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Associations of abdominal intermuscular adipose tissue and inflammation: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Objective: This study examined the associations between abdominal IMAT *area* and *density* with inflammatory markers associated with cardiometabolic disease.

Methods: 1897 participants enrolled in the Multi-Ethnic Study of Atherosclerosis underwent computed tomography to quantify body composition and measurements of adiponectin, leptin, interleukin-6 (IL-6), C-reactive protein (CRP), and resistin.

Results: The mean age and body mass index of participants was 65 years and 28 kg/m^2, respectively, and 50% were female. After adjustment for age, sex, and race/ethnicity, as IMAT *area* increased and density *decreased* from the first to fourth quartile, markers of inflammation increased linearly ($p<0.01$). Using linear regression, and with adjustment for demographics, cardiovascular disease risk factors, and abdominal muscle area and density, a 1-standard deviation (SD) increase in total abdominal IMAT *area* was associated with a 21%, 36% and 20% higher IL-6, leptin, and CRP, respectively, and 19% lower adiponectin ($p<0.001$). With similar adjustment, a 1-SD decrease in total abdominal IMAT *density* was associated with a 14%, 32%, and 15% higher IL-6, leptin, and CRP, respectively, and 22% lower adiponectin ($p<0.001$). These associations were attenuated with the addition of visceral fat ($p>0.05$).

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Ethical Statement:

The authors declare that all experiments on human subjects were conducted in accordance with the Declaration of Helsinki, http://www.wma.net, and that all procedures were carried out with the adequate understanding and written consent of the subjects.

The authors also certify that formal approval to conduct the experiments described has been obtained from the human subjects review board of their institution and could be provided upon request.

Declarations of Interest: None.

Disclosures: All authors have approved the final manuscript.

Declarations of Interest: The authors report no conflict of interest.

Disclosures: CV and MA designed the study. MA ran the statistical analyses. CV wrote the manuscript. MA critically edited the manuscript. All authors have approved the final manuscript.

Conclusions: Abdominal IMAT *area* and *density* are associated with inflammatory markers, with these associations attenuated by central adiposity.

Keywords

Adipokines; cytokines; central obesity

1.1 Introduction

Adipose tissue is an endocrine organ that expresses and secretes a multitude of pro- and anti-inflammatory cytokines ("adipokines") that are critical in maintaining systemic homeostasis [1]. Excess adipose tissue can lead to an adipokine imbalance that creates a low- grade inflammatory state, which is thought to contribute to the development of metabolic dysfunction and cardiovascular disease [1]. Recently, there has been a growing interest in studying and understanding the different adipose tissue depots in relation to cardiometabolic disease. In this regard, evidence suggests that the location of excess adipose tissue, rather than the total amount of adipose tissue, may be important for the increased risk of chronic inflammation and cardiometabolic disease [1, 2]. It is well accepted that adipose tissue stored in the abdominal region, including subcutaneous and visceral fat, is linked to chronic inflammation and insulin resistance [3-6]. It is unknown whether adipose tissue depots in other areas contribute to the increased risk of cardiometabolic disease.

One less studied fat depot that is gaining interest is intermuscular adipose tissue (IMAT). IMAT is an ectopic fat depot found beneath the fascia of muscle and between muscle groups. This adipose tissue depot has been shown to vary by race and increase with advancing age and obesity [6-9. Compared to the subcutaneous fat depot, IMAT is a much smaller depot but it has been associated with insulin resistance [10, 11]. inflammation [3]. and decreased muscle quality and strength [2, 12]. Although the mechanism is unknown, it has been hypothesized that the close proximity of intermuscular adipose tissue to skeletal muscle may impair the local muscle environment through increased inflammatory markers, impaired blood flow, or increased rate of lipolysis in skeletal muscle [2].

Given the strong association between abdominal visceral and subcutaneous adipose tissue with inflammation in the MESA cohort [5, 6], investigation of the abdominal IMAT depot seems warranted. Therefore, this study examined the associations between abdominal IMAT *area* and *density* with inflammatory markers associated with cardiometabolic disease. Importantly, adipose tissue *area* derived from computed tomography provides information on the amount of adipose tissue whereas *density* provides information on the amount of lipid per adipocyte, with lower density indicating higher lipid content and lower "quality" of fat [6, 13]. We hypothesized that higher abdominal IMAT *area* and lower *density* would be associated with adverse levels of inflammatory markers and that these associations will be independent of relevant covariates.

1.2 Materials and Methods

1.2.1 Participants

The Multi-Ethnic Study of Atherosclerosis (MESA) is a longitudinal cohort study of adults from six regions across the US. The overall design of the MESA study has been published [14]. In brief, the cohort included a total of 6814 men and women aged 45-84 years who were free from clinically apparent cardiovascular disease at the time of enrollment (July 2000 to August 2002). The racial/ethnic groups of participants included African American, Chinese American, Hispanic and non-Hispanic white. Individuals with a history of diagnosed angina, heart attack, heart failure, stroke or transient ischemic attack, or having undergone an invasive procedure for cardiovascular disease were excluded from the study. Participants who were enrolled in the study returned for follow-up clinic visits approximately 2, 4, 6, and 10 years after the baseline clinic visit.

At clinic visits 2 and 3 (from 2002 to 2005), a random subset of 1970 participants was enrolled in an ancillary study where abdominal computed tomography scans were obtained and subsequently used to quantify *area* and *density* of abdominal muscle and intermuscular, visceral,and subcutaneous fat. Approximately half of the 1970 participants had their scan at visit 2 and the other half at visit 3. To make the measurements contemporaneous, demographic, physical activity and biomarkers data obtained during visit 2 or 3 were used in this study. Participants with complete data on abdominal computed tomography and blood levels of inflammatory markers (n=1897) comprise the sample for the current study. The MESA studies were approved by the Institutional Review Board of each study site and all participants provided written informed consent.

