HHS Public Access

Author manuscript

Obesity (Silver Spring). Author manuscript; available in PMC 2016 January 31.

Published in final edited form as:

Obesity (Silver Spring). 2015 February ; 23(2): 286–289. doi:10.1002/oby.20957.

Visceral and subcutaneous adipose tissue FDG uptake by PET/CT in metabolically healthy obese subjects

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Abstract

Objective—To measure FDG uptake in visceral (VAT) and subcutaneous (SAT) adipose tissue of metabolically healthy obese (MHO) and metabolically abnormal obese (MAO) compared to metabolically healthy lean (MHL) subjects. Given that MHO have increased metabolic risk, we hypothesized that MHO and MAO display similar VAT FDG uptake.

Design and Methods—We examined 18F-FDG-PET/CT studies of 141 adults (n=60 MHL, n=20 MHO, n=61 MAO) to determine VAT and SAT volumes and FDG uptake. Data on CVD risk factors (BMI, abdominal circumference, blood pressure, serum lipids, and fasting plasma glucose) were collected.

Results—MHO and MAO had similar VAT FDG uptake (P=0.74), both significantly lower than MHL (P<0.01) independent of age and gender. SAT FDG uptake was similar across all groups (P>0.2) independent of age and gender. In all groups, VAT FDG uptake was higher than SAT (P<0.0001). In separate sub-analyses of obese groups, VAT FDG uptake was more broadly negatively associated with whole-body adiposity than SAT FDG uptake, and FDG uptake in abdominal adipose depots was positively associated with liver density (P<0.05).

Conclusions—FDG uptake in VAT of MHO is similar to MAO and lower than MHL, suggesting these subjects may present similar VAT dysfunction.

Keywords

Obesity; adipose tissue; metabolic syndrome; intra-abdominal fat; 18F-FDG-PET/CT

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The authors have no competing interests.

Introduction

A subset of apparently healthy obese subjects – known as metabolically healthy obese (MHO) – does not display the metabolic abnormalities associated with obesity (1, 2). MHO have high levels of insulin sensitivity, low prevalence of hypertension, and a favorable lipid and inflammatory profile (3–5). MHO account for 9-41% of the obese population depending on the definition of metabolic health (6). Despite this favorable metabolic profile, MHO have elevated mortality and cardiovascular disease (CVD) risk compared to metabolically healthy lean (MHL) subjects and similar mortality risk compared to metabolically abnormal obese (MAO) subjects (6, 7). Importantly, limited information is available on potentially distinct adipose tissue phenotypes across these sub-groups.

Increased visceral adipose tissue (VAT) portends higher cardiometabolic risk compared to expansion of subcutaneous adipose tissue (SAT) (8). Volumes of abdominal fat depots and *in vivo* adipose tissue glucose uptake can be measured using 18-fluorodeoxy-glucose positron emission tomography CT (FDG-PET/CT). Prior studies in fasting subjects have shown higher VAT FDG uptake compared to SAT (9), and markedly decreased VAT and SAT glucose uptake during insulin stimulation in insulin-resistant obese subjects compared to nonobese subjects (10).

Our goal was to measure FDG uptake in VAT and SAT of MHO and MAO, with MHL subjects as a reference. Given that MHO have increased cardiovascular risk despite a favorable metabolic profile, we hypothesized MHO and MAO subjects would display similar FDG uptake in abdominal adipose tissue.

Design and Methods

Study subjects and protocol

This study was approved by the Institutional Review Board of Partners HealthCare, Inc. with exemption for individual informed consent. We retrospectively identified consecutive FDG- PET/CT examinations of adults (age≥18 years) obtained for clinical purposes (e.g., cancer follow-up and benign etiologies) between August 2009 and October 2013. Inclusion criteria were: fasting glucose preceding FDG-PET/CT; blood pressure and serum lipids measured within 12 months of FDG-PET/CT; and no malignancy at imaging. We excluded subjects with: abdominal pathology, radiation therapy or surgery; and with insufficient data to determine metabolic syndrome by the National Cholesterol Education Program (NCEP ATP III) criteria (11). Systolic (SBP) and diastolic blood pressure (DBP), triglycerides, total, LDL-, and HDL- cholesterol within 12 months of imaging, and fasting glucose were obtained from medical records. Waist circumference was measured using CT as described below. Metabolic syndrome was confirmed by three or more NCEP ATP III criteria (11). Those without metabolic syndrome were considered metabolically healthy. Obesity was defined by BMI (in kg/m^2) cut-offs (12), with lean considered <28 (males) and <24 (females), and obese considered ≥28 (males) and ≥24 (females).

