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Invited Perspective

Brown Adipose Tissue Activity Following Exposure to the Cold and [^{18}F]FDG Uptake: from Possible Pitfall in Early PET Scans to Metabolic Biomarker

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Short running title: Brown adipose tissue activity

There are three types of fat in the human body: White, Brown and Beige (*1*). White adipocytes deposit extra energy into triglycerides, while beige and brown adipocytes have the unique ability to convert mitochondrial energy into heat (rather than ATP) via uncoupling protein 1 (UCP-1). Obesity, especially excess fat in tissue that is normally lean, increases the risk of cardiovascular disease (*2*). In addition to the amount of fat, the distribution of fat, especially increased abdominal fat, evaluated by the ratio of waist to hip circumferences, predicts glucose intolerance, insulin resistance, hypertension and hypertriglyceridemia (*3,4*). PET/CT with 2-deoxy-2-fluoro-D-glucose provides a unique opportunity to view the metabolic activity of brown fat (brown adipose tissue, BAT). However, even though visceral and subcutaneous fat are substantially less metabolically active than BAT, both are metabolically active tissues (*5*). Visceral adipose tissue is more metabolically active than subcutaneous fat.

BAT is a thermoregulatory organ that consumes stored energy to produce heat through the expression of UCP1. This phenomenon is called "non-shivering thermogenesis" and plays an important role in glucose and lipid metabolism (*6*). It is particularly intense in newborns, where it helps to maintain a normal body temperature; although declining with age, islets of brown adipocytes remain in the white adipose tissue of adult humans (7). Such islets are activated by cold exposure, with a higher prevalence in youngsters, in women, and in lean subjects (*8*). Experimental evidence suggests that BAT may also play an important role in the development and progression of cancer – through secretion of adipokines, inflammatory cytokines, growth factors, and free fatty acids (*9*). In this regard, the biological mechanism of BAT hypermetabolism as quantified by [^{18}F]FDG PET/CT is similar to hypermetabolism of cancer cells.

In this issue of the *Journal*, Crandall et al. report the metabolic changes associated with the cold-activation of BAT in a group of young adult volunteers. The investigators injected [^{18}F]FDG for PET/CT imaging immediately following two hours of cold exposure. In addition to the imaging study the investigators compared baseline blood metabolites in participants with varying amounts of active BAT (*10*). From the perspective of a clinician with expertise in glucose and lipid metabolism, there are at least four puzzling points in the results: a) the surprising variability of BAT volume (0–430 mL) and [^{18}F]FDG uptake in BAT (SUL_{MAX} ranging between 0 and 38) in a rather homogeneous cohort of young healthy individuals, b) the impressive correlation of fasting insulin with both BAT volume (r=0.90) and BAT [^{18}F]FDG uptake (r=0.74), c) the substantial differences in lifestyle between the BAT_{low} and BAT_{high} groups, who were neither on a calorie restriction diet nor engaged on regular physical exercise and had only a marginally higher BMI (1.4 kg/m^2), d) the decline in glucose and insulin levels induced by acute cold exposure observed only in the BAT_{high} subjects.

Such extreme physiologic heterogeneity of BAT volume and activated metabolism raises several questions: is there any relationship between volume and function (i.e., activated glucose uptake)? Does BAT volume or activation correlate with the individual tolerance to cold exposure (shivering threshold)? Elucidation of these issues would be relevant to understand whether or not BAT can be "trained" and/or expanded by exposure to cold.

The amazing association between insulin and BAT volume suggests that BAT is expanded in subjects with relative insulin resistance, which is confirmed by the concomitantly higher glucose values. If this is this case, then these individuals are probably at a higher risk of developing diabetes.

On the other hand, the extreme difference in lifestyle, despite a minor difference in BMI, suggests that these subjects with expanded BAT are less prone to become obese. The decline in glucose observed after cold exposure only in the BAT_{high} subjects suggests that these individuals are more resistant to the stress induced by cold exposure. Indeed, BAT-negative lean subjects display reduced epinephrine levels after cold exposure when compared to BAT-positive subjects, despite a similar increase in energy expenditure (*11*). This could be interpreted as a higher sensitivity of thermogenesis to catecholamines and could be another mechanism that protect the BAT_{high} subjects from developing obesity. The possibility that BAT expansion would protect from developing diabetes might be related to this protection.

