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# **Lower thigh subcutaneous and higher visceral abdominal adipose tissue content both contribute to insulin resistance**

Running head: Regional adipose tissue and insulin resistance

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## **ABSTRACT**

It is well known that visceral adipose tissue (VAT) is associated with insulin resistance (IR). Considerable debate remains concerning the potential positive effect of thigh subcutaneous adipose tissue (TSAT). Our objective was to observe whether VAT and TSAT are opposite, synergistic or additive for both peripheral and hepatic IR.

Fifty-two volunteers (21M/31F) between 30 and 75 years old were recruited from the general population. All subjects were sedentary overweight or obese (mean BMI  $33.0 \pm 3.4$  kg/m<sup>2</sup>).

Insulin sensitivity was determined by a 4-hr hyperinsulinemic euglycemic clamp with stable isotope tracer dilution. Total body fat and lean body mass (LBM) was determined by dual x-ray absorptiometry. Abdominal and mid-thigh adiposity was determined by computed tomography.

VAT was negatively associated with peripheral insulin sensitivity, while TSAT, in contrast, was positively associated with peripheral insulin sensitivity. Subjects with a combination of low VAT and high TSAT had the highest insulin sensitivity, subjects with a combination of high VAT and low TSAT were the most insulin resistant. These associations remained significant after adjusting for age and gender.

These data confirm that visceral excess abdominal adiposity is associated with insulin resistance across a range of middle-age to older men and women, and further suggest that higher thigh subcutaneous fat is favorably associated with better insulin sensitivity. This strongly suggests that these two distinct fat distribution phenotypes should both be considered in insulin resistance as important determinants of cardiometabolic risk.

## **INTRODUCTION**

Visceral adipose tissue (VAT) (1) and intermuscular adipose tissue (IMAT) have been shown to be associated with insulin resistance in middle age adults (2). More recently, lower body subcutaneous adipose tissue (3), particularly thigh subcutaneous fat (4), has been identified as a potential metabolically protective fat depot. We reported that higher VAT was associated with a higher prevalence of metabolic syndrome in older normal weight subjects, but that higher thigh subcutaneous adipose tissue (TSAT) was associated with lower prevalence of metabolic syndrome in overweight and obese older women (5). Van Pelt et al. confirmed the favorable association of leg fat mass with metabolic risk outcomes in both older men and women (6; 7). Recent publications (8; 9) point to the potential positive associations between subcutaneous thigh fat tissue and both markers of insulin resistance and the metabolic syndrome, but it is unclear whether subcutaneous thigh fat is positively associated with both peripheral and hepatic insulin sensitivity measured directly. Thus, the main objective of this study was to examine whether VAT and TSAT have opposite, synergistic or additive associations with both peripheral and hepatic insulin resistance.

## **METHODS AND PROCEDURES**

### *Subjects*

Volunteers from the general population were included if they were between 30 and 75 years old, overweight or obese (BMI 25 to 40 m/kg<sup>2</sup>), weight stable (<6 lbs weight change in the past 6 months), sedentary (self-report of <2 days per week of regular physical activity), non smoker, and had a resting systolic blood pressure (SBP) <150mmHg and diastolic blood pressure (DBP) <95 mmHg. They were excluded if they had a history of diabetes or taking any

medication known to affect glucose homeostasis. The protocol was approved by the University of Pittsburgh Institutional Review Board, and all volunteers gave written informed consent.

### *Body composition*

Body weight was measured on a calibrated medical digital scale (BWB-800, Tanita Corporation, Tokyo, Japan) in undergarments. Height was measured at the same time with a wall-mounted stadiometer. A whole body dual energy X-ray absorptiometry (DXA) scan was performed to measure whole body fat mass (FM) and lean body mass (LBM) (Lunar Prodigy and encore 2005 software version 9.30; GE Healthcare, Milwaukee, MI). Computed tomography (9800 CT scanner, General Electrics, Milwaukee, WI) was used to measure cross-sectional area total abdominal fat, abdominal subcutaneous (Abdominal SAT), visceral adipose tissue (VAT), right mid-thigh subcutaneous adipose tissue (TSAT), intermuscular fat (IMAT), muscle as well as muscle attenuation as a marker of muscle lipid content as described elsewhere (10; 11).

### *Insulin sensitivity*

A hyperinsulinemic euglycemic glucose clamp was performed to determine rates of insulin-stimulated glucose disposal (Rd). This was coupled with stable isotope tracer dilution to distinguish and quantify peripheral and hepatic insulin resistance, as well as to quantify basal hepatic glucose production (HGP) as described elsewhere (12).