Body composition, VAT and SAT measures by FDG-PET/CT

FDG-PET/CT was obtained after a 6-hour fast on an integrated scanner (Siemens, Erlangen, Germany). ^{18}F-FDG was injected only if blood glucose≤250mg/dl with a BMI-based dose (BMI<30, 15mCi dose; 30.1≤BMI≤44, 20mCi; BMI>44.1, 25mCi). 3-dimensional PET was acquired from skull base to mid-thigh, with 6-8 bed positions lasting 3-7 min each, and reconstructed to 2.4 mm slice thickness. Attenuation correction CT was obtained in mid-expiration without intravenous contrast using voltage/current of 120kVp/11mAs; 5mm slice; 18mm feed; 0.5s time; 20cm field-of-view.

VAT and SAT volumes (cm^3) were calculated from L1 through L5 using semi-automated tracings (TeraRecon, San Mateo, CA). Whole-body volumes of fat free tissue (FFT, cm^3), fat (cm^3), and %-fat were calculated by multiplying fat areas by slice thickness (5 mm) from slices through orbits, humeral heads, L4, femoral heads, and proximal thighs. PET/CT images were fused using OsiriX software (http://www.osirix-viewer.com) and FDG uptake was measured in regions of interest (ROI) within largest cross-section of omental VAT, posterolateral SAT and psoas muscle. ROIs yielded mean standardized uptake values (SUV), defined as activity per milliliter of tissue divided by injected dose in megabecquerels per gram of body weight.

Statistical analyses

Multiple pair comparisons between groups were performed with and without adjustment for either age and gender, fasting glucose, or fasting glucose and liver density using the Tukey-Kramer test. Associations were examined using Spearman's correlation. The Wilcoxon test compared SUV of VAT versus SAT. Multivariate modeling adjusted for age and gender examined correlations between VAT and SAT FDG uptake with body composition. Analyses were performed using JMP 11 (SAS, Cary, NC). $P<0.05$ indicated statistical significance.

Results

We identified 191 subjects of which 45 were excluded due to prior abdominal surgery and 5 due to abdominal pathology. The final cohort comprised 141 subjects, with characteristics detailed in Table 1. The mean delay between FDG injection and imaging was 65±16 minutes and similar between groups ($P>0.1$).

MHO and MAO had similar age, gender, BMI, blood pressure, total- and LDL- cholesterol. MAO subjects had higher fasting glucose and serum triglycerides, and lower HDL-cholesterol (all $P<0.05$). MAO had higher abdominal circumference ($P=0.01$) and VAT volume ($P<0.0001$) compared to MHO, despite similar BMI and SAT volume ($P=0.56$). Whole-body fat and %fat were higher ($P<0.0001$) and similar ($P>0.3$) in MHO and MAO compared to MHL.

VAT FDG uptake in MHO and MAO was similar ($P=0.74$) but significantly lower than MHL ($P<0.01$; $P<0.01$ after adjustments). SAT FDG uptake was similar across all groups ($P>0.2$; $P>0.1$ after adjustments) (Figure 1). In all groups, FDG uptake in VAT was higher than SAT ($P<0.0001$). Liver density was similar in MHL and MHO ($P=0.66$), both higher

than MAO ($P<0.05$), suggesting increased fat content in MAO. Muscle FDG uptake was similar in MHO and MAO ($P=0.38$), with both higher compared to MHL ($P<0.02$).

VAT FDG uptake was more broadly negatively associated with whole-body adiposity across subgroups, with most associations being independent of age and gender (Table 2). In all subjects, VAT and SAT FDG uptake was positively associated with liver density (Table 2), and VAT ($r=-0.47$) and SAT ($r=-0.30$) volume were negatively associated with liver density ($P<0.001$).

