

Brown Adipose Tissue and Seasonal Variation in Humans

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OBJECTIVE—Brown adipose tissue (BAT) is present in adult humans where it may be important in the prevention of obesity, although the main factors regulating its abundance are not well established. BAT demonstrates seasonal variation relating to ambient temperature and photoperiod in mammals. The objective of our study was therefore to determine whether seasonal variation in BAT activity in humans was more closely related to the prevailing photoperiod or temperature.

RESEARCH DESIGN AND METHODS—We studied 3,614 consecutive patients who underwent positron emission tomography followed by computed tomography scans. The presence and location of BAT depots were documented and correlated with monthly changes in photoperiod and ambient temperature.

RESULTS—BAT activity was demonstrated in 167 (4.6%) scans. BAT was demonstrated in 52/724 scans (7.2%) in winter compared with 27/1,067 (2.5%) in summer months ($P < 0.00001$, χ^2 test). Monthly changes in the occurrence of BAT were more closely related to differences in photoperiod ($r^2 = 0.876$) rather than ambient temperature ($r^2 = 0.696$). Individuals with serial scans also demonstrated strong seasonal variation in BAT activity (average standardized uptake value [SUV_{max}] 1.5 in July and 9.4 in January). BAT was also more common in female patients (female: $n = 107$, 7.2%; male: $n = 60$, 2.8%; $P < 0.00001$, χ^2 test).

CONCLUSIONS—Our study demonstrates a very strong seasonal variation in the presence of BAT. This effect is more closely associated with photoperiod than ambient temperature, suggesting a previously undescribed mechanism for mediating BAT function in humans that could now potentially be recruited for the prevention or reversal of obesity. *Diabetes* 58:2583–2587, 2009

Brown adipose tissue (BAT) was first discovered several hundreds of years ago (1). Extensive research has been conducted in animals to elucidate its function. BAT has been proven to be important in small mammals for nonshivering thermogenesis, particularly following hibernation (2). BAT often coexists with white adipose tissue (WAT) and is structur-

ally very different (3). WAT is unilocular containing a large single vacuole, whereas BAT is multilocular containing large complex mitochondria with a rich vascular supply and is extensively innervated by the sympathetic nervous system. The functions of WAT and BAT differ. WAT acts as a chemical store and an insulator. BAT, however, enables rapid heat production directly from the metabolism of triglycerides, suitable for nonshivering thermogenesis. This function is important in mammals and also helps to counteract the cold stress of birth in newborn mammals including humans (4). BAT is activated by the cold, a function mediated by the sympathetic nervous system (2), and is capable of producing up to 300 times more heat per unit mass compared with all other tissues (5). Uncoupling protein (UCP)-1 is exclusively expressed in brown adipocytes and uncouples oxidative phosphorylation from respiration and the production of ATP, resulting in the production of large amounts of heat (2).

BAT is thought to have a protective role against obesity because genetic knockout mice lacking BAT become obese (6). Strong recent evidence for the existence of active BAT in adults has come from positron emission tomography (PET)/computed tomography (CT) imaging, a technique enabling the visualization and anatomical localization of sites of glucose metabolism. Sites of high activity are seen within adipose tissue, particularly in adipose located in the supraclavicular regions but also in paraspinal and suprarenal regions. Three recent studies have demonstrated the presence of UCP-1 in areas corresponding to these areas of activity on PET/CT. Biopsy of the supraclavicular areas of activity confirmed the presence of BAT at this site, providing conclusive evidence for the presence of active BAT in adult humans (7,8,9). Although very likely to represent BAT, the other sites of presumed BAT activity have not been definitively confirmed on biopsy samples.

The purpose of our study was to further examine the characteristics of BAT expression in a large cohort of adults undergoing PET/CT at our institution and to determine how this related to time of year. We specifically focused on the impact of photoperiod and ambient temperature because these are two key factors determining BAT function in small mammals (10,11).