### *Statistical analyses*

Pearson product-moment correlations were used to determine the relationship between adiposity and insulin resistance. A one-way ANOVA with Tukey HSD adjustment was used to compare Rd between different fat distribution phenotypes. All analyses were performed using JMP version 5.0.1.2. for Macintosh (SAS, Cary, NC) with an alpha level of 0.05.

## RESULTS

### *Subjects' characteristics*

Fifty-two subjects (31 women and 21 men) were included in this study. Mean age was  $57.1 \pm 12.5$  years (range 31 to 74), mean weight  $92.4 \pm 11.8$  kg (range 65.5 to 116.7) and mean BMI  $33 \pm 3.35$  kg/m<sup>2</sup> (range 26.9 to 39.7).

### *Associations between regional fat distribution and insulin resistance*

Body weight was negatively correlated with Rd ( $r=-0.41$ ,  $P=0.003$ ). Of the various regional fat deposition parameters, only VAT and TSAT were significantly correlated with Rd ( $r=-0.37$ ,  $P=0.007$  and  $r=0.39$ ,  $P=0.005$  respectively). These associations, however, were in opposite directions; higher VAT was associated with lower insulin sensitivity, while higher TSAT was associated with higher insulin sensitivity. This remained true when adjusting for total body fat. Neither abdominal subcutaneous adipose tissue nor thigh intermuscular adipose tissue were significantly correlated with Rd. We did not observe significant correlations between regional fat depots and hepatic insulin resistance (the degree of hepatic glucose suppression by insulin). These associations remained significant after adjusting for age and gender.

Based on VAT and TSAT having opposing associations with insulin sensitivity, we compared Rd in four distinct phenotypes defined according to whether VAT or TSAT were higher or lower than the median value for the entire study sample (Figure 1): high VAT and low TSAT ( $n=13$ ), high VAT and high TSAT ( $n=10$ ), low VAT and low TSAT ( $n=12$ ), low VAT and high TSAT ( $n=16$ ). The overall ANOVA ( $F=3.83$ ,  $P<0.05$ ) was explained by a significant difference between the low VAT and high TSAT group compared to the high VAT and low TSAT group.

## DISCUSSION

The particularly novel finding of the current study was that greater thigh subcutaneous adipose tissue was positively associated with insulin sensitivity across middle age to older overweight to obese subjects. Thus visceral adipose tissue and thigh subcutaneous tissue had markedly opposite associations with insulin sensitivity. This is the first report to our knowledge of this favorable association between thigh subcutaneous adipose tissue content and direct assessments of peripheral insulin sensitivity. This finding is in accord with other studies demonstrating that thigh subcutaneous adipose tissue content is associated with lower prevalence of the metabolic syndrome (5), lower fasting insulin as a marker of higher insulin sensitivity (13), better blood glycemetic and lipid profiles (4; 9) and inflammation (8).

Subjects with lower visceral adipose tissue and higher thigh subcutaneous adipose tissue had the highest degree of insulin sensitivity. In contrast, those with higher visceral fat and lower thigh subcutaneous adipose tissue had the most severe insulin resistance. Thus this data strongly suggest that these fat depots should be considered together and not in isolation. This study was not powered to specifically examine gender differences, thus we were not able to demonstrate associations between regional fat depots separately within men and women. Nevertheless, multivariate regression analysis indicated that these associations between the adipose tissue distribution phenotypes and insulin sensitivity remained significant adjusting for gender. Moreover, some men had high insulin sensitivity, high thigh subcutaneous fat and low visceral fat, whereas some women were insulin resistant with low thigh subcutaneous fat and high visceral fat. These data strongly suggest that these fat distribution phenotypes can be present in both men and women.

In summary, subcutaneous thigh adipose tissue appears to exert a protective influence against peripheral insulin resistance in obesity regardless of age and gender, which is independent of the opposite and negative association observed between visceral abdominal fat and insulin sensitivity. Further investigations are needed to examine the mechanisms underlying individual variation in fat distribution, how these mechanisms are affected by aging, and how this may be implicated in the prevention and treatment of insulin resistance and cardiometabolic risk.

## **DISCLOSURES**

The authors have no conflict of interest to disclose

## **ACKNOWLEDGEMENTS**

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## FIGURE LEGENDS

**Figure 1** Insulin sensitivity (Rd) distribution by phenotype group

Box plots and means (black square). VAT: visceral adipose tissue, TSAT: thigh subcutaneous adipose tissue.

Figure 1

