A role of active brown adipose tissue in cancer cachexia?

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Abstract

Until a few years ago, adult humans were not thought to have brown adipose tissue (BAT). Now, this is a rapidly evolving field of research with perspectives in metabolic syndromes such as obesity and new therapies targeting its bio-energetic pathways. White, brown and so-called brite adipose fat seem to be able to trans-differentiate into each other, emphasizing the dynamic nature of fat tissue for metabolism. Human and animal data in cancer cachexia to date provide some evidence for BAT activation, but its quantitative impact on energy expenditure and weight loss is controversial. Prospective clinical studies can address the potential role of BAT in cancer cachexia using 18 F-fluorodeoxyglucose positron emission tomography-computed tomography (PET-CT) scanning, with careful consideration of co-factors such as diet, exposure to the cold, physical activity and body mass index, that all seem to act on BAT recruitment and activity.

Introduction

Cancer cachexia and hypermetabolism

Cancer cachexia is recognized as a distinct clinical disorder with a negative impact on quality of life, therapeutic success and prognosis. The recently redefined criteria for cachexia are weight loss of more than 5% over the previous six months or weight loss of more than 2% in individuals who already show a state of depletion according to decreased bodyweight (Body Mass Index or BMI<20 kg/m2) or skeletal muscle index (sarcopenia).1 Cancer cachexia frequency varies with the type of malignancy, occurring more frequently in patients with lung and upper gastrointestinal cancer and less often in patients with breast cancer or lower gastrointestinal cancer.2 Current evidence on the pathogenesis of the cachexia syndrome points to a central disturbance of the hypothalamic pathways controlling energy homeostasis, resulting in reduced energy intake and anorexia, increased energy expenditure, and loss of body tissue, i.e. muscle proteolysis and lipolysis.3 Resting energy expenditure or metabolic rate (RMR) accounts for the major proportion of up to 70% of total energy expenditure in sedentary subjects.3 Hypermetabolism has been found to be elevated in some but not all cancer patients; for example, in approximately 50% of a mixed cancer population6 and in up to 74% of primary lung cancer patients.8 Cancer patients who lose weight have higher RMR than patients with a constant weight.6 Several pathophysiological mechanisms for an inappropriately elevated RMR in cancer cachexia have been proposed, i.e. abnormalities in the carbohydrate, fat or protein metabolism, systemic inflammation, hyperadrenergic activity and an increased liver mass.4,6,9 In addition, it was suggested as early as 1981 that activation of brown adipose tissue (BAT) results in a hypermetabolic state and is partially responsible for weight loss in cancer patients12 but this was in contrast to the widespread view that BAT is only present in newborns and that it disappeared in human adulthood. The human and animal studies discussed here were retrieved from a systematic literature search of relevant medical databases (Medline, Embase, Cochrane Library) using the key words brown adipose tissue, cancer and cachexia (Supplementary Figure S1).

Brown adipose tissue activity

In 2002, Hany et al.13 suggested the existence of functional BAT in adults with the introduction of combined positron emission tomography-computed tomography (PET-CT) scans, showing increased metabolism and glucose uptake with 18F-fluoro-deoxyglucose (¹⁸F-FDG) in
areas that were unmistakably fat tissue on the basis of Hounsfield units on the CT. Nedergaard et al. discussed the perspectives presented by this observation to study BAT function in humans. So far, several independent studies have confirmed the existence of functional BAT in adult humans, using cold-induced BAT activation, 18F-FDG PET-CT scanning and biopsy verification.

The primary function of BAT is facultative thermogenesis, i.e., regulated heat production in response to a decrease in core body temperature with environmental cold exposure. For this, BAT cells are characterized by an abundance of mitochondria, in contrast to white adipose tissue (WAT). The thermogenic effect of BAT is due to the exclusive presence of uncoupling protein 1 (UCP1) which mediates proton leakage across the inner mitochondrial membrane, thus decreasing the level of coupling of respiration to ADP phosphorylation. In this way, heat is produced instead of energy stored as ATP (Figure 1). Environmental cold exposure causes BAT cells to increase their number of mitochondria and UCP1 synthesis through sympathetic adrenergic stimulation. Human studies have demonstrated that 18FDG uptake in BAT is directly proportional to the expression of UCP1 and the cold-induced rise in energy expenditure. Therefore, 18FDG activity on PET-CT scan can be used as a surrogate marker as a non-invasive technique to measure BAT activity in vivo (Figure 2).