RESEARCH DESIGN AND METHODS

A total of 3,614 consecutive patients underwent PET/CT scans between 14 March 2006 and 30 October 2008 at the Nottingham PET/CT center (53.00°N 1.20°W). These scans were mostly performed for cancer staging. Patients were fasted for at least 6 h prior to their appointments. All scans were acquired using a Siemens Biograph 16 HiRez LSO PET/CT scanner. The majority of scans were performed from skull vertex to upper thigh. Temperature was not kept constant at the PET/CT center throughout the year, although there is a thermostat in the room and indoor temperature significantly exceeds outdoor temperature. Patients were indoors for at least 75 min to allow for 18F-fluorodeoxyglucose injection and uptake prior to imaging.

Patients expressing BAT activity were identified via retrospective review of radiology reports. The presence of BAT activity is routinely included in the radiology report at our institution. The 154 patients with BAT activity

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TABLE 1
Frequency of reporting of BAT-positive anatomical depots with average age in years for each depot

	<i>n</i>	Average age (years)
Supraclavicular/cervical	138	48.7 ± 1.74
Axillary	22	46.1 ± 4.81
Paravertebral	32	54.6 ± 3.43
Mediastinum	63	48.9 ± 2.62
Abdomen	13	36.4 ± 5.46

Data are means ± SE.

constituted the study group. Data were also obtained about age, sex, BMI, serum glucose, month scanned, and disease. The location of BAT depots was recorded in each of these patients.

Patients who underwent serial scans were identified, and variation of BAT expression in these individuals was recorded. BAT activity was quantified by calculating the maximum standardized uptake value (SUV_{max}) within a specified region of interest using a Leonardo workstation in the area of maximal activity in these patients. Assessment of depots was made by a single observer experienced in PET/CT interpretation.

Quantification. The SUV_{max} is dependent on a number of factors including time between injection and imaging, blood glucose, patient weight, and the equipment used (12). Although serial SUV_{max} measurements are more reproducible in individuals, a semiquantitative method of analyzing the intensity of BAT depots was also developed to give an approximate estimate of the amount of BAT present in an individual. The five main depots (supraclavicular, mediastinal, axillary, paravertebral, and abdominal) were analyzed, and the amount of activity in each was assigned a score (0 = absent, 1 = low grade, 2 = moderate, 3 = high grade) that was then summed for the five major depot sites to provide a total intensity score (0–15). The total number of positive depots was also used as a quantitative index.

Statistical analysis. All statistical analyses were performed using SPSS version 16.0 for windows (SPSS, Chicago, IL). A χ^2 test was performed to ascertain whether there was a significant relationship between sex and total number of BAT-positive scans and between season and total number of BAT-positive scans.

RESULTS

Characteristics of BAT expression. The prevalence of BAT activity in this cohort of patients was 4.6% ($n = 167/3,614$) with the location summarized in Table 1. Overall, BAT was most often observed in the supraclavicular region.

Sexual dimorphism. In male patients, 2.8% of scans demonstrated BAT activity ($n = 60/2,131$) compared with 7.2% of scans in female patients ($n = 107/1,483$). The difference between male and female patients was highly significant ($P = 0.00005$, χ^2 test). Irrespective of sex, for the 57 patients in whom BMI data were available, there was a trend for BAT-positive individuals to have a low BMI, with a smaller proportion being obese.

Seasonal variation. The proportion of patients with BAT activity showed a very striking seasonal variation, being highest in winter and lowest in summer (Fig. 1A and B). The month-to-month circannual variation is even more striking because it is inversely correlated with average monthly temperatures and positively related to night length in Nottingham as recorded through the study period (Fig. 1C and D). Additionally, the number of depots identified also varied with season, with more depots identified in winter than summer (Fig. 1E). The difference in the monthly number of patients in which BAT activity observed was therefore positively correlated with night length ($r^2 = 0.876$; $P < 0.00001$; Pearson Correlation) and negatively correlated with ambient temperature ($r^2 = 0.696$; $P < 0.001$).

The seasonal variation in BAT activity was also apparent

in those individuals who were scanned in different months (Fig. 2), with the mean SUV_{max} value being ~4 times higher in winter compared with summer (average SUV_{max} 1.5 in July and 9.8 in January). Indeed, some patients with active BAT in winter showed no activity in the summer. These effects were all independent of sex.

Age. The age range of the BAT-positive cohort was 13–88 years (average age 51.8 years), and there was a trend for both the average number of depots identified and the semiquantitative BAT score to decrease with increasing age (see Fig. 3A and B), although the latter effect is primarily due to the decreasing number of depots.

