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Abdominal Muscle Density is Inversely Related to Adiposity Inflammatory Mediators

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Abstract

Purpose—Skeletal muscle is the largest regulator of glucose metabolism but few population-based studies have examined the associations between muscle and inflammation. We studied the relationships between abdominal muscle area and density with selected adiposity associated inflammatory mediators.

Methods—Nearly 2,000 subjects underwent computed tomography (CT) of the abdomen and had venous fasting blood drawn concomitantly. The CT scans were interrogated for visceral and subcutaneous fat, as well as abdominal lean muscle areas and densities. We then categorized the muscle into locomotion (psoas) and stabilization (rectus, obliques and paraspinal) groups. Blood samples were assayed for interleukin-6 (IL-6), resistin, C-reactive protein (CRP), and tumor necrosis factor-alpha (TNF-α).

Results—The mean age was 64.7 years and 49% were female. Forty percent were White, 26% Hispanic/Latino American, 21% African American, and 13% Chinese American. The mean BMI was 28.0 kg/m2 and 30% were obese (BMI >30 kg/m2). Using multivariable linear regression models that included adjustment for abdominal muscle area, a 1-SD increment in the mean *densities* for total, stabilization and locomotive abdominal muscle were each significantly associated with lower levels of IL-6 (β= −15%, −15% and −9%, $p < 0.01$ for all) and resistin (β= −0.11, −0.11 and −0.07 ng/ml, $p < 0.02$ for all), but not CRP or TNF-α. Conversely, muscle *area* was not independently associated with any of the inflammatory mediators studied.

Conclusions—Higher densities of several muscle groups in the abdomen are significantly associated with lower IL-6 and resistin levels, independent of the muscle area in these groups. Techniques that enhance muscle density may reduce levels of adiposity associated inflammatory mediators.

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The results of the present study do not constitute endorsement by ACSM.

The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

Keywords

muscle; body composition; inflammation; adiposity; race/ethnicity

Introduction

Obesity is a burgeoning public health problem associated with multiple comorbidities including diabetes, hypertension, dyslipidemia, and incident cardiovascular disease (CVD).(1) Obesity is most often defined by BMI. However, this measure does not differentiate between contributions from adipose and muscle tissue. Indeed, some studies suggest that BMI is better correlated with lean muscle mass than body fat percentage.(2) Moreover, muscle accounts for approximately 40% of total body mass,(3) and it has the potential to considerably impact metabolic activity, physiologic function and health. In this regard, and among sedentary individuals, the main determinant of energy expenditure is muscle mass, with higher levels increasing insulin sensitivity.(3)

Obesity leads to an increased expression of pro-inflammatory adipokines and diminished expression of anti-inflammatory adipokines. The resulting adipokine imbalance creates a low grade inflammatory state believed to contribute to metabolic dysfunction and heart disease.(4) Notably, there is scant literature on the associations between muscle and adiposity associated inflammation. In one study on this topic, muscle protein synthesis rates were negatively correlated with both interleukin-6 (IL-6) and C-reactive protein (CRP) levels.(5)

Computed tomography (CT) differentiates tissue types on the basis of their attenuation characteristics, which are primarily a function of tissue density and composition.(6) Using attenuation values expressed as Hounsfield Units (HU), CT can discern fat (negative attenuation value) from muscle (positive attenuation value). Reduced mean skeletal muscle attenuation, a measure of decreased density, is seen in obesity and diabetes mellitus.(7) Also, weight loss increases the mean attenuation value of muscle.(8) In accordance with these observations, an increase in skeletal muscle lipid has been shown to be associated with a decrease in muscle density measured as CT attenuation values.(9) Moreover, a greater abundance of adipocytes within muscle not only decreases muscle density, but is believed to increase local concentrations of inflammatory cytokines.(10)

Upon this background, the objective of our present analysis was to test the hypothesis that abdominal muscle area and density by computed tomography would be significantly and inversely associated with concentrations of several different adiposity associated inflammatory mediators.

Methods

Participants

The Multi-Ethnic Study of Atherosclerosis (MESA) is a longitudinal cohort study of African American, Chinese, Hispanic, and non-Hispanic Whites. Details of the study have been published previously.(11) Enrolled from six centers across the United States, 6814 men and

women aged 46 – 88 years underwent a baseline study visit between July 2000 and August 2002. Participants were free of clinically evident CVD and exclusion criteria included history of physician diagnosed heart attack, angina, heart failure, stroke or transient ischemic attack, and CVD-related procedures (coronary artery bypass graft, angioplasty, valve replacement, or pacemaker placement).

Enrolled participants returned for four subsequent follow up visits at 18 – 21 month intervals. At exams 2 and 3, a random subset of 1970 participants was enrolled in an ancillary study on body composition, inflammation, and CVD. Individuals with incident CVD after visit 1 were excluded from the current analysis. The protocol for this study was approved by the institutional review boards for all participating field centers. All study participants provided written informed consent.

