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Activated BAT and its Relationship to Adiposity and Metabolic Markers

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Background

- More than a third of U.S. adults are obese with a BMI ≥ 30 kg/m^2
- Imbalance of energy expenditure and energy intake plays a key role in obesity
- Activated brown adipose tissue (BAT) may increase energy expenditure and protect against the development of obesity
- Individuals with active BAT have a greater rise in energy expenditure after cold exposure and food intake compared to those without active BAT[1,2]
- Prior studies suggest BAT may improve insulin sensitivity, glucose homeostasis, modulate energy expenditure and decrease weight gain[3]
- Paracrine or endocrine actions of interleukin 6 (IL-6) and fibroblast growth factor 21 (FGF21) may contribute to favorable metabolic changes seen in the presence of active BAT[4]
- BAT activation is regulated by the sympathetic nervous system, which is activated by cold exposure and thyroid hormone and suppressed by fasting[5]

Objectives

- To explore the relationships between cold-activated BAT visualized on PET/CT, measures of adiposity and metabolic markers including fasting glucose, insulin, thyroid hormone, FGF21, IL-6, adiponectin and leptin levels in young healthy men
- We postulated that obese men would have less active BAT than lean men and that men with more active BAT would have a more favorable metabolic profile

Methods

- A post-hoc analysis was conducted using data from a study comparing PET/CT to MRI for imaging BAT (Deng et al, JMRI; 2018,47(4):936-47).
- 25 healthy men were included, ages 18-24 yrs, with BMI ranging 19.4 to 35.9 kg/m2
- Physical exam and fasting labs were performed during a screening visit, prior to cold exposure and imaging
- The Homeostatic Model Assessment 2 to estimate insulin resistance (HOMA2 IR) was calculated from fasting glucose and insulin levels
- Body composition was measured using dual energy X-ray absorptiometry (DXA)
- An individualized cooling protocol was utilized to activate BAT. Subjects were wrapped in a water-infused suit (CritiCool® System, Mennen Medical, Israel) and cooled to achieve non-shivering thermogenesis prior to imaging
- Measures of cold-activated BAT, including mean standardized uptake value (SUV_{mean}), maximum SUV (SUV_{max}),) BAT volume and total BAT activity were determined from PET/CT images
- Pearson and Spearman's rank correlations were used to relate measures of active BAT to adiposity and metabolic parameters

Methods (contd)

- Exclusion criteria:
  - HbA1c ≥ 7.0% or fasting plasma glucose > 150 mg/dL, use of diabetes medication
  - Presence of any medical condition or use of medication that affects energy metabolism or brown fat activity
  - Contraindications to MRI
  - Weight loss >2% in the last 2 months or current weight ≥ 3% below maximal body weight

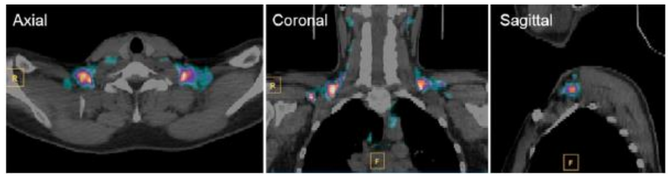

Figure 1. Metabolically active BAT from neck to axillary regions identified by FDG uptake on PET/CT images.

Table 1. Participant characteristics

Characteristics	N (%)
Race	
Asian	6 (24%)
African American	4 (16%)
White	15 (60%)
Ethnicity	
Hispanic/Latino	4 (16%)
Non Hispanic/Latino	21 (84%)
	Mean (SD)
Age (years)	21.1 (1.8)
Weight (kg)	80.5 (17.4)
BMI (kg/m^2)	25.2 (4.8)
Waist circumference (cm)	88.4 (15.2)
Body fat (%)	22.2 (9.4)
Glucose (mg/dL)	85.6 (6.0)
Insulin (µU/mL)	9.5 (5.6)
HbA1c (%)	5.3 (0.2)
HDL (mg/dL)	49.4 (14.8)
LDL (mg/dL)	86.9 (23.6)
Triglycerides (mg/dL)	74.9 (29.3)
Total cholesterol (mg/dL)	149.6 (28.6)
	Median (25th, 75th percentile)
FGF21 (pg/mL)	77.7 (43.2, 120.1)
Leptin (ng/mL)	2.9 (1.2, 7.3)

Results

Variable	Mean (SD)
SUV_{mean} (g/mL)	3.56 (1.93)
SUV_{max} (g/mL)	10.52 (7.31)
	Median (25th, 75th percentile)
Total BAT activity (KBq)	362.9 (93.7, 1045.2)
BAT volume (mL)	37.6 (10.6, 86.7)

Table 2. BAT characteristics from PET/CT images

Metabolic parameter	SUV_{mean} R (p value)[a]	SUV_{max} R (p value)[a]	BAT activity R (p-value) [b]	BAT volume R (p value)[b]
Glucose	-0.30 (0.14)	-0.38 (0.06)	**-0.40 (0.05)**	**-0.48 (0.048)**
FGF21	0.35 (0.09)	**0.51 (0.01)**	0.31 (0.14)	0.29 (0.17)
IL-6	0.34 (0.09)	0.37 (0.07)	-0.17 (0.42)	-0.11 (0.59)

Table 3. Correlations between metabolic parameters and PET/CT measures of active BAT. [a] Pearson correlation, [b] Spearman's rank correlation

- 21 participants (84%) had active BAT on PET/CT
- There were no differences in SUV_{mean}, SUV_{max} , BAT activity or volume by race or ethnicity
- Fasting glucose at screening was inversely related to the volume of activated BAT and the total BAT activity on subsequent PET/CT imaging
- A positive correlation was observed between FGF21 and SUV_{max}
- No other statistically significant relationships were noted between measures of active BAT and indicators of adiposity or glucose metabolism
- No significant correlations were noted between PET/CT measures of active BAT and ambient temperatures

Conclusions

- Data from this exploratory study suggest active BAT may be associated with lower fasting glucose in healthy young men
- Presence of BAT may also be correlated with FGF21, an insulin sensitizer, suggesting BAT may lower glucose levels via an FGF21 dependent pathway
- Further studies are needed to clarify potential mechanisms by which active BAT may impact glucose metabolism and the relationship between BAT and adiposity

References

1. Yoneshiro T, Aita S, Matsushita M, Kameya T, Nakada K, Kawai Y, et al. Brown adipose tissue, whole-body energy expenditure, and thermogenesis in healthy adult men. *Obesity*. 2011;19(1):13-6.
2. Hibi M, Oishi S, Matsushita M, Yoneshiro T, Yamaguchi T, Usui C, et al. Brown adipose tissue is involved in diet-induced thermogenesis and whole-body fat utilization in healthy humans. *International journal of obesity*. 2016;40(11):1655-61.
3. Chondronikola M, Volpi E, Borsheim E, Porter C, Annamalai P, Enerback S, et al. Brown adipose tissue improves whole-body glucose homeostasis and insulin sensitivity in humans. *Diabetes.* 2014;63(12):4089-99.
4. Stanford KI, Middelbeek RJ, Townsend KL, An D, Nygaard EB, Hitchcox KM, et al. Brown adipose tissue regulates glucose homeostasis and insulin sensitivity. *The Journal of clinical investigation*. 2013;123(1):215-23.
5. Hanssen MJ, Wierts R, Hoeks J, Gemmink A, Brans B, Mottaghy FM, et al. Glucose uptake in human brown adipose tissue is impaired upon fasting-induced insulin resistance. *Diabetologia*. 2015;58(3):586-95.