Another relevant recent discovery has been the identification of so-called brite (or beige or systemic) adipose cells which reside among the much larger area of WAT tissue in both subcutaneous and trunk (visceral) compartments. These were so named because they have the same origin (from a myogenic factor 5 (myf5)-negative mesodermal stem cell) as WAT cells, but different from the myf5-positive adipomyoblast that gives rise to myocytes and the classical brown adipocytes that occupy the deposits, as seen in Figure 2. Although genotypically different, the thermogenic phenotype of brite and brown cells has been shown to be similar. Importantly, differentiated brite and white fat cells have the capacity for reversible trans-differentiation into each other, a process that is also closely related to the activity of the sympathetic system. This system provides a large metabolic reservoir for recruitable combustion (WAT→BAT conversion) or storage (BAT→WAT conversion) of energy and lipid tissue metabolites.

Several review publications over the last few years have addressed the developments in this growing field, hypothesizing on the possible importance of BAT function on substrate and energy homeostasis of the body. Many of these have focussed on obesity, with the prospect of therapeutic WAT→BAT conversion, thermogenic activity, weight loss and conversion of metabolic abnormalities. Along these chain of events,
the possibility that cancer cachexia is partly mediated by BAT has also re-emerged. New research in this field is facilitated by the availability of PET-CT scans in cancer centers.

Animal studies on cancer cachexia and brown adipose tissue function

Table 1 shows previous studies that examined the effects of subcutaneous tumor xenograft models on BAT activity in rodents. In the early study of Brooks et al., which was later confirmed by Roe and co-workers, resting oxygen consumption (VO₂) as well as core body temperature showed significantly higher values in cachetic tumor-bearing mice as compared to pair-fed, non-tumor bearing controls, and these coincided with sympathetic activation of BAT, as judged by mitochondrial guanosine diphosphate (GDP) binding. These results seem to indicate the presence of a state of excessive energy expenditure and thermogenic activity of BAT in cancer cachexia, but they do not establish the corresponding degree of changes in BAT activity, energy expenditure and weight loss. On the other hand, in a study by Oudart, suggesting that BAT activity, as induced in tumor-bearing animals, is almost exclusively functional and that full fledged BAT tissue development or recruitment is unlikely in cancer cachexia. However, in this study there was no significant difference in final carcass mass between tumor-bearing animals and pair-fed control animals, so there seemed to be a lesser extent of cachexia. Other studies (Table 1) have focussed on the determination of BAT constituents but lack correlation to changes in body temperature and energy expenditure, while different parameters were used to measure BAT activity. For example, lipo-protein lipase (LPL) activity which is synthesized and released from the BAT cells in response to adrenergic stimulation to provide for combustable fatty acids is also strongly confounded by external factors such as insulin levels. These data demonstrate the importance of methodology to the results in these metabolic studies.

The most recent studies have focussed on the effects of several tumor mediators on BAT activity (Table 2). A recent systematic review found circulating levels of tumor necrosis factor-alpha (TNF-α) to be elevated, unchanged or undetectable in cancer patients with cachexia, and no association between systemic serum levels of TNF-α and weight loss was found, with the exception of one study in advanced breast cancer. Emphasizing the importance of a central nervous signalling pathway by TNF-α, Arruda et al. demonstrated a moderate but significant body weight loss and BAT stimulation by intra-cerebro-ventricular administration of TNF-α. Importantly, BAT activity as well as coinciding body mass loss, body hyperthermia and inhibition of food intake could be attenuated by prior BAT denervation or administration of a β-3 antagonist (SR59230A), suggesting a causal link between BAT hyperactivity and cachexia hypermetabolism, as well as therapeutic activity of a β-3 adrenoceptor antagonist.