Somewhat less impressive, from a clinical perspective, are the differences in basal glucose, insulin and triglycerides between low and high BAT, which might be driven by the difference in BMI. Also the different changes in lipids profiles induced by such a short-term cold exposure are difficult to interpret, considering the extremely slow kinetics of these substrates.

Overall, Crandall et al. are to be congratulated on their novel use of PET/CT to investigate thermogenesis, a study that casts novel perspectives for the applications of a "mature" imaging method, as PET with [^{18}F]FDG is. In this regard, accurate imaging quantification made possible by recent scientific and technological advances allows addressing the combined challenges of deriving robust imaging biomarkers for artificial intelligence applications and of capitalizing the full potential of long axial field-of-view PET systems. An exciting application for such new systems is the possibility to determine the kinetics of tracer biodistribution through different compartments of the body – given the possibility to record quasi-dynamic acquisitions of virtually the whole body (*12*). These developments cast our interest back to the origin, by reminding us that the essence of [^{18}F]FDG PET/CT is not just reporting the presence of uptake in a target lesion: every single PET/CT scan has much more than this to

offer, and "signals" are there just to be detected and correctly interpreted. [^{18}F]FDG uptake in BAT is the perfect example for this scenario (*13*).

Disclosure

The authors have no potential conflicts of interest to disclose.

References

1. Okla M, Kim J, Koehler K, Chung S. Dietary factors promoting brown and beige fat development and thermogenesis. Adv Nutr. 2017;8:473-83.
2. Piche ME, Tchernof A, Despres J-P. Obesity phenotypes, diabetes, and cardiovascular diseases. *Circ Res*. 2020;126:1477-500
3. Kalkhoff RK, Hartz AH, Rupley D, Kissebah AH, Kelber S. Relationship of body fat distribution to blood pressure, carbohydrate tolerance, and plasma lipids in healthy obese women. *J Lab Clin Med*. 1983;102:621-7.
4. Krotkiewski M, Björntorp P, Sjöström L, Smith U. Impact of obesity on metabolism in men and women. Importance of regional adipose tissue distribution. *J Clin Invest*. 1983;72:1150-62.
5. Christen T, Sheikine Y, Rocha VZ, et al. Increased glucose uptake in visceral versus subcutaneous adipose tissue revealed by PET imaging. *JACC Cardiovasc Imaging*. 2010:3;843-51.
6. Bos SA, Gill CM, Martinez-Salazar EL, Torriani M, Bredella MA. Preliminary investigation of brown adipose tissue assessed by PET/CT and cancer activity. *Skeletal R*adiol. 2019;48:413-9.
7. Huang Y-C, Chen T-B, Hsu C-C, Lee B-F, et al. The relationship between brown adipose tissue activity and neoplastic status: an ^{18}F-FDG PET/CT study in the tropics. *Lipids Health Dis*. 2011 Dec 20;10:238.
8. Cypess AM, Lehman S, Williams G, et al. Identification and importance of brown adipose tissue in adult humans. *N Engl J Med*. 200;360:1509-17.
9. Himbert C, Delphan M, Scherer D, Bowers LW, Hursting S, Ulrich CM. Signals from the adipose microenvironment and the obesity-cancer link — A systematic review. *Cancer Prev Res*. 2017;10:494–506.
10. Crandall JP, Fraum TJ, Wahl RL. Brown adipose tissue: a protective 1 mechanism in "pre-prediabetes"? *J Nucl Med*. 2022 Apr 7;jnumed.121.263357 [Online ahead of print].

11. Kulterer OC, Herz CT, Prager M, et al. Brown adipose tissue prevalence is lower in obesity but its metabolic activity is intact. *Front Endocrinol*. 31 March 2022 doi.org/10.3389/ fendo.2022.858417.
12. Pantel AR, Mankoff DA, Karp JS. Total-body PET: will it change science and practice? *J Nucl Med*. 2022;63:646-8.
13. Crandall JP, Wahl RL. Perspectives on brown adipose tissue imaging: insights from preclinical and clinical observations from the last and current century. *J Nucl Med*. 2021;62(Suppl 2):34S-43S.