the following criteria: same examination date, same sex, and similar age in descending order of importance. Only the first BAT-positive scan and the most appropriate control examination were selected. All patients gave their written informed consent for the scientific use of their data. The study was approved by the local ethics committee.

FDG-PET/CT Examination

All whole-body PET/CT examinations were performed with a Hi-Rez Biopraph 16 (Siemens Medical solutions, Knoxville, TN), comprising a 3D-lutetium oxyorthosilicate-PET and a multislice CT (peak voltage 120 kVp, tube current 250 mAs, rotation time 0.5 seconds, table feed thorax and abdomen 12 and 24 mm, respectively, and collimation thorax and abdomen 0.75 and 1.5 mm, respectively). All patients had fasted overnight for a minimum of 6 hours and had plasma glucose levels below 11 mmol/L. After an injection of 300–450 MBq FDG, the patients rested comfortably in a waiting area with a fixed room temperature of 22°C. The patients were hydrated orally with 100 mL mannitol (2.5%) as a negative oral contrast agent during the uptake time of 60 minutes. All patients were positioned in the scanner with raised arms to reduce beam-hardening artifacts, and in a vacuum mattress to reduce motion artifacts. PET was acquired from the skull base to the thighs with 3 minutes/bed over six to eight beds and reconstructed with a 2D ordered subset expectation maximization algorithm (four iterations, eight subsets, Gaussian filter 4 mm, and slice thickness 2.0 mm).

CT examinations were performed with a 90–120 mL intravenous CT contrast agent (Ultravist 370; Schering AG, Berlin, Germany) in the portal venous phase ($n = 472$), in the late arterial phase ($n = 22$), or without a contrast agent ($n = 108$), depending on the clinical indication. A preceding native series was performed before the contrast agent injection in 322 patients. CT images were reconstructed with an axial slice thickness of 3 mm and an increment of 2 mm.

Image Analysis and Data Collection

The presence of active BAT was determined in fused PET/CT datasets on routine viewing software Syngo TrueD (Siemens Medical Solutions, Erlangen, Germany). The BAT activity was measured as SUVmean (corrected on body weight) in a volume of interest (isocontour at SUV 2.0). In patients without BAT activity, a control volume of interest was set bilaterally in the nuchal fat.

The volumes of VAT and SCAT as approximated measurements for the fat masses were assessed in abdominal CT data ranging from the upper liver pole to the femur heads as easily reproducible structures. VAT and SCAT were segmented semiautomatically using MATLAB-based in-house software (The MathWorks Inc., Natick, MA) with exclusion of the background, the examination table, and lean tissue (22). LF content was measured with the software Amide (http://amide.sourceforege.net) using a large 2D region of interest in nonenhanced CT scans. The amount of LF corresponds inversely to the mean density in Hounsfield unit. Care was taken to avoid involvement of the gall bladder or the central liver vessels in the region of interest. The age, sex, height, weight, blood glucose level, and actual TSH values were recorded and the BMI was calculated for each patient. The mean daily temperature was obtained from the local meteorological service for each examination date.

Statistical Analysis

Differences of continuous characteristics between BAT-positive and BAT-negative patients were evaluated using the Wilcoxon test; differences of nominal parameters were