Discussion

MHO and MAO had similar VAT FDG uptake that was lower compared to MHL, suggesting MHO may present abnormal adipose glucose handling despite a favorable metabolic profile. Our data also suggest reduced VAT FDG uptake – possibly due to insulin-resistant adipocytes – may outweigh uptake increase from higher macrophage burden in obesity (9, 10). Lower VAT FDG activity in MHO and MAO could also reflect abnormal perfusion, vascular function and capillary density, which are impaired in obesity (13, 14). Although the mechanism of lower VAT FDG activity cannot be determined in our cohort, abnormal glucose uptake may occur in MHO and MAO irrespective of metabolic syndrome being present.

In insulin-stimulated obese versus nonobese subjects, Virtanen et al. (10) showed marked decrease in VAT, SAT, muscle, and whole-body glucose uptake. In contrast, Christen et al. (9) found similar VAT and SAT FDG uptake in fasting lean versus obese subjects. In our study, although VAT FDG uptake was lower in obese, SAT FDG uptake was similar across subgroups likely from lower glucose uptake during fasting. Regarding muscle FDG uptake, SUV were higher in MHO and MAO independent of fasting glucose. Interestingly, although muscle (but not adipose tissue) SUV may mildly increase during hyperglycemia (15), MHO were normoglycemic similar to MHL. While our findings suggest fasting MHO may have altered VAT and muscle glucose uptake, further examination under steady-state conditions with dynamic PET are warranted to precisely determine glucose flux.

As previously shown, VAT volume was higher in MAO followed by MHO (16–18), and both groups had similar and elevated SAT and whole-body %fat compared to MHL (18). Although SAT metabolic activity was lower than VAT as in prior studies (9, 10), the more extensive SAT and whole-body fat depots have a greater impact in whole-body glucose metabolism (10) with overall adipose tissue mass itself playing a more important role than metabolic activity alone. Nonetheless, VAT FDG uptake in our fasting cohort was more strongly associated with whole-body adiposity supporting a link between generalized adipose expansion and VAT dysfunction. An interesting finding was the positive association between VAT and SAT FDG uptake with liver density in all subjects, suggesting a connection between lower adipose metabolic activity with liver fat accumulation. As expected, VAT volume more strongly correlated with lower liver density (i.e., more liver fat). However, MHL and MHO had similar liver density while MAO had highest liver fat. Although concordant with a prior study (18), this contrasts with reported higher prevalence of fatty liver in MHO that partially explained increased risk of type 2 diabetes (19). Our

results support that MHO may be heterogeneous regarding body composition and insulin sensitivity, with ectopic fat accumulation and lack of physical activity having potential roles in increasing risk of diabetes, CVD and mortality (6, 19, 20).

Limitations of this study include its retrospective design and lack of fasting insulin, indices of physical activity, inflammation and aerobic fitness. Our FDG uptake measurements were not performed under steady-state conditions, which are best suited to examine glucose tissue dynamics. Strengths of our study include a large number of subjects examined at a single center and the ability to compare obese subgroups to MHL subjects, with imaging obtained at similar timeframes after FDG administration.

In conclusion, MHO and MAO had similar VAT FDG uptake that was lower compared to MHL, suggesting MHO may present VAT dysfunction that warrants further characterization.

ACKNOWLEGDGEMENTS

Funding: Supported in part by NIH/NIDDK P30DK040561 Pilot and Feasibility Grant, Nutrition and Obesity Research Center at Harvard

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What is already known about this subject?

- Despite a favorable metabolic profile, metabolically healthy obese (MHO) subjects have increased cardiovascular and mortality risk compared to metabolically healthy lean (MHL) subjects.
- Visceral adipose tissue (VAT) has higher metabolic activity than subcutaneous adipose tissue (SAT) in lean and obese subjects, as measured by glucose uptake on 18F-FDG- PET/CT.
- Recent studies show that MHO subjects have differences in body composition, such as high prevalence of fatty liver and lower VAT compared to metabolically abnormal obese subjects (MAO), but there is limited information on potentially distinct adipose tissue phenotypes across these sub-groups.

What does this study add?

- Despite a more favorable metabolic profile, VAT FDG uptake in MHO was similar to MAO, and both groups had lower VAT FDG uptake compared to MHL subjects independent of age and gender.
- SAT FDG uptake did not differ between MHL, MHO and MAO subjects independent of age and gender.
- VAT FDG uptake correlated negatively with adiposity and positively with liver density.