Standard questionnaires were used to obtain information on participant sociodemographics, ethnicity and health history. Height and weight were measured to the nearest 0.1 cm and 0.5 kg, respectively. Participants self-reported their time spent engaged in sedentary behavior and physical activity using the Typical Week Physical Activity Survey. This survey was adapted from the Cross-Cultural Activity Participation Study [15] and designed to identify the frequency of and time spent in sedentary behavior and in various physical activities during a typical week in the previous month. Body mass index, waist circumference and blood pressure were measured using standard procedures.

1.2.2 Laboratory

At each visit, venous blood was collected after a 12-hour fast and shipped to the MESA central laboratory for measurement of total and HDL cholesterol, triglycerides, and glucose concentrations. Insulin, CRP, adiponectin, leptin, tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and resistin concentrations were measured in stored samples from visits 2 or 3 using Bio-Rad Luminex flow cytometry (Millipore, Billerica, MA, USA) at the laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, VT, USA). Average analytic coefficients of variation across several control samples ranged from 6.0% to 13.0%.

In MESA dyslipidemia was defined as a total cholesterol/HDL-cholesterol ratio >5.0 or if the participant was taking medication to reduce cholesterol, hypertension was defined as

systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or taking antihypertensive medication, and diabetes was defined as fasting glucose ≥126 mg dL^{-1} or use of diabetes medication.

1.2.3 Abdominal muscle and fat measurements

Abdominal muscle and intermuscular, visceral and subcutaneous fat were measured from computed tomography scans obtained at visit 2 or 3. Abdominal slices from these scans were processed using MIPAV 4.1.2 software (National Institutes of Health, Bethesda, MD, USA) that measured abdominal fat and lean tissues using a semi-automated method. Fat tissue was identified as being between −190 and −30 Hounsfield units (HU), whereas lean tissue was identified as being between 0 and 100 HU. Densities between 0 and −30 HU were labeled as undefined tissue type.

Using the pixel intensities of a single slice obtained at L4/L5, and the HU criteria provided above, fat areas were calculated for intermuscular, subcutaneous and visceral fat, while muscle areas were computed for the abdominal muscle groups of bilateral oblique, rectus abdominis, paraspinus and psoas muscles. These muscles were grouped into muscles of stabilization (oblique, rectus abdominis, paraspinus muscles), muscles of locomotion (psoas muscle), and total abdominal muscle (oblique, rectus abdominis, paraspinus muscles, and psoas). For each muscle group, area was determined by summing the number of pixels of 0 to 100 HU within that muscle's corresponding fascial plane. Muscle density was the average HU measurement within the muscle's distinct fascial plane. IMAT was defined as the fat (−30 to −190 HU) located within the fascia for each individual muscle group. Subcutaneous adipose tissue was defined as the fat outside of the visceral cavity, not including the fat located within the muscular fascia. Visceral fat area was computed as the sum of the pixels of the appropriate HU range and within the visceral cavity.

1.2.4 Statistics

Characteristics of the population are summarized with mean and standard deviation (SD) for continuous variables and frequency and percentage for categorical variables. Skewed variables are presented as median with interquartile range. IMAT was treated as a continuous (per 1 SD increment) and categorical variable (i.e., quartiles). For IMAT density, larger negative numbers (e.g. −100) indicate lower density than smaller negative numbers (e.g. −50). As such, higher quartiles of IMAT *density* indicate a lower density of fat. ANCOVA was used to determine mean demographic variables, adipokines and inflammatory markers by quartile of IMAT *area* and *density*, after adjusting for age, gender, and race/ethnicity.

Multivariable linear regression was used to determine the associations between both abdominal IMAT *area* and *density* (total, locomotor, and stability) and the adipokines, while controlling for covariates. The initial model (Model 1) adjusted for age, gender, race/ethnicity, income, moderate-to-vigorous physical activity, sedentary behavior and smoking. Model 2 included Model 1 plus dyslipidemia, diabetes, hypertension, height, total abdominal muscle area and density. Model 3 included Model 2 plus inflammatory markers (leptin, resistin, CRP, adiponectin, IL-6 [minus the outcome variable of interest in the model]). Model 4 included Model 3 plus subcutaneous fat area, visceral fat area, visceral fat density,

and total IMAT density or area (i.e. if outcome variable of interest was fat area we included fat density). Multivariable interactions between IMAT and race/ethnicity and sex for the different adipokines were assessed. All statistical analyses were conducted using Stata (Version 13; StataCorp, College Station, TX, USA) and a p- value <0.05 was used to determine statistical significance.

1.3 Results

The study cohort characteristics are presented in Table 1. Overall, the mean age was 64.6 years and 50% were female. Forty percent of participants were non-Hispanic white, 21% were African American, 26% were Hispanic/Latino, and 13% were Chinese American. On average, participants were overweight, with a mean BMI and waist circumference of 28 $kg \cdot m^{-2}$ and 97.9 cm, respectively. Thirty percent of participants had a BMI greater than 30 $kg \cdot m^{-2}$. Almost half (47%) of participants were hypertensive, 39% were dyslipidemic, and 14% had diabetes mellitus.

