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Regional variation in skeletal muscle and adipose tissue FDG uptake using PET/CT and their relation to BMI

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Abstract

Rationale and Objectives—Skeletal muscle metabolism is a primary contributor to whole-body energy expenditure. Currently, methods to measure changes in skeletal muscle metabolism in vivo are limited. Our objectives were to characterize the regional variation in skeletal muscle and adipose tissue FDG uptake as a surrogate for glycolytic metabolism using FDG-PET/CT in healthy men, and to correlate these findings to body mass index (BMI).

Materials and Methods—Eighteen healthy men were enrolled and underwent FDG-PET/CT. Mean standardized uptake value (SUV_{mean}) of 14 skeletal muscles and 2 adipose tissue regions were measured and linear regression analysis was performed to identify metabolic predictors of BMI

Results—FDG-PET/CT reliably detected changes in skeletal muscle and adipose tissue depot metabolic activity based on location. The most metabolically active muscles were those used for posture and breathing, which have the highest percentage of reported type I muscle myofiber content. Visceral adipose tissue (VAT) tended to have higher FDG uptake than subcutaneous adipose tissue (SAT). The SUV_{mean} of VAT, pectoralis major, and gluteus maximus muscles accounted for 64% of the variance in BMI.

Conclusions—FDG-PET/CT can be used to quantify the regional variation in glucose metabolism of multiple skeletal muscle groups and adipose tissue depots.

Keywords

skeletal muscle; adipose tissue; metabolism; FDG-PET/CT

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Contributions: M.D.G. and D.A.T. conceived and designed the study. M.D.G. collected the data, performed the statistical analysis, and drafted the manuscript. D.A.T. assisted in statistical analysis, manuscript design, and manuscript preparation. A.A. and J.G-M. assisted in study design and manuscript preparation. All authors read and approved the final manuscript.

Introduction

Body mass is maintained by balancing changes in energy intake with energy expenditure. Skeletal muscle is a primary contributor to energy expenditure because of the substantial amount of energy used to maintain posture and mediate locomotion. For example, skeletal muscle can account for up to 90% of the whole body energy usage during physical activity (1). Skeletal muscle generates energy to power muscle contraction mostly via oxidation of glucose. Slow twitch (type I) muscle fibers are rich in mitochondria, rely on oxidative metabolism, and are resistant to fatigue; whereas, fast twitch (type II) fibers more readily fatigue and contain more glycolytic enzymes.

Skeletal muscle metabolism is difficult to measure *in vivo*. Estimates can be made using blood gas exchange, indirect calorimetry, or serum metabolites such as glucose and lactate but direct nutrient uptake is not routinely measured. Muscle biopsies can be done; however, these biopsies are invasive and only one skeletal muscle is usually assessed (most commonly the vastus lateralis).

Positron emission tomography (PET) using ^{18}F -2-fluorodeoxyglucose (FDG) can non-invasively quantify the metabolic activity of skeletal muscle, adipose tissue, and other organs of the body such as the liver, brain, and bowel (2–5). FDG, like glucose, is transported into cells but cannot be further processed down the glycolytic pathway (6, 7). In skeletal muscle, the amount of glucose uptake suggests energy consumption during aerobic activity (8). Factors that influence the glucose uptake of skeletal muscle include muscle fiber composition, muscle activity, plasma glucose levels, and insulin concentrations (9–11). Therefore, the standardized uptake value (SUV) derived from FDG-PET imaging is proportional to the metabolic activity of skeletal muscle and correlates well with whole-body measurements of energy expenditure (12–15).

In this study, we use FDG-PET/computed tomography (CT) to characterize the regional variation in skeletal muscle and adipose tissue activity in healthy men. Furthermore, we correlate these findings to clinical data and develop a model for predicting body mass index (BMI).