Another tumor mediator that has been implicated in cancer cachexia with regard to BAT activation has been zinc-alphaglycoprotein (ZAG), or lipid-mobilizing factor, which was isolated from the urine of cachectic cancer patients. Its activity in subcutaneous fat biopsies was recently shown to inversely correlate with weight loss in patients with cancer cachexia. In animal studies, ZAG purified from the murine adenocarcinoma MAC-16 induced profound cachexia by lipolysis, but not muscle breakdown. Russell et al. showed a dose-dependent increase in gross body weight loss and BAT UCP1 protein expression with increasing doses of i.p. administered ZAG. This was accompanied by an increase in BAT oxygen consumption indicating thermogenesis, although its effect on overall energy expenditure was not reported. Presumably, according to these authors, increased levels of plasma fatty acids as a result of ZAG induced lipolysis contributed to an increase in BAT UCP1 and thermogenesis. Interestingly, TNF-α but not ZAG has also been found to up-regulate other UCP subtypes, i.e. UCP2 that is found in low levels in many tissues, and UCP3 found in BAT and skeletal muscle. One should, therefore, also consider the possibility of cytokine driven heat production in other tissues.

Up to now, not many studies have explored the functional response of BAT activity in response to cold in this context. Edstrom et al. examined cold-induced thermogenesis in cachectic tumor-bearing mice...
mice. Exposure of cold in tumor-bearing mice produced a significantly elevated BAT thermogenic response, although there was no significant difference in carcass weight between animals kept at a temperature of 5°C compared to those kept at 25°C. In this study, neither β-blockade nor BAT tissue extirpation was shown to impact on body composition. Therefore, these authors concluded that full-blown BAT proliferation and activation was unlikely in cancer cachexia. However, these experiments were not pair-fed controlled because food restriction at 5°C resulted in 100% mortality. Animals kept at 5°C had double the food intake of those kept at 25°C. Recently, Tsoli et al., 47 found increased BAT activity in C26-induced cachetic mice, as judged by BAT UCP1 protein. This persisted when the animals were acclimatized to 28°C, despite a dramatically reduced food intake. According to these authors, this confirmed the existence of an inappropriate activation of BAT, representing a maladaptive response to nutrient deprivation in cancer cachexia. Furthermore, 18F-FDG PET imaging showed similar kinetics in these cachetic C26 mice as compared to freely-fed, non-tumor-bearing animals despite the fact that uptake of 18F-FDG is normally reduced in fasting mice, 48 supporting the concept of an increase in metabolic activity in cancer cachexia.

In summary, Tables 1 and 2 show that most animal studies indicate some degree of BAT activation in cancer cachexia. However, these data do not establish the quantitative impact on the amount of hypermetabolism that is relevant to the development of cachexia. The human and animal studies were retrieved from a systematic literature search of relevant medical databases (Medline, Embase, Cochrane Library) using the key words brown adipose tissue, cancer and cachexia (Supplementary Figure S1).

Human studies on cancer and brown adipose tissue function

Hibernoma, a rare soft tissue benign tumor composed of brown fat cells, has been associated with massive weight loss as a primary symptom, 49 suggesting the potential of BAT to significantly contribute to body weight loss in cachexia in humans. Abundant BAT hyperactivity can also be seen on 18F-FDG PET scanning in cases of pheochromocytoma as a result of chronic stimulation of the sympathetic nervous system by high levels of circulating catecholamines, such as epinephrine and norepinephrine. 50 In one case, after removing the pheochromocytoma, and thus the excess of norepinephrine, the intense uptake of 18F-FDG in BAT was no longer seen, 51 presumably reflecting an inactivation of BAT. However, such extreme levels of circulating catecholamines in pheochromocytoma are not representative of other cancer types.

In retrospective studies of mixed cancer populations referred for routine 18F-FDG PET scanning, single scan observations have shown a prevalence of 5-10% of BAT positivity in a general oncology patient group 52 (Figure 2) Rousseau analyzed serial PET-CT scans performed during neo-adjuvant breast cancer chemotherapy in 33 patients. 53 A total of 82% of patients showed BAT activity on at least one occasion. However, positive PET-CT scans were randomly distributed between patients and time points which, according to the authors, suggested an association of an increased chance of a sufficiently cold environment activating BAT with an increasing number of scans, rather than any correlation to cancer progression or response. Three retrospective studies 18,54,55 addressed a possible relationship of BAT 18F-FDG activity

Table 2. Rodent studies on cancer cachexia and brown adipose tissue activity, studying the effect of tumour mediators.