1.3.1 Characteristics by quartiles of intermuscular fat *area* and *density*

After adjusting for age, sex and race/ethnicity, there were higher mean levels of age, BMI, waist circumference, triglycerides, glucose, blood pressure, leptin, adiponectin, resistin, IL-6, CRP, visceral fat, subcutaneous fat and lower mean levels of HDL and total abdominal muscle area and density, with increasing quartiles total abdominal IMAT *area* (Table 2, $p<0.05$). More specifically, leptin, adiponectin, resistin, IL-6 and C-reactive protein were 136%, 19%, 15%, 61% and 67% higher in the highest, compared to the lowest, quartile of IMAT *area*, respectively. The prevalence of obesity, diabetes, dyslipidemia and hypertension also increased across higher quartiles of IMAT *area* ($p<0.05$). The findings were similar for IMAT *density* with the exception of adiponectin, which decreased 17% as IMAT *density* decreased ($p<0.001$), and resistin, which was not significantly different by quartile of total IMAT *density* ($p=0.314$). TNF-α was not different across quartiles of total IMAT *area* or *density* and were not included in further analyses ($p>0.05$). Findings were similar but not as robust with quartiles of locomotor and stabilization IMAT *area* and *density* (data not shown).

1.3.2 Associations between intermuscular fat *area* and *density* with inflammatory markers

Multivariable-adjusted linear regression models were used to determine the independent associations between IMAT *area* and *density* with each inflammatory marker (Table 3).

IL-6.—With adjustment for age, sex, race/ethnicity, income, moderate-to-vigorous physical activity, sedentary behavior and smoking (model 1), a one standard deviation (1-SD) increment in total abdominal, locomotor, and stability IMAT *area* was associated with a 27%, 15%, and 27% higher IL-6 level, respectively ($p<0.001$ for all). These associations were slightly attenuated but remained significant with the addition of dyslipidemia, diabetes, hypertension, height, and total abdominal muscle area and density (model 2; 21%, 7%, 21%, respectively; $p<0.05$ for all). With the addition of inflammatory markers (model 3), total and stability IMAT *area* remained significantly associated with IL-6 ($p<0.05$). With the addition

of visceral and subcutaneous fat (model 4), only stability IMAT *area* remained significant ($p<0.05$).

With adjustment for variables in model 1, a 1-SD decrease in total abdominal, locomotor, and stability IMAT *density* was associated with a 20%, 14% and 19% higher IL-6 level, respectively. These associations were slightly attenuated but remained significant with the addition of dyslipidemia, diabetes, hypertension, height, total abdominal muscle area and density (model 2; $p<0.001$ for all). These associations were attenuated with the addition inflammatory markers (model 3, $p>0.05$).

Leptin.—The associations between IMAT *area* and *density* were stronger for leptin than the other inflammatory markers. With adjustment for variables in model 1, a 1-SD increment in total abdominal, locomotor and stability IMAT *area* was associated with a 34%, 23%, and 33% higher leptin level, respectively. These associations remained significant in models 2 and 3, but were attenuated with the addition of subcutaneous fat, visceral fat, and total IMAT density (model 4, $p>0.05$). Similarly, with adjustment for variables in model 1, a 1-SD decrease in total abdominal,locomotor and stability IMAT *density* was associated with a 34.4%, 23.6%, and 32.8% higher leptin level, respectively. These associations remained significant ($p<0.001$) in models 2 and 3 but were attenuated in the fully adjusted model.

Adiponectin.—With adjustment for the variables in model 2, a 1-SD increment in total abdominal, locomotor, and stability IMAT *area* was associated with an 19%, 18%, and 16% lower adiponectin level, respectively ($p<0.001$). These associations were slightly attenuated but remained significant with the addition of inflammatory markers. In the fully adjusted model, total and stability IMAT *area* were associated with a 10% higher adiponectin level ($p<0.05$). Similarly, and for model 2, a 1-SD lower total abdominal, locomotor, and stability IMAT *density* was associated with a 22%, 19%, and 18% lower adiponectin level, respectively ($p<0.001$). These associations remained significant with the addition of inflammatory markers (model 3, $p<0.001$) but were attenuated in the fully adjusted model.

CRP.—The associations between IMAT *area* and *density* were significant in models 1 and 2 for CRP and indicate between a 6.9 to 20% increase in CRP with an increase in IMAT *area* and decrease in IMAT *density*. These associations were largely attenuated with the addition of inflammatory markers (model 3).

Resistin.—Only total and stability IMAT *area* were associated with a 9.6% and 8.4% higher level of resistin, respectively, in model 1, but these associations were attenuated with the addition of cardiovascular disease risk factors and total abdominal muscle area and density (model 2, $p>0.05$).

1.3.3 Associations of intermuscular fat *area* and *density* quartiles with inflammatory markers

Multivariable-adjusted linear regression analysis using quartiles of total abdominal IMAT *area* and *density* are presented in Figure 1.

IL-6.—Compared with the lowest quartile, and after the same adjustment, the third and fourth quartiles of total abdominal IMAT *area* were associated with an 8.6% and 8.4% higher IL-6 level ($p<0.05$). These associations were attenuated in the fully adjusted model. The associations between quartiles of total abdominal IMAT *density* and IL-6 were not significant.

Leptin.—Compared with the lowest quartile, and after adjustment for variables in model 3, there was a stepwise increase in leptin with each higher quartile of total abdominal IMAT *area* (13%, 22%, 36%, respectively; $p<0.001$), as well as total abdominal IMAT *density* (14%, 18%, 30%, respectively; $p<0.001$). After full adjustment the associations were attenuated ($p>0.05$).

Adiponectin.—In model 3, compared with the lowest quartile, the third and fourth quartiles of total abdominal IMAT *density* were associated with a 7% ($p<0.05$) and 11% ($p<0.001$) lower adiponectin level that was attenuated in the fully adjusted model. In the fully adjusted model, the third and fourth quartiles of total abdominal IMAT *area* were associated with a 7.6% and 8.7% increase in adiponectin ($p<0.05$).

