^{18}F-FDG Uptake in Brown Adipose Tissue After Exposure to the Cold: From Possible Pitfall in Early PET Scans to Metabolic Biomarker

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There are 3 types of fat in the human body: white, brown, and beige (*1*). White adipocytes deposit extra energy into triglycerides, whereas beige and brown adipocytes have the unique ability to convert mitochondrial energy into heat (rather than adenosine triphosphate) via uncoupling protein 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 ^{18}F-FDG provides a unique opportunity to view the metabolic activity of 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 uncoupling protein 1. This phenomenon is called nonshivering thermogenesis and plays an important role in glucose and lipid metabolism (*6*). It is particularly intense in newborns, in whom 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 exposure to cold, with a higher prevalence in children, women, and 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 biologic 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 of Nuclear Medicine,* 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 after 2 h of exposure to cold. 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 4 puzzling points in the results: the surprising variability in BAT volume (0–430 cm^3) and ^{18}F-FDG uptake in BAT (SUV_{max} normalized to lean body weight, 0–38) in a rather homogeneous cohort of young, healthy individuals; the impressive correlation of fasting insulin with both BAT volume (r = 0.90) and BAT ^{18}F-FDG uptake (r = 0.74); the substantial differences in lifestyle between the low-BAT and high-BAT groups, who were neither on a calorie-restricted diet nor engaging in regular physical exercise and had only a marginally higher body mass index (1.4 kg/m^2); and the decline in glucose and insulin levels induced by acute exposure to cold observed only in the high-BAT subjects.

Such extreme physiologic heterogeneity in BAT volume and activated metabolism raises 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 (shivering threshold)? Elucidation of these issues would help us learn whether BAT can be "trained," 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 body mass index, suggests that these subjects with expanded BAT are less prone to becoming obese. The decline in glucose observed after exposure to cold only in the high-BAT subjects suggests that these individuals are more resistant to the stress induced by cold. Indeed, BAT-negative lean subjects display reduced epinephrine levels after exposure to cold when compared with BAT-positive subjects, despite a similar increase in energy expenditure (*11*). This finding could be interpreted as a higher sensitivity of thermogenesis to catecholamines and could be another mechanism that protects the high-BAT subjects from developing obesity. The possibility that BAT expansion would protect from development of diabetes might be related to this protection.

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Somewhat less impressive, from a clinical perspective, are the differences in basal glucose, insulin, and triglycerides between low and high BAT, as might be driven by the difference in body mass index. Also, the different changes in lipid profiles induced by such a short-term exposure to cold 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 in a study that casts novel perspectives on the application of a mature imaging method such as PET with ^{18}F-FDG. In this regard, accurate imaging quantification made possible by recent scientific and technologic advances can address the combined challenges of deriving robust imaging biomarkers for artificial intelligence applications and of capitalizing the full potential of PET systems with a long axial field of view. An exciting application for such new systems is the possibility of determining the kinetics of tracer biodistribution through different compartments of the body—given the possibility of recording quasidynamic 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 of this scenario (*13*).

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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