Cancer versus noncancer patients and type of medication. In the BAT cohort, 11/167 (6.6%) of patients did not have a diagnosis of cancer, and all were investigated for solitary pulmonary nodules. Of those with cancer, 111/156 (71.2%) had active disease and 45/156 were in remission (28.9%). A similar distribution was seen in scans of patients not exhibiting BAT activity. There was also no relationship between the plasma glucose and the occurrence of BAT activity, with all patients being normoglycaemic (data not shown).

DISCUSSION

Obesity is a significant cause of morbidity and mortality, and there has been considerable recent interest in studying the physiology of BAT in humans, given its protective role against obesity in animal experiments (6). A greater understanding of BAT function could thus help to develop treatment strategies for obesity, especially because it appears that white adipocyte area is smaller in individuals possessing UCP-1 (13). One of the most striking findings of our study is the pronounced seasonal variation in BAT expression seen in the entire cohort of patients, in individuals, and in the number of depots that are active. To our knowledge, this is the largest study of its kind documenting the distribution of active BAT in multiple depots in adults and how BAT varies with season. Two smaller studies have demonstrated increased BAT activity in winter and/or early spring (14), although other studies have not confirmed this finding (15,16). We thus extend the findings from a small Japanese cohort (17) in which the variation in temperature was much greater than in the U.K. Importantly, we raise the question whether it is the prevailing ambient temperature or photoperiod that may be the primary factor determining BAT activity.

Cold exposure is established to promote BAT activity in both rodents (2) and humans (8). The extent to which it is the primary regulator of BAT function remains uncertain because photoperiod can also determine BAT activity irrespective of ambient temperature, although this effect is enhanced in the cold (18,19). Photoperiod is known to impact on prolactin release (20), which increases with day length (21). Prolactin administration also promotes the loss of UCP-1 (22), and prolactin secretion can be temperature sensitive (23). The prolactin receptor is essential for BAT function in the newborn (24), in whom the direct stimulation of prolactin receptor promotes BAT thermogenesis (25). It is thus possible that prolactin is an important factor determining the overall activity of BAT we have observed with season. This would explain why BAT that is inactive in the summer is then recruited in the winter for nonshivering thermogenesis, evidenced by increased activity within depots and a greater number of depots. Furthermore, it should be noted that patients