CRP.—Compared with the lowest quartile, and after adjustment for variables in model 2, there was a stepwise increase in CRP (9%, 11%, 21%, respectively) with each higher quartile of total abdominal IMAT *area*, which was attenuated with the addition of inflammatory markers (model 3). Compared with the lowest quartile, the third and fourth quartiles of total abdominal IMAT *density* were associated with a 9.6%, 16.1% higher CRP level, respectively. After addition of inflammatory markers the associations were attenuated ($p>0.05$).

Resistin.—There were few significant associations with resistin across quartiles of IMAT *area* and *density* ($p>0.05$). Overall, results were similar, but less robust, across inflammatory markers for locomotor and stability IMAT *area* and *density* (data not shown).

Using multiplicative interaction terms, we tested for significant differences in the magnitudes of the associations between the IMAT *area* and *density* of the different muscle groups and each inflammatory marker, by race/ethnicity and sex. There were no significant or robust differences across race/ethnicity or sex.

1.4 Discussion

In this study of a large, multi-ethnic population-based cohort from multiple sites across the United States, higher levels of abdominal IMAT *area* were associated with significantly higher levels of IL-6, leptin, and CRP and lower levels of adiponectin. Notably, these associations were independent of relevant covariates including cardiovascular disease risk factors, physical activity, sedentary behavior, abdominal muscle area and density, and other markers of inflammation. However, most were attenuated to non-significance by including measures of central adiposity (i.e. abdominal subcutaneous and visceral fat). Similarly, lower levels of abdominal IMAT *density* were independently associated with higher levels of IL-6, leptin and CRP and lower levels of adiponectin. However, the associations with IL-6 and

CRP were not independent of other inflammatory markers. Overall, the associations of abdominal IMAT *area* and *density* were more robust for leptin and adiponectin than the other inflammatory markers. These results suggest that abdominal IMAT may contribute to the chronic inflammation associated with obesity and increased risk of cardiometabolic disease but that a significant proportion of this effect is likely mediated by central adiposity.

Despite the emerging evidence of IMAT as an independent risk factor for metabolic dysfunction and frailty, few studies have examined the independent associations between the IMAT and inflammation [3, 8, 9]. Those that have studied this depot have examined fat in the thigh or calf. For example, Beasley et al [3] reported significant independent associations between thigh IMAT and proinflammatory cytokines in 2651 older adults from the Health ABC study. In contrast, other studies that were limited by small samples sizes, reported few or no independent associations between IMAT and markers of inflammation [8, 9]. Our research extends the findings that IMAT *area* and *density* are associated with inflammation to a large multiethnic cohort of middle-aged to older adults. Additionally, we studied whether the associations with inflammation were independent of visceral adipose tissue. We found this measure significantly attenuated the association between IMAT and markers of inflammation. Studies investigating IMAT have used thigh [10, 17] or erector spinae [9] and have only controlled for total adiposity using BMI. Previous studies have shown that abdominal visceral fat is significantly and positively associated with IL-6 and CRP in older adults [3, 18]. Our findings further support the growing body of evidence that visceral fat is important for inflammation and extend the literature by showing abdominal IMAT contributes to inflammation. Together these findings suggest IMAT may be associated with adverse health outcomes in older adults. Notably, there were low to moderate correlations between IMAT and abdominal subcutaneous and visceral fat (range 0.29 to 0.56). These correlations indicate there may be overlap in explained variance between these three fat depots and inflammation, making the contributions of IMAT, independent of these other depots, difficult to determine and likely underestimated.

We observed a strong association between IMAT and leptin levels. This is consistent with others [9] who reported significant associations between IMAT in the erector spinae and leptin levels in a small sample of obese, elderly men. High leptin levels have been suggested as a surrogate marker of leptin resistance [19]. Leptin resistance may lead to lower fatty acid oxidation in skeletal muscle, resulting in the accumulation of ectopic fat [19]. Notably, in the present study IMAT *area* was positively associated with leptin whereas *density* was negatively associated with leptin. A lower density of adipose tissue indicates a greater amount of lipid per adipocyte. These associations may reflect the positive correlation between leptin and body fat, as the adjustment for central obesity attenuated these associations. Strong associations were also found between IMAT and adiponectin. Like leptin, adiponectin is involved in the regulation of skeletal muscle fat metabolism, with lower levels leading to increased fatty acid uptake and decreased oxidation, resulting accumulation of intermuscular lipids [19].

Our findings suggest that as IMAT increases, markers of inflammation increase correspondingly. That is, as IMAT increased from the first to fourth quartile, markers of inflammation increased in a linear manner. Notably, there was a decrease in total abdominal

muscle area and density across increasing quartiles of IMAT, suggesting that IMAT may be related to the development of sarcopenia. Sarcopenia is the age-related loss of muscle mass and quality. Recently, muscle density has emerged as an important marker of muscle quality. In this respect, density of muscle derived from computed tomography has been inversely associated with body fat, fat infiltration of muscle, and muscle strength and function [20, 21]. Data from a large prospective population-based study [17] showed that thigh IMAT area and density were strong indicators of incident mobility limitation and poor performance in in older men and women. Others have linked IMAT with decreased muscle strength and function [2]. Interestingly, research suggests the loss of muscle mass does not fully explain the loss in muscle function [2, 22]. IMAT is thought to contribute to this decline in muscle function with age but the mechanisms are unknown [2]. Inflammation has been shown to have catabolic effects on muscle mass and function and is hypothesized to mediate the link between higher fat mass and loss in muscle mass and strength [23]. Our data show that abdominal muscle area and density decreased across increasing IMAT quartiles, providing support for a link between IMAT and skeletal muscle health.