<table>
<thead>
<tr>
<th>Study</th>
<th>Cachexia group</th>
<th>Control group</th>
<th>Cachexia induction (ex control group)*</th>
<th>BAT activation (parameter)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coombes36</td>
<td>1x. TNF-α in Wistar rats, 6 days</td>
<td>NaCl sham injected animals</td>
<td>++ P&lt;0.01 (BW -10% of controls)</td>
<td>+ P&lt;0.05 (mitochondrial GDP binding)</td>
</tr>
<tr>
<td>Lopez-Soriano37</td>
<td>Lewis lung carcinoma cells in rTNF-α/1 Wistar rats, 11 days</td>
<td>Wild type and non-tumor bearing animals</td>
<td>++ P&lt;0.01 (cachexia weight loss up to -26% in wild type es -18% in TNF-α/1)</td>
<td>+ P&lt;0.05 es non-tumour (BAT LPL activity)</td>
</tr>
<tr>
<td>Arruda15</td>
<td>ICF TNF-α in Wistar rats, 4 days</td>
<td>Pair fed, sham injected animals</td>
<td>++ P&lt;0.05 (final BM 241.02 +/- 5.70 g es 270.06 +/- 7.23 g)</td>
<td>+ P&lt;0.05 (BAT UCP1 mRNA and protein)</td>
</tr>
<tr>
<td>Russell38</td>
<td>1x. LMF from urine of weight losing pancreatic cancer patients, in NMRI mice, 2 days</td>
<td>PBS sham injected animals</td>
<td>++ P=n.s. (BW -42%)</td>
<td>+ P&lt;0.01 (BAT utilization of 3H-2-deoxyglucose (2DG))</td>
</tr>
<tr>
<td>Bing40</td>
<td>1x. LMF from the urine of cachetic cancer patients (&gt; 10% body weight loss), in NMRI mice, 3 days</td>
<td>Weight matched, PBS sham injected animals</td>
<td>++ P&lt;0.01 (BW -2.24 g es + 0.96 g)</td>
<td>+ P&lt;0.01 (BAT UCP1 mRNA)</td>
</tr>
<tr>
<td>Russell38</td>
<td>1p. ZAG in NMRI and MFI mice, 4 days</td>
<td>PBS and heat-inactivated ZAG sham injected animals</td>
<td>++ P&lt;0.001 (BW -3.8+/-0.5 g till -1.26+/-0.46 g es -1.2+/-0.3 g till -0.88+/-0.5 g dose-dependent)</td>
<td>+ P&lt;0.001 (dose-dependent) (BAT UCP1 protein)</td>
</tr>
<tr>
<td>Johner41</td>
<td>1p. MIC-1 in BALB/c nude mice after s.c. MIC-1 transfected 5.7x10⁶ DU145 prostate carcinoma cells, n.s.</td>
<td>PBS sham and empty plasmid vector injected animals</td>
<td>++ P&lt;0.001 (BW -5.3 g es -1.1 g)</td>
<td>-- P&lt;0.01 (BAT weight)</td>
</tr>
</tbody>
</table>

BAT, brown adipose tissue; UCP1, uncoupling protein 1; TNF-α, tumor necrosis factor-α; ZAG, zinc-α2-glycoprotein; BW, body weight; BM, body mass; 2-DG, 2-deoxyglucose; GDP, guanosine diphosphate; i.p., intraperitoneal; s.c., subcutaneous; iv, intravenous; ICV, intra-cerebro-ventricular; LMF, lipid mobilizing factor; LPL, lipoprotein lipase; MIC, macrophage inhibitory cytokine; n.s., not specified; PBS, phosphate buffered saline.