Data Collection

At all clinic visits, standardized questionnaires were used to obtain race, sociodemographic and health history information. Using the Typical Week Physical Activity Survey, participants self-reported their time spent in sedentary behavior and in various physical activities during a typical week in the previous month. Cigarette smoking was defined as current, former, or never. Height and weight were measured with participants wearing light clothing and without shoes, and BMI was calculated (weight [kg]/ height [m^2]). Waist and hip circumferences were measured with a standard flexible tape measure. Resting seated blood pressure was measured three times using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, Fl) and the average of the second and third readings was used in analysis. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90mm Hg, or current use of an anti-hypertensive medication.

Laboratory

At each visit, 12hr-fasting venous blood samples were obtained and processed using standard methods.(11) Total and high-density lipoprotein cholesterol, triglycerides, insulin and glucose levels were measured. Samples from clinic visits 2 and 3 were assayed for IL-6, resistin, CRP, and TNF-α as well as the adipokines leptin and adiponectin. CRP was measured by immunonephelometry using the BNII instrument (N High Sensitivity CRP, N Antiserum to Human Fibrinogen, Dade Behring Inc., Deerfield, Ill), while IL-6 was measured by ultrasensitive ELISA (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Minneapolis, Minn). Resistin, TNF-α, leptin, and adiponectin concentrations were measured using Bio-Rad Luminex flow cytometry (Millepore, Billerica, MA, USA). These analyses were performed at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, VT). Participants who used cholesterol reducing medication or with a total cholesterol/high-density lipoprotein cholesterol ratio > 5.0 were classified as dyslipidemic, whilst those who used hypoglycemic medication or with a fasting glucose ≥ 126 mg dl^{-1} were classified as diabetic.

Computed Tomography

Computed tomography of the chest was performed to measure the presence and extent of coronary artery calcium (CAC).(11) Of note, at visits 2 and 3, computed tomography of the abdomen was also performed to determine the presence and extent of atherosclerotic calcification of the abdominal aorta.(12)

Abdominal Muscle Measurements

Using a single CT slice at $L_4 – L_5$, abdominal muscle and fat were measured using the Medical Imaging Processing Analysis and Visualization (MIPAV) software version 4.1.2 (NIA/NIH, Bethesda, MD). Tissue was categorized into lean muscle, fat, and mixed connective based on the Hounsfield units (HU) observed. Zero to 100 HU was considered lean muscle, −190 to −30 HU was considered fat and the intervening HU range was considered mixed connective tissue. Bilateral oblique, rectus abdominus, paraspinal and psoas muscles were defined within their unique facial planes. These muscles were grouped into muscles of stabilization (oblique, rectus abdominus, paraspinal muscles) and muscles of locomotion (psoas muscle). For each muscle, *area* was determined by summing the number of pixels of 0 –100 HU within that muscle's corresponding fascial plane. Muscle *density* was the average HU measurement within the muscle's distinct fascial plane for those with an HU value within the appropriate range. A similar process was completed for visceral and subcutaneous fat.

Statistical Analysis

Characteristics of the population were determined with means and standard deviations for continuous variables, and counts and percentages for categorical variables. Resistin was normally distributed, while IL-6, CRP and TNF-α were log-transformed to reduce skewness. ANCOVA, adjusting for age, gender and race, was used to determine the means of muscle *area* and muscle *density* by quartile of each inflammatory mediator. To determine the association between the inflammatory mediator and both muscle *area* and *density*, we utilized multivariable linear regression and the continuous and categorical (in quartiles) forms of the muscle variables (separately). For all regression analyses, model 1 was adjusted for age, gender, race/ethnicity, dyslipidemia, hypertension, diabetes, estimated glomerular filtration rate, coronary artery calcium, physical activity and sedentary behavior. Model 2 additionally adjusted for leptin, adiponectin and the other measured adiposity associated inflammatory mediators that were not the primary outcome variable of interest in the specific model. In model 3 we added visceral and subcutaneous fat volumes to the variables listed in model 2. Finally, in sensitivity analysis, we modeled *both* muscle *area* and *density* simultaneously and included all of the aforementioned covariates. Of note, although leptin and adiponectin were included as covariates, we did not include them as primary outcome variables for this analysis because they are the focus of a separate report.

Multiplicative interactions between muscle *area and density* with both gender and race/ethnicity were separately assessed for each of the adiposity associated inflammatory mediators. None were significant. A two-tailed P-value <0.05 was considered statistically significant and all statistical analyses were conducted using STATA (Version 13; StataCorp, College Station, TX, USA).