Strengths of this study include a relatively large, well-characterized, multi-ethnic sample of men and women, the use of objective measures of abdominal IMAT via computed tomography scan, careful assessment of many potentially confounding factors, and inflammatory markers that were analyzed at a central laboratory, with a high level of reproducibility. The primary limitation is the cross-sectional study design that precludes causal inferences between abdominal IMAT and circulating adipokines levels. It is possible that higher levels of inflammatory markers resulted in changes in IMAT (i.e., reverse causation). Given this, prospective studies are needed to determine relationships of IMAT with markers of inflammation over time.

In summary, abdominal IMAT *area* and *density* were significantly associated with markers of inflammation. These associations were independent of relevant covariates including moderate-to-vigorous physical activity, sedentary behavior, cardiovascular disease risk factors, abdominal muscle area and density, and other markers of inflammation, but not visceral fat. Our data suggest that abdominal IMAT contributes to chronic inflammation, and in turn, may increase risk of cardiometabolic disease and sarcopenia. Future prospective studies examining changes in adipose tissue area and density across depots may assist in understanding the mechanisms associated with IMAT and increased risk of cardiometabolic disease and sarcopenia.

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References

[1]. Nakamura K, Fuster JJ, Walsh K. Adipokines: a link between obesity and cardiovascular disease. J Cardiol 2014;63:250–259. [PubMed: 24355497]

[2]. Addison O, Marcus RL, LaStayo PC, Ryan AS. Intermuscular fat: a review of the consequences and causes. Int J Endocrinol 2014; Article ID 309570, doi:10.1155/2014/309570.

[3]. Beasley LE, Koster A, Newman AB, Javaid MK, Ferrucci L, Kritchevsky SB et al. Body composition measures from CT and inflammation. Obesity (Silver Spring) 2009;17(5):1062–1069. doi:10.1038/oby.2008.627. [PubMed: 19165157]

[4]. Gustafson B Adipose tissue, inflammation and atherosclerosis. J Atheroscler Thromb 2010;17(4): 332–341. [PubMed: 20124732]

[5]. Shah RV, Murthy VL, Abbasi SA, Blankstein R, Kwong RY, Goldfine AB et al. Visceral adiposity and the risk of metabolic syndrome across body mass index: The MESA Study. JACC Cardiovasc Imaging 2014; 7(12):1221–1235. doi:10.1016/j.jcmg.2014.07.017. [PubMed: 25440591]

[6]. Shah R, Allison M, Lima JAC, Abbasi SA, Eisman A, Lai C et al. Abdominal fat radiodensity, quantity and cardiometabolic risk: the Multi-Ethnic Study of Atherosclerosis. Nutr Metab Cardiovasc Dis 2016; 26(2):114–122. doi:10.1016/j.numecd.2015.12.002 [PubMed: 26817938]

[7]. Delmonico MJ, Harris TB, Visser M et al. Longitudinal study of muscle strength, quality, and adipose tissue infiltration. Am J Clin Nutr 2009;90:1579–1585. [PubMed: 19864405]

[8]. Mazzali G, Di Francesco V, Zoico E et al. Interrelations between fat distribution, muscle lipid content, adipocytokines, and insulin resistance: effect of moderate weight loss in older women. Am J Clin Nutr 2006;84:1193–1199. [PubMed: 17093174]

[9]. Zoico E, Rossi A, Di Francesco V et al. Adipose tissue infiltration in skeletal muscle of healthy elderly men: relationships with body composition, insulin resistance, and inflammation at the systemic and tissue level. Gerontol A Biol Sci Med Sci 2010;65A(3):295–299.

[10]. Goodpaster BH, Thaete FL, Kelley DE. Thigh adipose tissue distribution is associated with insulin resistance in obesity and in type 2 diabetes mellitus. Am J Clin Nutr 2000;71: 885–892. [PubMed: 10731493]

[11]. Goodpaster BH, Krishnaswami S, Resnick H et al. Association between regional adipose tissue distribution and both type 2 diabetes and impaired glucose tolerance in elderly men and women. Diabetes Care 2003;26:372–379. [PubMed: 12547865]

[12]. Manini TM, Clark BC, Nalls MA, Goodpaster BH, Ploutz-Snyder LL, Harris TB. Reduced physical activity increases intermuscular adipose tissue in healthy young adults. Am J Clin Nutr 2007;85:377–384. [PubMed: 17284732]

[13]. Murphy RA, Register TC, Shively CA, Carr JJ, Yaorong G, Heilbrun ME et al. Adipose tissue density, a novel biomarker predicting mortality risk in older adults. J Gerontol A Biol Sci Med Sci 2014y;69(1):109–117 doi:10.1093/gerona/glt070. [PubMed: 23707956]

[14]. Bild DE, Bluemke DA, Burke GL et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. Am J Epidemiol 2002;156(9):871–881. [PubMed: 12397006]

[15]. Ainsworth BE, Irwin ML, Addy CL, Whitt MC, Stolarczyk LM. Moderate physical activity patterns of minority women: the Cross-Cultural Activity Participation Study. J Women's Health Gend Based Med 1999;8(6):805–813. [PubMed: 10495261]

[16]. Ainsworth BE, Haskell WL, Whitt MC et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exer 2000;32(suppl9):S498–S504.