*p values represent the strength of the difference in mean +/- standard deviation or standard error of mean between the intervention group (cancer, cachexia) and the methodologically best available control group (pair-fed rather than freely fed, carcass weight rather than body weight) and BAT activity parameter (UCP1, functional test rather than BAT, fat or protein weight).
with cancer (Table 3). However, none of these observed a significantly higher incidence of BAT activity in active and/or 18F-FDG PET-positive cancer patients. Lee et al.15 found BAT activity in 50% of the scans in patients with evidence of active malignancy compared with 44% of scans in which there was no 18F-FDG PET-CT evidence of active disease. Other studies16,54 have applied a univariate and multivariate analysis on patients with BAT activity and found outdoor temperature, age, sex, BMI and diabetes to be significant variables, but not active cancer16 or indication for PET scanning (cancer/no cancer).16 The study of van Marken Lichtenbelt et al.17 showed a BAT prevalence of as high as 96% in healthy, young volunteers after a standardized protocol of cold exposure, suggesting that almost all adults possess active or at least potentially active BAT, depending on the degree of BAT stimulation at that moment. The prevalence of BAT activity in cancer patients may thus be considerably higher than that observed so far because these non-controlled studies do not indicate the degree of BAT stimulation represented by the scan at that moment. Routine preparation for 18F-FDG PET scanning in oncology is aimed at reducing BAT uptake by keeping patients warm and sober to avoid false positive findings for a tumor. The sharp discrepancy between the reported 5-10% in the general population and 96% in stimulated conditions has led some to conclude that quantitative and qualitative data from retrospective studies must not be considered as indications of the true prevalence of BAT and its physiological control.25 Careful consideration of factors co-acting on BAT recruitment and activity, such as diet, cold exposure, physical activity, insulin levels and BMI makes this type of metabolic study challenging, especially for patients.

Virtanen and colleagues16 estimated that, by calculating the metabolic rate of glucose uptake (rGU) from dynamic scanning and pharmacokinetic modelling, constant activation of the supraventricular BAT deposit by moderate cold could burn energy levels equivalent to approximatley 4.1 kg of adipose tissue in one year in healthy subjects. It is unclear how this can relate to the situation in cancer cachexia patients. This amount may be considered an overestimation when comparing the intensity of BAT activity after cold with that in the occasional cancer patient (Figure 2) and considering the fact that most of the patients are thermoneutral, i.e. an environmental temperature at which heat production is not stimulated, which is during most of the day. However, it may be an underestimation if one considers a much larger area of BAT tissue that is activated, not only the supraventricular deposit, and if brite fat thermogenesis is to be taken into account. These issues need further investigation and require more refined quantitative methods for the 18F-FDG-PET-CT scanner to include diffuse nests of brite fat that may falsely appear as areas of low activity as a result of the limited spatial resolution of the PET scanner.

Two previous studies examined fat tissue in cancer patients. Bianchi et al.27 assessed BAT activity from GDP binding to mitochondria prepared from peroperative samples, and found this to be significantly elevated (by 3-fold) in children with various malignancies as compared to children undergoing exploratory renal surgery without cancer. In another study by Shellock et al.,28 the presence of BAT, as assessed by histological light-microscopic criteria, was determined in peri-adrenal fat tissue acquired during autopsy. In a group of cachectic adult cancer patients BAT was found in 80% but in only 13% of patients who died from other illnesses without cancer or cachexia.

In summary, in humans there is no evidence linking BAT activity with cancer cachexia, although studies report a widely variable prevalence of BAT activity depending on the individual metabolic demand at the time of 18F-FDG-PET scanning.

### Brown adipose tissue energetics

Humans and rodents share an identical cell composition of the adipose organ, as well as functional BAT characteristics: dense different vascularization, sympathetic innervation with predominately α3 adrenoceptors, UCP1 as the characteristic mitochondrial membrane protein in brown adipocytes; dependency on ambient temperature.29 In smaller mammals, such as rodents, cold activated BAT thermogenesis has a substantial impact on total energy expenditure. From mice studies, the maximum heat-producing capacity has been established to be 300 W/kg.34 For the moment, no information is available on the contribution of BAT thermogenesis to whole body energy expenditure in humans, although a recent study using 11C-acetate PET-CT provides evidence of metabolic factors contributing to non-shivering thermogenesis.60 In mammals, mass-specific energy expenditure (i.e. per unit mass) is negatively related to body size. Taking such allometric relations into account, it can be calculated from the data from rodents that human activated BAT would spend 45 W/kg.41 Rothwell and Stock estimated 40-50 g BAT in humans;62 this would result in 3-5% of basal metabolic rate (BMR). Using 18F-FDG-PET-CT scanning, Virtanen16 estimated BAT volume to be slightly higher at 63 g, while assuming the contribution of glucose to overall BAT substrate use to be 10%.63 This resulted in an estimated heat production of activated BAT of 55 W/kg, or approximately 4.5% of BMR. These calculations suggest that BAT activity can have a substantial impact on daily energy expenditure.