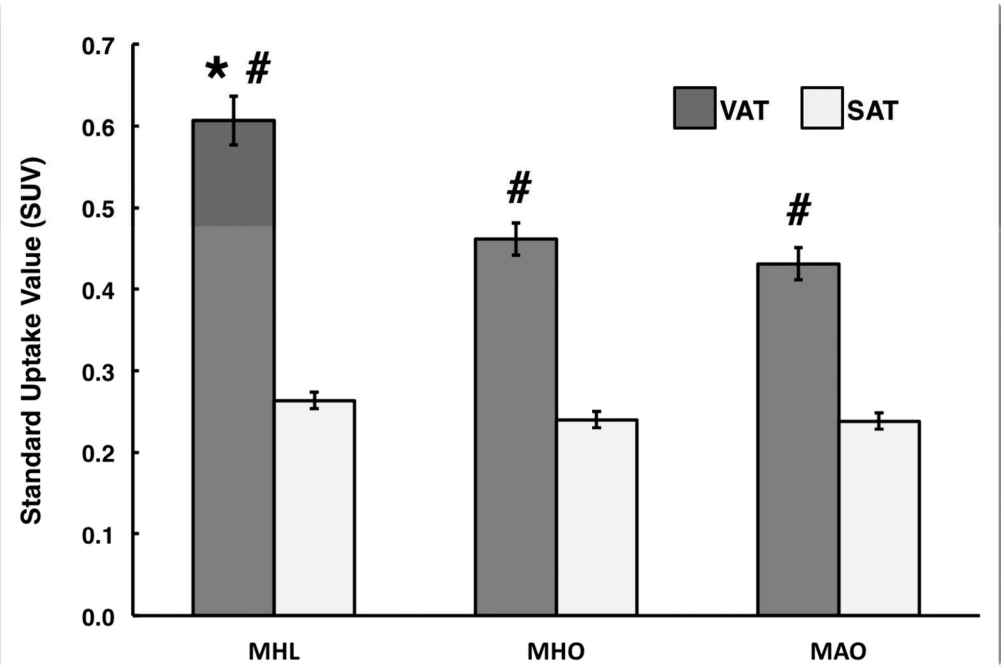

Figure 1.

FDG uptake in VAT (dark bars) compared to SAT (light bars) in MHL, MHO and MAO subjects. Data are shown as mean ± SEM. * $P<0.01$ when comparing VAT MHL to MHO and MHL to MAO. # $P<0.0001$ when comparing VAT SUV to SAT SUV within each group.

Obesity (Silver Spring). Author manuscript; available in PMC 2016 January 31.

Table 1

Clinical characteristics of study subjects.

	MHL	MHO	*P*-value MHL vs. MHO	MAO	*P*-value MHL vs. MAO	*P*-value MHO vs. MAO
Age (years)	49.6±18.9 (60)	50.1±14.3 (20)	0.99	57.5±15.5 (61)	0.03	0.20
Gender (female:male)	29F:31M	14F:6M	0.12	29F:32M	1.00	0.12
BMI (kg/m^2)	23.0±2.6 (60)	30.7±5.2 (20)	<.0001	32.1±4.5 (61)	<.0001	0.34
Abdominal circumf. (cm)	83.8±8.7 (60)	98.7±9.9 (20)	<.0001	106.2±10.7 (61)	<.0001	0.01
VAT volume (cm^3)	185.5±135.4 (60)	289.1±131.5 (20)	0.03	497.2±182.0 (61)	<.0001	<.0001
SAT volume (cm^3)	315.0±140.3 (60)	660.6±220.9 (20)	<.0001	713.8±239.9 (61)	<.0001	0.56
VAT FDG uptake	0.61±0.20 (60)	0.46±0.11 (20)	<0.002*	0.43±0.13 (61)	<.0001*	0.74§
SAT FDG uptake	0.26±0.10 (60)	0.24±0.06 (20)	0.51§	0.24±0.07 (61)	0.22§	1.00§
Muscle FDG uptake	0.70±0.18 (60)	0.87±0.29 (20)	0.02	0.95±0.27 (61)	<.0001	0.38
Whole-body fat (cm^3)	409.0±122.7 (60)	717.7±180.6 (20)	<.0001	784.6±220.6 (61)	<.0001	0.32
Whole-body FFT (cm^3)	436.3±72.9 (60)	460.7±132.0 (20)	0.59	510.6±103.0 (61)	<.0001	0.11
Whole-body %fat	48±9% (60)	61±8% (20)	<.0001	60±8% (61)	<.0001	0.93
Liver density (HU)	54.9±8.0 (57)	52.3±13.3 (19)	0.66	45.4±13.8 (61)	<.0001	0.06
Fasting glucose (mg/dL)	102.3±13 (60)	103.4±15.3 (20)	0.98	124.3±34.3 (61)	<.0001	0.004
Total cholesterol (mg/dL)	205.3±42.1 (28)	211.6±63.5 (17)	0.93	181.9±58.2 (36)	0.21	0.16
HDL-cholesterol (mg/dL)	62.8±21.3 (28)	57.5±11.2 (17)	0.61	42.5±17.8 (37)	<0.0001	0.02
LDL-cholesterol (mg/dL)	121.3±36.2 (27)	128.8±54.5 (16)	0.86	97.6±47.0 (34)	0.11	0.07
Triglycerides (mg/dL)	100.8±61.4 (31)	116.8±60.7 (17)	0.86	208.8±137.5 (37)	0.0001	0.008
SBP (mmHg)	117.6±11.3 (58)	125.5±17.3 (20)	0.15	127.7±19.5 (60)	0.003	0.87
DBP (mmHg)	72.4±7.5 (58)	72.6±9 (20)	1.0	75.8±9.6 (60)	0.09	0.31