Results

Cohort Characteristics

The characteristics of the study cohort are provided in Table 1. The mean age was 64.7 years and 49% were female. Forty percent were non-Hispanic White, 26% were Hispanic/ Latino American, 21% were African American, 13% were Chinese American. The mean BMI was 28.0 kg/m^2 and 30% were obese (BMI > 30 kg/m^2). Forty-six percent were former or current smokers, 47% had hypertension, 39% had dyslipidemia, and 14% had diabetes mellitus. Fifty seven percent had any coronary artery calcium (CAC) and the median CAC score was 8.82. The mean serum creatinine and eGFR were 0.94 mg/dl and 79 ml/min/ 1.73m^2, respectively.

Mean (SD) concentrations of IL-6, resistin, CRP and TNF-α were: 2.4 pg/ml (1.8), 16.4 ng/ml (8.4), 3.2 mg/L (7.0) and 5.8 pg/ml (9.7), respectively. The mean areas (in cm^2) of abdominal subcutaneous and visceral fat were 253.7 (117.7) and 146.6 (68.4). The mean area of total abdominal muscle was 98.3 (27.6), while stabilization muscle was 74.6 (21.8) and locomotive muscle was 23.7 (7.4). The mean densities (in HU) for total, stabilization and locomotive abdominal muscle were 42.2 (5.5), 39.5 (6.1) and 50.2 (5.2), respectively.

Mean Levels of Muscle Area and Density by Quartiles of the Inflammatory Mediators

In general, higher levels of the adiposity associated inflammatory mediators (as quartiles) were associated with lower levels of abdominal muscle *area* and *density* [Table 2], with the associations being stronger for *density*. More specifically, and across quartiles of both IL-6 and CRP, the mean levels of locomotive muscle *area* decreased significantly ($p \leq 0.01$), but the decreases in total (IL-6: p=0.69; CRP: p=0.75) and stabilization (IL-6: p=0.63; CRP: p=0.79) muscle *area* were not significant. In contrast, significantly lower levels of total, stabilization, and locomotive muscle *density* were seen across all quartiles of IL-6 and CRP ($p < 0.01$ for each density variable). Across quartiles of resistin, no significant trend with muscle *area* was seen (total: p=0.86; stabilization: p=0.70; locomotive: p=0.58). However, there was a significant decrease in total muscle *density* (p=0.02) and stabilization muscle *density* (p=0.03), but the decrease in locomotive muscle *density* was not significant (p=0.11). Finally, the trends were largely non-significant for TNF-α, with only total (p=0.06) and stabilization (p=0.03) muscle *areas* showing moderately significant decreases across quartiles. Given this, and that TNF-α was not significantly associated with any of the muscle area or density variables, we did not conduct multivariable analyses for this mediator.

Associations of Muscle Area and Density (as continuous variables) with the Inflammatory Mediators

After adjustment for cardiovascular risk factors (model 1) and adiposity associated inflammatory mediators (model 2), a 1-SD increment of locomotive muscle *area* was significantly associated with an 8.9% (p = 0.01) lower IL-6 level that became non-significant after additional adjustment for subcutaneous and visceral fat (β= −0.061, p=0.11) [Table 3]. Total and stabilization muscle *area* were not significantly associated with IL-6. In contrast, and with full adjustment (model 3), a 1-SD increment of total, stabilization, and locomotive

muscle *density* was significantly associated with 15.3%, 14.8%, and 8.8% ($p< 0.01$ for each) lower IL-6 levels.

Resistin showed a somewhat stronger association with *area* than the other selected mediators, such that, after full adjustment, a 1-SD increment of both total and locomotive muscle *area* were significantly associated with lower levels of resistin ($\beta=-0.083$ ng/mL, $p=0.03$ & $\beta=-0.092$, $p=0.03$; respectively). The association with stabilization *area* was of borderline significance ($\beta=-0.064$, $p=0.07$). As was the case for IL-6, a 1-SD increment of total, stabilization, and locomotive muscle *density* was significantly associated with 0.111 ($p< 0.01$), 0.107 ($p< 0.01$), and 0.069 ($p= 0.02$) ng/mL lower resistin levels, after full adjustment.

For all of the models, CRP was not significantly associated with the muscle *area* variables. However, after adjustment for CVD risk factors and the other adiposity associated inflammatory mediators (model 2), a 1-SD increment of total, stabilization, and locomotive muscle *density* was significantly associated with 8.5% ($p<0.01$), 8.3% ($p<0.01$), and 5.1% ($p=0.02$) lower CRP levels, respectively. This association became non-significant with additional adjustment for subcutaneous and visceral fat.