[17]. Murphy RA, Register TC, Shively CA et al. Adipose tissue density, a novel biomarker predicting mortality risk in older adults. J Gerontol A Biol Sci Med Sci 2014;69(1): 109–117 doi:10.1093/gerona/glt070. [PubMed: 23707956]

[18]. Pou KM, Massaro JM, Hoffmann U et al. Visceral and subcutaneous adipose tissue volumes are cross-sectionally related to markers of inflammation and oxidative stress: the Framingham Heart Study. Circulation 2007;116:1234–1241. [PubMed: 17709633]

[19]. Dyck DJ, Heigenhauser GJF, Bruce CR. The role of adipokines as regulators of skeletal muscle fatty acid metabolism and insulin sensitivity. Acta Physiol (Oxf) 2006;186:5–16. [PubMed: 16497175]

[20]. Goodpaster BH, Carlson CL, Visser M et al. Attenuation of skeletal muscle and strength in elderly: The Health ABC Study. J Appl Physiol 2001;90:2157–2165. [PubMed: 11356778]

[21]. Mikkelsen UR, Agergaard J, Couppe C et al. Skeletal muscle morphology and regulatory signaling in endurance-trained and sedentary individuals: the influence of ageing. Exp Gerontol 2017;93:54–67. [PubMed: 28411009]

[22]. Koster A, Ding J, Stenholm S et al. Does the amount of fat mass predict age-related loss of lean mass, muscle strength, and muscle quality in older adults? J Gerontol: Medical Sciences 2011:66A(8);888–895.

[23]. Jensen GL. Inflammation: roles in aging and sarcopenia. J Parenter Enteral Nutr 2008;32(6):656–659. doi: 10.1177/0148607108324585.

Highlights

- Intermuscular adipose tissue area and density are associated with adverse levels of inflammatory markers independent of relevant covariates.
- Intermuscular adipose tissue may contribute to the chronic inflammation associated with obesity and increased risk of cardiometabolic disease.

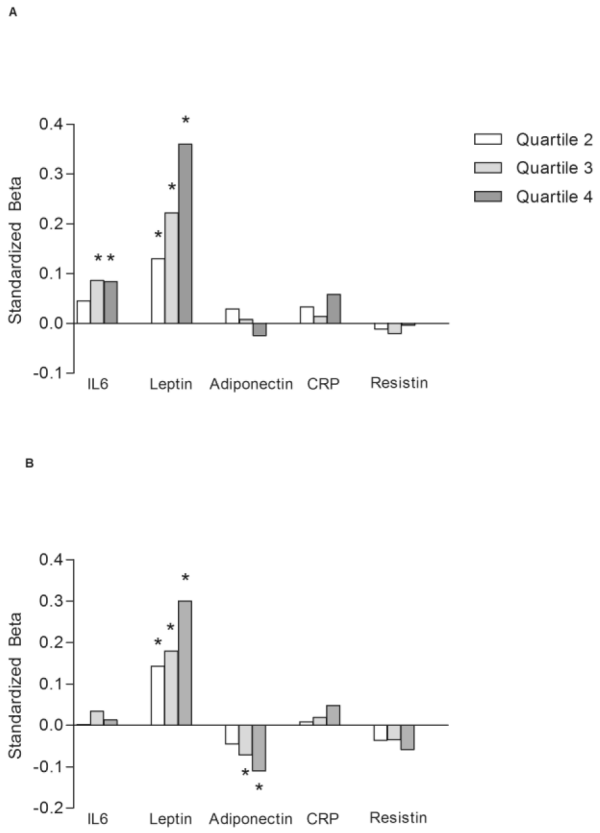

Figure 1.

Multivariable-adjusted associations between quartiles of total abdominal intermuscular adipose tissue (IMAT) area (A) and density (B) with inflammatory markers.

Referent category: Quartile 1. Quartile cutpoints for total abdominal IMAT area: Q1 ≤16.32, Q2 16.33 – 22.16, Q3 22.17 – 30.71, Q4 >30.71 cm^2 and total abdominal IMAT density: Q1≥−57.43, Q2 −57.44 – −60.35, Q3 −60.36 – −63.09, Q4 < −63.09 HU. *p<0.05; Covariates include age, sex, race/ethnicity, income, moderate-to-vigorous physical activity, sedentary behavior, smoking, dyslipidemia, diabetes, hypertension, height, total abdominal muscle area, total abdominal muscle density, leptin, resistin, CRP, IL-6, adiponectin (minus outcome variable of interest in the model).

Table 1.

Characteristics of the study cohort: The Multi-Ethnic Study of Atherosclerosis (n=1897)

Characteristic	Mean (SD) / % (n)
Demographics	
Age (years, M [SD])	64.6 (9.6)
Male (% [n])	49.8 (947)
Race/Ethnicity (% [n])	
White	40.1 (763)
Chinese American	13.2 (251)
African American	20.9 (398)
Hispanic	25.8 (490)
Ever Smoker (% [n])	54.1 (1026)
BMI ($kg \cdot m^{-2}$, M [SD])	28.0 (5.1)
Dyslipidemia (% [n])	39.3 (730)
Diabetes (% [n])	14.3 (271)
Hypertension (% [n])	47.1 (886)
Body composition variables	
Waist circumference (cm, M [SD])	97.9 (13.9)
Subcutaneous fat area (cm^2, M [SD])	253.7 (117.7)
Visceral fat area (cm^2, M [SD])	146.4 (68.3)
Locomotor intermuscular fat area (cm^2, M [SD])	2.0 (1.6)
Locomotor intermuscular fat density (HU, M [SD])	−57.3 (6.2)
Stability intermuscular fat area (cm^2, M [SD])	22.8 (11.3)
Stability intermuscular fat density (HU, M [SD])	−61.4 (4.6)
Total abdominal intermuscular fat area (cm^2, M [SD])	24.8 (12.2)
Total abdominal intermuscular fat density (HU, M [SD])	−60.4 (4.3)
Total abdominal muscle area (cm^2, M [SD])	98.3 (27.6)
Total abdominal muscle density (HU, M [SD])	42.2 (5.5)
Cardiovascular disease risk factors	
Sedentary Behavior (MET $min \cdot wk^{-1}$, Mdn [IQR])	1470.0 (1440)
MVPA (MET-$min \cdot wk^{-1}$, Mdn [IQR])	3585.0 (4530)
Insulin ($pg \cdot mL^{-1}$)	287.7 (347.8)
Glucose ($mg \cdot dL^{-1}$, M [SD])	98.2 (27.8)
Triglycerides ($mg \cdot dL^{-1}$, M [SD])	133.3 (95.6)
High-density lipoprotein ($mg \cdot dL^{-1}$, M [SD])	51.6 (15.1)
Inflammatory markers	
C-reactive protein ($mg \cdot L^{-1}$, Mdn [IQR]	1.5 (3.2)
Adiponectin $\mu g \cdot mL^{-1}$, Mdn [IQR])	17.5 (14.5)
Leptin ($ng \cdot mL^{-1}$, Mdn [IQR])	13.2 (22.6)