Materials and Methods

Study Sample

Twenty healthy men were previously recruited in a non-blinded prospective pilot cohort study between January 2010 and August 2011 to assess the metabolic effects of chronic tobacco use (16). Data from 18 participants who permitted use of their data for other future studies were used in our current study to quantify regional differences in skeletal muscle and adipose tissue metabolism on FDG-PET/CT. The median age was 46 (range 30–50), the median height was 175 cm (range 161–188), the median weight was 79.6 kg (range 63.4–103.4kg), the median BMI was 25.3 kg/m² (22.8–30.7), the median fasting plasma glucose was 98 mg/dL (range 62–109), and the median serum testosterone concentration was 457 ng/dL (range 290–1252).

FDG-PET/CT Image Acquisition

Subjects fasted for a minimum of 6 hours prior to PET/CT imaging, and were confirmed to have non-fasting fingerstick blood glucose levels of ≤ 130 mg/dL prior to FDG administration. A 16 detector-row LYSO whole-body PET/CT scanner with time-of-flight capabilities (Gemini TF, Philips Healthcare, Bothell, WA) was used to acquire whole-body FDG-PET/CT images. Approximately 15 mCi (range 14.41–16.49 mCi) of FDG were administered intravenously to subjects during quiet resting in a chair. Subsequently, 3-D PET emission data were acquired from the skull vertex to the toes in supine position beginning 60 ± 15 minutes later for 3 minutes per bed position. A list-mode maximum-likelihood expectation-maximization algorithm was utilized to perform image reconstruction. The system model included time-of-flight, normalization, randoms, attenuation, and scatter corrections. Attenuation correction of PET images was done utilizing rescaled low-dose CT. PET and CT images were reconstructed at 5 mm slice thickness.

FDG-PET/CT Image Analysis

After qualitative review of PET and CT images, mean standardized uptake value (SUV_{mean}) measurements were obtained from 2-D or 3-D regions of interest (ROIs) manually placed on transverse PET slices passing through 14 skeletal muscle and 2 adipose tissue regions to quantify their metabolic activity using a dedicated PET/CT analysis workstation (Extended Brilliance Workstation, Philips Healthcare, Bothell, WA). In particular, 3-D spherical ROIs were placed bilaterally within muscles on transverse slices passing through the following structures using low-dose CT images (Figure 1) for anatomic guidance: (1) the sternocleidomastoid (SM) muscles at the levels of the hyoid bone and vocal cords, (2) the pectoralis major (PM) muscles at the levels of the superior manubrium and the sternomanubrial junction, (3) the intercostal (Int) muscles between ribs 1&2, 6&7, and 10&11, (4) the serratus anterior (SA) muscles anterolateral to rib 5, (5) the centers of the erector spinae (ES) muscle bellies at the levels of the superior manubrium, inferior sternum, and L3 vertebra, (6) the mid-belly of the psoas (PS) muscles at the L3 vertebral level, (7&8) the rectus abdominis (RA) and internal oblique (IO) muscles, respectively, at the levels of the L3 vertebra and superior iliac crest, (9) the gluteus maximus (GM) muscles at the level of the iliac crest, (10–12) the rectus femoris (RF), adductor magnus (AM), and vastus lateralis (VL) muscles, respectively, at the level of the mid-femur, and (13&14) the soleus (S) and medial gastrocnemius (MG) muscles at the level of the proximal tibia. ROIs were kept similar in size and the reported SUV_{mean} values are the average of the bilateral measurements. These muscles were chosen as representatives of axial and limb muscles of varying reported type I fiber content.

For adipose tissue measurements, 2-D circular ROIs of maximum possible diameter were placed bilaterally in one plane within: (1) the anterior abdominal subcutaneous adipose tissue (SAT) at the level of the umbilicus, and (2) the retroperitoneal visceral adipose tissue (VAT) at a level inferior to the kidneys and posterior to the bowel (Figure 1) as previously described (5). For each adipose tissue depot, SUV_{mean} measurements from left and right were averaged in each subject.

Data Analysis

Tabulations of averages, standard deviations, and ranges of SUV_{mean} based on subject and skeletal muscle/AT location were performed. SUV_{mean} was recorded and averaged across all subjects for each individual muscle group and compared for statistically significant differences. SUV_{mean} measurements were correlated to the composition of type 1 muscle fibers using data from Johnson et al.(17).