Values are mean ± standard deviation (*n* subjects).

MHL: metabolically healthy lean; MHO: metabolically healthy obese; MAO: metabolically abnormal obese.

FFT: fat free tissue; HU: Hounsfield units; SUV: standard uptake value.

*P<0.01 after adjustment for either age + gender; fasting glucose; or fasting glucose + liver density.

§P>0.1 after adjustment for either age + gender; fasting glucose; or fasting glucose + liver density.

Obesity (Silver Spring). Author manuscript; available in PMC 2016 January 31.

Table 2

Correlations between FDG uptake of VAT and SAT with body composition parameters.

	VAT FDG uptake (SUV)				SAT FDG uptake (SUV)			
	MHL	**MHO**	**MAO**	**All**	**MHL**	**MHO**	**MAO**	**All**
***n* subjects**	***60***	***20***	***61***	***141***	***60***	***20***	***61***	***141***
BMI (kg/m^2)	-0.39^{c}	-0.64^{c*}	-0.27^{c}	-0.53^{a*}	-0.45^{b*}	-	-	-0.27^{c*}
Abdominal circumf. (cm)	-0.41^{c*}	-0.58^{c*}	-0.27^{c}	-0.53^{a*}	-0.57^{a*}	-	-	-0.28^{b*}
VAT volume (cm^3)	-0.46^{b*}	-0.76^{b*}	-0.46^{b*}	-0.60^{a*}	-0.41^{c*}	-	-0.36^{c}	-0.31^{b*}
SAT volume (cm^3)	-0.34^{c*}	-0.71^{c**}	-	-0.46^{a*}	-0.68^{a*}	-	-	-0.25^{c*}
Whole-body fat (cm^3)	-0.39^{c*}	-	-0.27^{c*}	-0.50^{a*}	-0.58^{a*}	-	-	-0.22^{c*}
Whole-body FFT (cm^3)	-	-0.55^{c}	-	-0.31^{b*}	-	-0.45^{c}	-0.38^{c}	-0.27^{c}
Whole-body %fat	-0.27^{c*}	-	-	-0.32^{b*}	-0.44^{b*}	-	-	-0.53^{a**}
Liver density (HU)	-	-	0.26^{c*}	0.26^{c*}	-	-	-	0.32^{c**}

Data are *r*-values from multivariate linear regression.

- not significant.

SUV: standardized uptake values.

MHL: metabolically healthy lean; MHO: metabolically healthy obese; MAO: metabolically abnormal obese.

FFT: fat free tissue.

HU: Hounsfield unit.

^{a}P<0.0001

^{b}P<0.001

^{c}P<0.05.

**P*<0.05 after adjustment for age and gender.

***P*<0.05 only after adjustment for age and gender.