Characteristic	Mean (SD) / % (n)
Resistin (ng·mL^{-1}, Mdn [IQR])	15.0 (7.2)
Interleukin-6 (pg·mL^{-1}, Mdn [IQR])	1.8 (1.7)
Tumor necrosis factor-alpha (pg·mL^{-1}, Mdn [IQR])	4.6 (2.9)

SD, standard deviation; %, percent; Freq, frequency; BMI, body mass index; HU, Hounsfield units; IQR, interquartile range; M, mean; MET, metabolic equivalents; Mdn, median; MVPA, moderate-to-vigorons physical activity. SI conversion factors: To convert glucose, cholesterol, and triglycerides to mmol/L, multiply values by 0.0555, 0.0259, and 0.0113, respectively. To convert C-reactive protein to nmol/L multiply values by 9.524.

Table 2.

Participant characteristics across quartiles of total abdominal intermuscular fat *area* and *density*.

	Total Abdominal Muscle Intermuscular Fat *Area*					Total Abdominal Muscle Intermuscular Fat *Density*				
	Q1	**Q2**	**Q3**	**Q4**	**P**	**Q1**	**Q2**	**Q3**	**Q4**	**P**
Age (years)	60.7	63.5	66.4	68.0	<0.001	64.2	64.0	65.4	64.9	0.105
BMI (kg·m-^{2})[a]	25.1	27.1	28.8	31.1	<0.001	25.2	27.1	28.9	30.9	<0.001
Waist (cm)[a]	88.3	94.9	100.7	107.7	<0.001	88.8	94.9	100.8	106.9	<0.001
Cholesterol[a]	191.5	189.9	189.3	188.1	0.119	189.3	189.6	189.3	190.6	0.641
LDL[a]	114.7	112.7	110.9	109.7	0.206	111.8	112.2	111.7	112.5	0.648
HDL cholesterol (mg·dL^{-1})[a]	53.2	52.2	51.1	50.0	<0.001	55.2	52.5	50.3	48.4	<0.001
Triglycerides (mg·dL^{-1})[a]	118.2	126.9	139.8	148.4	<0.001	111.6	126.5	140.4	154.9	<0.001
Glucose (mg·dL^{-1})[a]	95.1	96.7	99.3	101.7	<0.001	94.2	97.0	99.7	102.0	<0.001
Systolic blood pressure (mmHg)[a]	120.7	122.8	124.9	127.6	0.002	122.6	123.3	124.8	125.3	0.003
Diastolic blood pressure (mmHg)[a]	71.1	70.5	69.4	69.3	0.235	69.8	70.2	70.2	70.2	0.044
MVPA (MET-min·wk^{-1})[a]	5510	5217	4680	4375	0.081	5268	5141	4752	4633	0.004
Sedentary (MET-min·wk^{-1})[a]	1470	1627	1741	1878	0.004	1630	1649	1704	1733	0.108
Leptin (ng·mL^{-1})[a]	12.5	17.5	22.6	29.5	<0.001	13.6	17.9	22.5	28.0	<0.001
Adiponectin (mg·mL^{-1})[a]	18.8	20.4	21.9	22.3	0.025	23.0	21.3	20.0	19.0	<0.001
Resistin (ng·mL^{-1})[a]	15.2	16.0	16.7	17.5	0.003	16.2	16.2	16.5	16.5	0.314
TNF-α (pg·mL^{-1}) [a]	5.5	5.7	5.9	5.9	0.693	5.6	5.7	5.8	5.8	0.982
Interleukin-6 (pg·mL^{-1})[a]	1.8	2.2	2.5	2.9	<0.001	2.0	2.2	2.5	2.7	<0.001
C-reactive protein (mg·L^{-1})[a]	2.4	2.9	3.4	4.0	0.005	2.5	2.9	3.4	3.9	0.003
Visceral fat (cm^2)[a]	99.9	132.0	162.5	192.1	<0.001	102.9	132.3	161.7	189.5	<0.001
Subcutaneous fat (cm^2)[a]	198.4	239.7	276.3	326.8	<0.001	201.0	239.4	275.7	320.8	<0.001