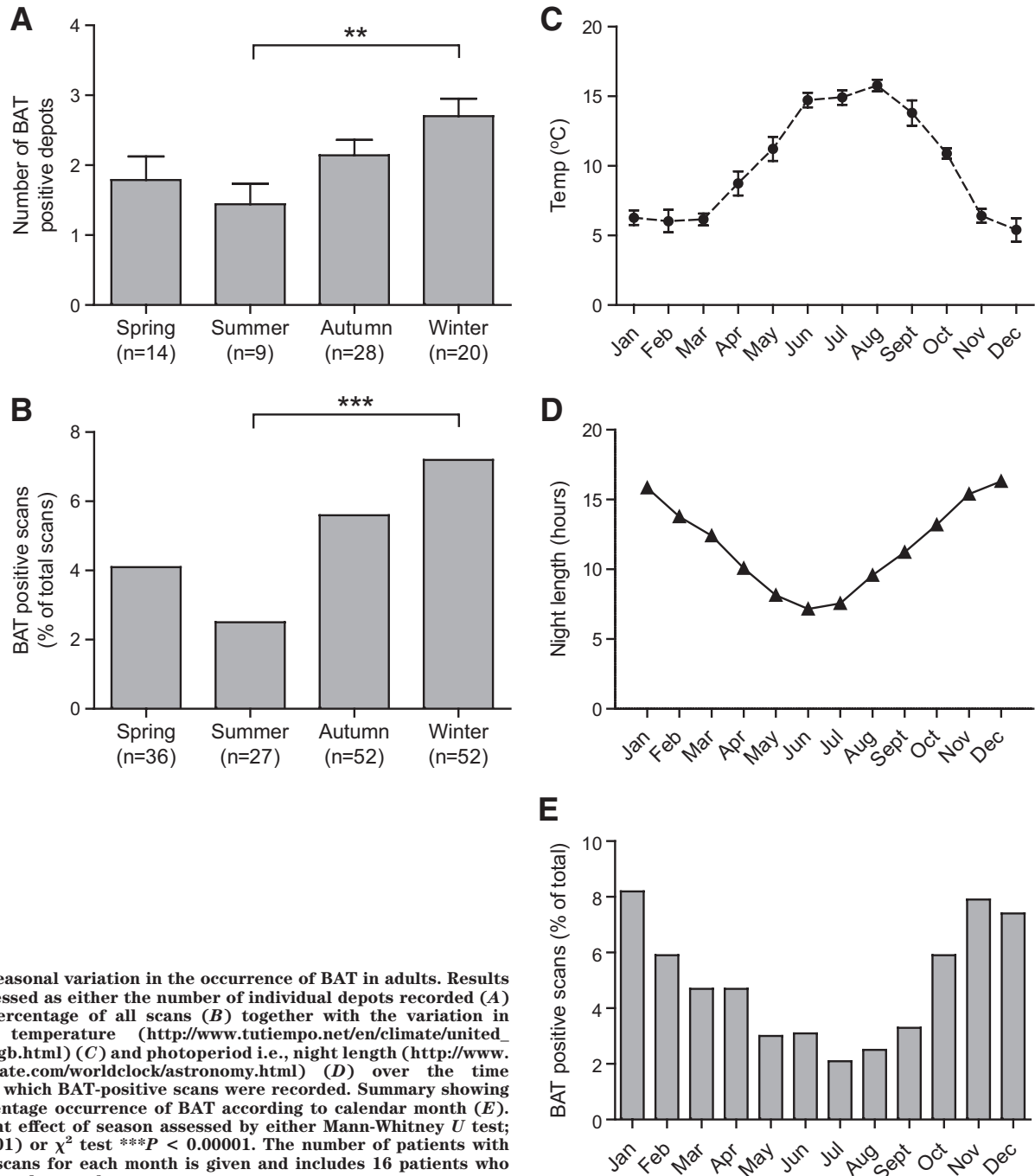


FIG. 1. Seasonal variation in the occurrence of BAT in adults. Results are expressed as either the number of individual depots recorded (A) or the percentage of all scans (B) together with the variation in ambient temperature (http://www.tutiempo.net/en/climate/united_kingdom/gb.html) (C) and photoperiod i.e., night length (<http://www.timeanddate.com/worldclock/astronomy.html>) (D) over the time period in which BAT-positive scans were recorded. Summary showing the percentage occurrence of BAT according to calendar month (E). Significant effect of season assessed by either Mann-Whitney *U* test; ** $P < 0.01$) or χ^2 test *** $P < 0.00001$. The number of patients with positive scans for each month is given and includes 16 patients who were scanned more than once.

undergoing scans are in a warm environment (indoors) while being prepared for their scans. The persistence of the strong variation in BAT activity despite stable indoor temperatures could thus relate to the longer-term recruitment of BAT depots (10). Although prolactin may be an important mediator, as discussed, the endocrine mechanisms controlling BAT expression are likely to be complex and other hormones, for example the key player in mediating circannual rhythms in mammals melatonin, are likely to be involved (26).

An understanding of the physiology of BAT is likely to be important if recruitment of BAT is to be considered as a strategy for weight loss in obese individuals. Global temperatures are rising in conjunction with increased use of artificial lighting and central heating (27). Our results

demonstrate that seasonality and, thus, photoperiod and/or ambient temperature are pivotal determinants of BAT activity in adult humans. In fact, the abundance of BAT quadrupled between the summer and winter months in our study, thus emphasizing the importance of considering the time of the year in weight loss programs. The success or the failure of dietary or pharmacological interventions aimed at weight loss in obesity could depend on the capacity of BAT to burn excess energy. This raises the question as to whether the greater quantity of BAT we possess during the winter could be used to promote fat mobilization at this time of year.