Statistical analysis including mean, standard deviations, range, and student's t-test were performed with Microsoft Office Excel (Microsoft, Redmond, WA) and figures were prepared with Prism (GraphPad Software, Inc., La Jolla, CA) where a p value of < 0.05 was considered to be statistically significant. Univariate correlation and multivariate linear regression were performed with SPSS version 17.0 (SPSS Inc., Chicago, IL). Pearson r correlation values, two-tailed p values, and unstandardized (β) and standardized (b) regression coefficients were calculated, and statistical significance was considered to be present for p values < 0.05 .

This study was conducted following approval from the Institutional Review Board at the Hospital of the University of Pennsylvania along with a Health Insurance Portability and Accountability Act (HIPAA) waiver.

Results

Table 1 reports the variation in SUV_{mean} for the 14 skeletal muscle groups and 2 adipose tissue depots measured. Using the intercostal muscle group as an arbitrary reference, the following muscle groups had significantly lower SUV_{mean} measurements: SA ($p = 0.029$), GM ($p = 0.005$), IO ($p < 0.001$), MG ($p = 0.002$), PS ($p < 0.001$), PM ($p < 0.001$), RF ($p < 0.001$), AM ($p < 0.001$), VL ($p < 0.001$), and RA ($p < 0.001$). VAT tended to have higher SUV_{mean} than SAT ($p = 0.058$).

To determine if skeletal muscle fiber distribution contributed to the observed variation in glucose uptake, we correlated our measured SUV_{mean} with previously published human skeletal muscle fiber composition data (17). We observed a statistically significant positive correlation ($r = 0.4617$, $p < 0.0001$) between SUV_{mean} and the content of type I, oxidative, fibers (Figure 2).

We assessed whether or not the SUV_{mean} measurements derived from FDG-PET/CT could predict BMI. Using univariate correlation analysis, BMI was significantly correlated to the SUV_{mean} of the PS, PM, GM, and VAT (Table 2). PS was positively correlated with PM ($r = 0.490$, $p = 0.039$) and GM ($r = 0.518$, $p = 0.027$) and contributed minimally to the linear regression model ($\beta = -0.088$), and so it was excluded in the multivariate linear regression model resulting in three predictor variables: PM, GM, and VAT. The VAT SUV_{mean} measurements were log transformed prior to analysis to reduce skewness. Descriptive statistics and regression coefficients are shown in Table 2. Each of the predictor variables had a significant ($p < 0.05$) zero-order correlation with BMI, but only the PM had significant ($p < 0.01$) partial effect in the full model. The three predictor model (PM, GM, VAT) was able to account for 64% of the variance in BMI ($p = 0.002$).

Discussion

In this study, we report that significant regional metabolic differences can be non-invasively detected and quantified between different muscle groups at rest using FDG-PET/CT. We found the highest uptake of FDG in muscles used for posture (SM, ES, S) and breathing (Int). Glucose and FDG uptake is influenced by muscle fiber composition and muscle activity level (9–11). Consistent with these effectors, our results show a significant correlation between SUV_{mean} and the composition of type I fibers (Figure 2). This finding is biologically consistent as vastus lateralis muscle biopsies from sedentary subjects showed that insulin sensitivity and maximal oxygen uptake correlated with the proportion of type I fibers (18) which is likely due to the type I muscle fiber having a greater number of glucose transporters, GLUT4 (19–21) and a higher number of surface membrane receptors for insulin (22, 23).

Fiber composition accounted for ~20% of the variation ($r = 0.4617$) in muscle FDG uptake and, with exception of the soleus muscles, the variance in fiber composition across all the muscle groups was less than 18% (17). Therefore, we speculate that the differences in muscle FDG uptake were partially the result of contraction-related glucose uptake, as subjects initially walked to the nuclear medicine department prior to receiving intravenous FDG and then, per protocol, walked to the rest room to void following FDG administration. These movements can stimulate FDG uptake into muscles used for posture (e.g. SM, ES, S), breathing (e.g. Int), and walking (8, 24, 25). Concurrently, the lowest amount of FDG uptake was measured in the muscles of the anterior thigh (RF, AM, VL) and anterior abdominal wall (RA), which have relatively low type I fiber content and are not typically used for walking in young patients (8, 17, 26–28).