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	Total Abdominal Muscle Intermuscular Fat *Area*					Total Abdominal Muscle Intermuscular Fat *Density*				
Total abdominal muscle area (cm^2)[a]	106.6	102.1	94.2	90.5	<0.001	100.5	100.2	97.3	95.4	<0.001
Total abdominal muscle density (HU)[a]	47.0	43.9	40.4	37.5	<0.001	44.4	43.1	41.4	40.0	<0.001
Obese (%)[a]	8	23	36	53	<0.001	9	23	36	51	<0.001
Ever smoke (%)[a]	49	54	55	58	0.026	51	54	55	56	0.370
Dyslipidemia (%)[a]	34	38	42	44	0.036	32	37	42	46	0.001
Diabetes (%)[a]	12	13	15	17	0.001	12	14	15	16	0.026
Hypertension (%)[a]	38	44	50	57	<0.001	42	45	50	52	<0.001

Quartile cutpoints for total intermuscular fat area: Q1 ≤16.32, Q2 16.33 – 22.16, Q3 22.17 – 30.71, Q4 >30.71 cm^2 and total intermuscular fat density: Ql≥ −57.43, Q2 −57.44 – −60.35, Q3 −60.36 – −63.09, Q4 < −63.09 HU.

[a]Adjusted for age and sex; Q, quartile; BMI, body mass index; HDL, high-density lipoprotein; MVPA, moderate-to-vigorous physical activity; TNF- α, tumor necrosis factor alpha.

Table 3.

Multivariable linear regression models for the associations between intermuscular fat *area* and *density* with inflammatory markers. Data are presented as standardized betas.

	Model							
Interleukin-6	**1**	**P**	**2**	**P**	**3**	**P**	**4**	**P**
Area								
Total intermuscular fat area	0.273	<0.001	0.206	<0.001	0.083	0.005	0.081	0.058
Locomotor intermuscular fat area	0.147	<0.001	0.072	0.004	0.010	0.647	−0.057	0.084
Stability intermuscular fat area	0.273	<0.001	0.205	<0.001	0.086	0.004	0.097	0.022
Density								
Total intermuscular fat density	−0.200	<0.001	−0.139	<0.001	−0.038	0.098	0.023	0.505
Locomotor intermuscular fat density	−0.140	<0.001	−0.087	<0.001	−0.022	0.294	−0.042	0.176
Stability intermuscular fat density	−0.190	<0.001	−0.130	<0.001	−0.035	0.124	0.035	0.306
Leptin								
Area								
Total intermuscular fat area	0.340	<0.001	0.356	<0.001	0.314	<0.001	−0.037	0.239
Locomotor intermuscular fat area	0.227	<0.001	0.179	<0.001	0.149	<0.001	−0.019	0.444
Stability intermuscular fat area	0.334	<0.001	0.339	<0.001	0.301	<0.001	−0.038	0.227
Density								
Total intermuscular fat density	−0.344	<0.001	−0.315	<0.001	−0.282	<0.001	−0.025	0.332
Locomotor intermuscular fat density	−0.236	<0.001	−0.192	<0.001	−0.160	<0.001	−0.009	0.681
Stability intermuscular fat density	−0.328	<0.001	−0.296	<0.001	−0.267	<0.001	−0.028	0.267
Adiponectin								
Area								
Total intermuscular fat area	−0.054	0.018	−0.189	<0.001	−0.074	0.019	0.104	0.014
Locomotor intermuscular fat area	−0.095	<0.001	−0.177	<0.001	−0.124	<0.001	−0.018	0.582
Stability intermuscular fat area	−0.043	0.061	−0.161	<0.001	−0.047	0.130	0.097	0.020
Density								
Total intermuscular fat density	0.161	<0.001	0.217	<0.001	0.124	<0.001	0.026	0.449
Locomotor intermuscular fat density	0.153	<0.001	0.193	<0.001	0.130	<0.001	0.015	0.627
Stability intermuscular fat density	0.131	<0.001	0.177	<0.001	0.083	<0.001	0.007	0.846
C-reactive protein								
Area								
Total intermuscular fat area	0.203	<0.001	0.203	<0.001	0.060	0.052	0.043	0.327
Locomotor intermuscular fat area	0.106	<0.001	0.069	0.007	0.005	0.820	0.031	0.357
Stability intermuscular fat area	0.204	<0.001	0.202	<0.001	0.062	0.042	0.034	0.440
Density								
Total intermuscular fat density	−0.172	<0.001	−0.151	<0.001	−0.040	0.097	0.018	0.612
Locomotor intermuscular fat density	−0.121	<0.001	−0.093	<0.001	−0.009	0.688	0.030	0.340
Stability intermuscular fat density	−0.163	<0.001	−0.142	<0.001	−0.043	0.064	0.007	0.838

	Model							
Resistin								
Area								
Total intermuscular fat area	0.073	0.004	0.023	0.507	−0.017	0.652	0.040	0.444
Locomotor intermuscular fat area	0.024	0.295	−0.014	0.605	−0.023	0.412	−0.019	0.639
Stability intermuscular fat area	0.075	0.003	0.028	0.418	−0.012	0.742	0.032	0.539
Density								
Total intermuscular fat density	−0.018	0.460	0.024	0.356	0.055	0.058	0.068	0.111
Locomotor intermuscular fat density	0.005	0.845	0.039	0.113	0.052	0.047	0.048	0.208
Stability intermuscular fat density	−0.023	0.324	0.011	0.671	0.039	0.165	0.037	0.372

Model 1, age, sex, race/ethnicity, income, moderate-to-vigorous physical activity, sedentary behavior, smoking; Model 2, Model 1+ dyslipidemia, diabetes, hypertension, height, total abdominal muscle area, total abdominal muscle density; Model 3, Model 2+ leptin, resistin, CRP, IL6, adiponectin (minus outcome variable of interest in the model); Model 4, Model 3+ subcutaneous fat, visceral fat, visceral fat density, and total intramuscular fat density or area.