Our study also demonstrated significantly increased prevalence of BAT in female patients, a finding that is consistent with other studies (9,14). Sexual dimorphism

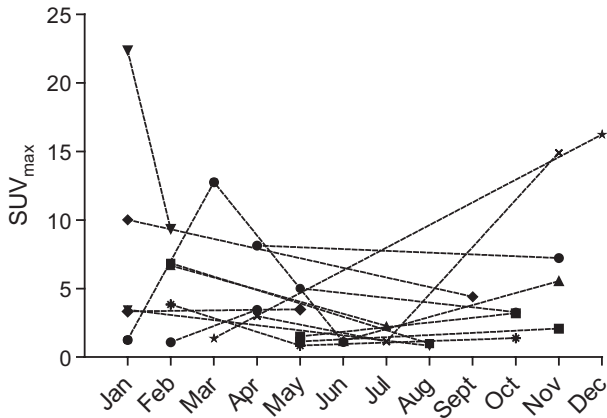


FIG. 2. Effect of month of year on individual changes in SUV_{max} of BAT. Each line represents an individual patient who underwent serial PET/CT scans throughout the study period, with the total number of patients being 16.

also exists in animal studies. Female rats have higher levels of UCP-1 in the interscapular BAT depot compared with males when housed at the same temperature, suggesting that they may have a lower temperature threshold for cold-induced thermogenesis (28). Sexual dimorphism in endocrine control of BAT may explain these differences. BAT function is dependent on thyroid hormones (29),

which may be under the control of estrogen in female rats. BAT also expresses estrogen receptors, which may further explain these differences (2).

One caveat is that the study group mostly consists of patients undergoing treatment for cancer, although this is unlikely to affect the seasonal variation in BAT activity. It has been suggested that BAT activity may in part relate to increased expression of UCP-1 in cancer patients (30). In the present study, however, BAT was shown to be present in a significant proportion of noncancer patients, as well as those that were in remission, indicating that the presence of BAT is not exclusively due to cancer-related factors.

In conclusion, our large retrospective study demonstrates the presence of a strong seasonal variation in BAT activity (9) both in a cohort and in individual patients. Improved understanding of the influence of both photoperiod and ambient temperature on BAT function is likely to lead to the development of novel treatments for obesity.

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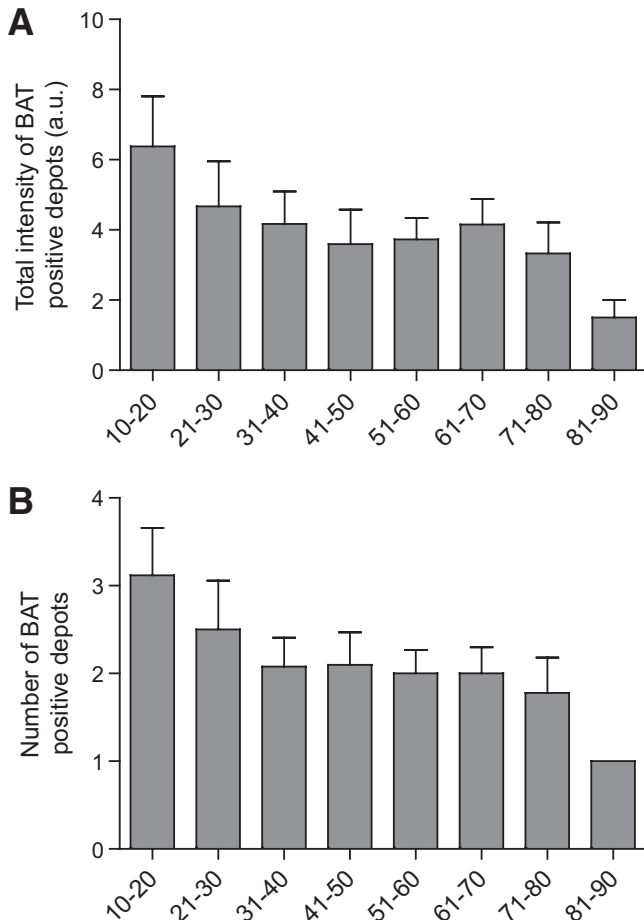


FIG. 3. Effect of age on the occurrence of BAT in adults. Results are expressed as either the mean total intensity (A) or the number of individual depots recorded (B). A total of 71 scans were analyzed because not all were available for this type of analysis.

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