In addition, BAT may be differently activated depending upon the physiological stimulus. Orava et al.44 showed that BAT is a highly

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**Table 3. Human studies on cancer cachexia and brown adipose tissue activity, studying the effect of tumour presence.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Cancer group</th>
<th>Control group</th>
<th>Cachexia induction</th>
<th>BAT activation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(vs control group)</td>
<td>(parameter)</td>
</tr>
<tr>
<td>Cypress18</td>
<td>Adults; lymphoma and other cancers from mixed PET population (n=1972)</td>
<td>No-cancer</td>
<td>n.s.</td>
<td>- P=n.s.d. (BAT 18F-FDG activity)</td>
</tr>
<tr>
<td>Quellet56</td>
<td>Adults; active cancer from mixed PET population (n=4842)</td>
<td>No-cancer</td>
<td>n.s.</td>
<td>- P=n.s.d. (BAT 18F-FDG activity)</td>
</tr>
<tr>
<td>Lee55</td>
<td>Adults; active (PET positive) malignancies from mixed cancer population (n=2834)</td>
<td>Tumor PET negative</td>
<td>n.s.</td>
<td>- P=n.s.d. (BAT 18F-FDG activity)</td>
</tr>
<tr>
<td>Bianchi57</td>
<td>Pediatric; mixed cancer types (n=8)</td>
<td>No-cancer (pyelo-plasty) (n=9)</td>
<td>+ P=n.s. (evidence of recent weight loss)</td>
<td>+ P&lt;0.05 (mitochondrial GDP binding in perirenal fat)</td>
</tr>
<tr>
<td>Shellock58</td>
<td>Adults; mixed cancer types (n=25); all cachexia; autopsy study</td>
<td>Age-matched, no-cancer, no-cachexia (n=15)</td>
<td>+ P=n.s. (cachexia according to pathologist)</td>
<td>+ P=n.s. (microscopic BAT in peri-adrenal fat)</td>
</tr>
</tbody>
</table>

18F-FDG, 18F-fluoro-deoxyglucose; PET, positron emission tomography; 18F-FDG, 18F-glucose diphosphate; n.s., not specified; s.d., not significant difference.
insulin-sensitive tissue. Insulin administration by an euglycemic, hyperinsulminemic clamp technique led to a 5-fold increase in BAT glucose uptake. This reinforces the view that BAT plays a role in human metabolism and may be of relevance in cancer cachexia in which many of the metabolic abnormalities of type II diabetes mellitus, including glucose intolerance, increased hepatic glucose production and recycling, and insulin resistance have been reported, even prior to the development of severe malnutrition.65

Conclusions

Animal experiments provide some evidence for an association between BAT activation and cancer cachexia. Given the similarities in anatomy and BAT function between rodents and humans, such a relation may also exist in humans. The proliferation of 18F-FDG PET-CT scanners in cancer centers supplies researchers with a new tool to study BAT and human energy balance. However, current retrospective observations in cancer patients do not support a clinically relevant association between BAT and cancer cachexia. Still, the large discrepancy between retrospective and prospective data shows that methodology is critical in these types of metabolic studies. Therefore, further prospective and well-controlled studies are warranted to provide more solid evidence in this field. In animal studies, cancer cachexia models should resemble the human situation as close as possible in terms of end points, degree of anorexia, muscle and fat loss, tumor to body weight, metabolic abnormalities, hormonal changes and cytokine profile.66 In human studies, 18F-FDG PET-CT scanning seems the preferred examination mode to establish patterns of BAT activation and recruitment during pre-cachexia development as compared to age and gender matched normal adults. Direct correlation to measurements of energy expenditure, body temperature and weight loss is essential. Scans should be performed in stimulated circumstances such as at cold temperatures, in order to evaluate the full amount of active BAT present. Co-factors that act on BAT should be controlled or simultaneously measured: age, gender, temperature conditions, season, BMI, physical activity, prior diet, medication (β-adrenoceptor agents), cytokines (CRP, TNF-α, IL-6), hormonal profile (thyroid hormones, insulin), body composition changes (fat mass, lean mass), presence of metabolic pathologies such as obesity, diabetes. In animal and human studies, UCP1 protein is the preferred parameter in brown and brite fat tissue biopsies to assess specific thermogenic activity. In intervention studies, 18F-FDG PET-CT can be used to study the effects of a β3-adrenoceptor antagonist on BAT activation and cachexia before, during and after initiation of treatment.

References