Our findings agree with other published reports that VAT is more metabolically active than SAT (5, 29–31). This result could stem from the fact that VAT is more cellular, more vascular, and more heavily innervated than SAT (32). In addition, human VAT may contain more beige adipose cells that generate heat by consuming large amounts of glucose like brown adipocytes when activated (33). These results would suggest that a more metabolically active VAT is protective against weight gain. Consistent with this theory, the metabolic activity of VAT as measured by FDG-PET/CT in this study was negatively associated with BMI. This result agrees with Oliveira et al. who reported that VAT FDG uptake in obese subjects was significantly lower than that in metabolically healthy lean subjects, whereas SAT FDG uptake did not differ between these groups (34).

In this study, we correlated skeletal muscle activity to BMI in an attempt to relate muscle metabolism to the regulation of whole-body mass. In combination with VAT, we identified two skeletal muscle groups (PM, GM) whose activity accounted for 64% of the variance in BMI (Table 2). In accordance with our findings, the GM was recently shown to be a highly reproducible location for measuring basal skeletal muscle FDG uptake with high intraclass correlation (0.88) and low within-subject variation (2.2%) (35). It is unclear why only the PM and GM correlated significantly with BMI, but we speculate that these sites are the most reliable measurements of basal muscle activity due to their relatively large volume and the lack of muscle activity at rest. For example, it is unlikely that the PM, and to a lesser extent

the GM, were actively contracting during the FDG uptake period prior to or during PET/CT image acquisition. Therefore, the FDG uptake in these groups was more likely representative of true basal muscle glucose uptake levels, which is positively correlated to BMI.

Our findings suggest that (a) enhanced glycolytic activity in large muscle groups contributes to weight gain, or (b) larger body mass requires more glycolytic muscle activity. Although the cause and effect relationship cannot be determined in a study of this nature, we believe this association is an insightful one which agrees with the current literature. Simoneau and Kelley report a positive correlation between BMI and skeletal muscle glycolytic enzyme markers (36). Additionally, weight loss (a decrease in BMI) is associated with a decrease in skeletal muscle glycolytic enzymes (37, 38). Both of these studies were done via biopsies of the vastus lateralis muscle whereas our study replicates their results through non-invasive molecular imaging.

Our study has several limitations. First, SUV is a semiquantitative metric that depends on patient preparation, scanning procedure, image reconstruction, and image analysis procedures. In this study, conditions were standardized as to limit patient to patient variation. Our the small sample size and lack of random selection of subjects could potentially lead to a selection bias and type II error in our analysis. Recent data, however, suggest that studies with as little as 6–8 subjects could detect significant changes in skeletal muscle SUV between groups (35). Additionally, our study only enrolled men between the ages of 30 and 50 years of age. As a result, we did not study the effects of gender or age upon muscle or adipose tissue metabolism. In this study, we did not inquire about use of medications, activity level, and demographic factors that could have influenced our findings. Although no subject had a reported history of diabetes mellitus, the insulin or hemoglobin A1c levels in the study cohort were not measured. However, non-fasting glucose levels did not exceed 140mg/dL. For adipose tissue measurements, the ROIs varied in size from subject to subject as they were of maximal diameter to cover the largest area of adipose tissue possible. However, this method was consistent between groups and intended to limit sampling error. Finally, we were limited by access to an independent cohort for validation of our data. Despite these limitations, we have demonstrated detectable, quantifiable, and biologically plausible differences in regional skeletal muscle and adipose tissue metabolism on FDG-PET/CT. Given these preliminary data, it may be useful to conduct future prospective longitudinal studies to study the changes in muscle metabolism that occur in association with obesity or weight loss where medication data, amounts of physical activity, and other demographic and serologic information is available.

Conclusions

In this study, we report quantitative data obtained from whole-body PET/CT studies regarding the regional variation in the metabolism of multiple skeletal muscle groups and adipose tissue depots. To our knowledge, we are the first to report an association of FDG uptake in skeletal muscle with BMI. We believe that the methodologies and data presented here will serve as a useful template for those interested in conducting future prospective research on skeletal muscle metabolism and obesity.

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Abbreviations List

PET	Positron emission tomography
FDG	^{18}F -2-fluorodeoxyglucose
CT	computed tomography
BMI	body mass index
SUV mean	mean standardized uptake value
ROIs	regions of interest
AT	adipose tissue
VAT	Visceral adipose tissue
SAT	Subcutaneous adipose tissue
VL	vastus lateralis
SM	sternocleidomastoid
PM	pectoralis major
Int	intercostal
SA	serratus anterior
ES	erector spinae
PS	psoas
RA	rectus abdominis
IO	nternal oblique
GM	gluteus maximus
RF	rectus femoris
AM	adductor magnus
VL	vastus lateralis
S	soleus
MG	medial gastrocnemius

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Figure 1.

Representative axial low-dose CT images from PET/CT showing specific muscles and adipose tissues that were assessed in this study. Sternocleidomastoid (SM), pectoralis major (PM), intercostal (Int), serratus anterior (SA), erector spinae (ES), psoas (PS), rectus abdominis (RA), internal oblique (IO), gluteus maximus (GM), rectus femoris (RF), adductor magnus (AM), vastus lateralis (VL), soleus (S), and medial gastrocnemius (MG) muscles as well as anterior abdominal subcutaneous adipose tissue (SAT) and retroperitoneal visceral adipose tissue (VAT) are depicted.

Figure 2.

Skeletal muscle metabolism in terms of mean standardized uptake value (SUV_{mean}) measured on FDG-PET/CT versus skeletal muscle fiber composition reported as the percentage of type I fibers. Rectus femoris (RF), vastus lateralis (VL), medial gastrocnemius (MG), rectus abdominis (RA), gluteus maximus (GM), erector spinae (ES), and soleus (S) muscles are displayed since fiber composition data was freely available. Pearson r correlation value and two-tailed p value are presented on the graph.

Table 1

Variation in Skeletal Muscle and Adipose Mean Standardized Uptake Value (SUV_{mean}).

	SUV_{mean}	p value
Int	0.68 ± 0.02	—
SM	0.67 ± 0.02	0.824
ES	0.67 ± 0.02	0.824
S	0.66 ± 0.03	0.606
SA	0.63 ± 0.02	0.029
GM	0.59 ± 0.02	0.005
IO	0.57 ± 0.02	0.000
MG	0.57 ± 0.03	0.002
PS	0.56 ± 0.02	0.000
PM	0.51 ± 0.02	0.000
RF	0.51 ± 0.02	0.000
AM	0.49 ± 0.02	0.000
VL	0.48 ± 0.02	0.000
RA	0.46 ± 0.02	0.000
SAT	0.24 ± 0.03	—
VAT	0.30 ± 0.02	0.058

Data are mean standardized uptake value (SUV_{mean}) $\pm$ SEM for intercostal (Int), sternocleidomastoid (SM), erector spinae (ES), soleus (S), serratus anterior (SA), gluteus maximus (GM), internal oblique (IO), medial gastrocnemius (MG), psoas (PS), pectoralis major (PM), rectus femoris (RF), adductor magnus (AM), vastus lateralis (VL), and rectus abdominis (RA) muscles, as well as for subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). Comparisons made by student's t-test using Int as a reference for muscles and SAT as a reference for adipose tissue depots.

Table 2

Relationship of body mass index (BMI) to FDG-PET tissue metabolic activity.

Variable	Pearson r correlation			β	b
	PM	GM	VAT		
PM	0.149	-0.214	0.596**	15.198**	0.472
GM		-0.331	0.517*	8.922	0.332
VAT			-0.556*	-7.749	-0.344
Intercept = 9.065					
$R^2 = 0.64^{**}$					

Pearson correlation values from a univariate analysis among independent and dependent variables (left) and the results of multivariate linear regression (right) for BMI based on independent variables: pectoralis major (PM), gluteus maximus (GM), and visceral adipose tissue (VAT). Pearson r correlation values, unstandardized (β) regression coefficients, and standardized (b) regression coefficients are presented. Two-tailed p values were

* p < 0.05 or

** p < 0.01.