In sensitivity analysis with both muscle area and density in the same model, as well as all of the aforementioned covariates, muscle *density* retained the significant associations described above, while the associations for muscle *area* became non-significant. Specifically, total muscle density was significantly associated with lower IL-6 (−15%, $p < 0.01$) and resistin (−0.10 ng/ml, $p = 0.01$) but total muscle area was not (4%, $p = 0.28$ and −0.04, $p = 0.37$; respectively). The magnitudes and significance of the associations for stabilization muscle density and area were essentially the same as those for total muscle, while the results for locomotive muscle density and area were similar.

Associations of Muscle Area and Density (as quartiles) with the Inflammatory Mediators

After full adjustment, and compared with the lowest quartile, the 3rd and 4th quartiles of total (Q3: $\beta=-0.13$, $p=0.01$; Q4: $\beta= -0.19$, $p<0.01$), stabilization (Q3: $\beta= -0.18$, $p<0.01$; Q4: $\beta= -0.23$, $p<0.01$), and locomotive (Q3: $\beta=-0.09$, $p=0.05$; Q4: $\beta=-0.15$, $p<0.01$) muscle *density* demonstrated significant and progressively lower values of IL-6 [Table 4]. Conversely, no significant associations were seen between IL-6 and the muscle *area* variables.

After adjusting for the variables in model 3, and compared with the lowest quartile, the 4th quartiles of *total* and *stabilization* muscle area were associated with 1.82 ($p=0.05$) and 1.69 ($p = 0.04$) ng/ml lower resistin levels, while the inverse associations with resistin were stronger and significant across all quartiles of *locomotive* muscle area (Q2: $\beta=-1.29$, $p=0.05$; Q3: $\beta=-1.93$, $p=0.02$; Q4: $\beta=-2.10$, $p=0.04$). Compared to the 1st quartile and after full adjustment, the 2nd, 3rd, and 4th quartiles of *total* muscle density were associated with 1.53 ($p=0.02$), 1.86 ($p=0.01$), and 2.09 ($p=0.01$) ng/ml lower resisitin levels. In contrast, resistin levels were similar across the 2nd and 3rd quartiles of *stabilization* muscle density (Q2: $\beta=-2.01$, $p<0.01$; Q3: $\beta=-1.92$, $p=0.01$) but modestly stronger in the 4th quartile (Q4:

β=−2.59, p>0.01). Resistin did not demonstrate a significant and consistent trend with *locomotive* muscle density.

Compared with the lowest quartile, and after adjustment for the variables in model 1, CRP levels were significantly lower across each quartile of total, stabilization, and locomotive abdominal muscle *density*. With additional adjustment for the other inflammatory mediators, these associations were only significant for the 4th quartiles of these muscle groups (total Q4: β=−0.19, p=0.02; stabilization Q4: β=−0.20, p=0.01; locomotive Q4: β=−0.14, p=0.04). However, with adjustment for subcutaneous and visceral fat, these associations were no longer significant. There were no significant associations between the muscle *area* variables and CRP.

We also conducted sensitivity analyses using quartiles of muscle area and density that were simultaneously adjusted for each other and the other covariates (Figures 1 and 2). The results demonstrated the same findings as before with the continuous muscle variables. That is, the significant associations between the muscle *density* variables and the adiposity associated inflammatory mediators were retained, while the few significant associations between muscle *area* and the mediators became non-significant.

Discussion

In this cross-sectional study of a large, multiethnic, 6-center population-based cohort in the United States, higher levels of abdominal muscle *density* were significantly associated with lower levels of selected adiposity associated inflammatory mediators independent of relative covariates, as well as abdominal muscle area. Specifically, after full adjustment, greater total, stabilization, and locomotive muscle density were significantly associated with lower levels of IL-6. Interestingly, there appeared to be a threshold effect such that those above the median had significantly lower IL-6 values and the associations by quartile for those above the median appeared to be linear. Similarly, each variable for continuous muscle density was significantly associated with lower resistin levels that appeared to be nonlinear across muscle density quartiles. Notably, TNF-α was not associated with muscle in univariable analyses, while CRP was not associated with either muscle area or density after multivariable adjustment. Taken together, these findings suggest a robust relationship between muscle *density* and specific measures of adiposity associated inflammation that may be relevant to the prevention of chronic disease.

Notably, the observed inverse relationship between specific adiposity associated inflammatory mediators and muscle density remained significant even after controlling for the all the other covariates including the other adiposity associated inflammatory mediators, subcutaneous and visceral fat, as well as abdominal muscle area. This suggests there may be alternative pathways mediating the relationship between inflammation and muscle density, relating to perhaps muscle composition and function rather than quantity (9,13), as well as the anti-inflammatory effects of muscle itself (14).

Mechanistically, an increase of lipid within myocytes has been shown to be associated with decreased muscle density measured as CT attenuation values.(9) More specifically, among

obese individuals, a positive energy imbalance leads to storage of excess energy in adipocytes resulting in adipocyte hypertrophy and hyperplasia.(15,16) This is associated with intracellular abnormalities of adipocyte function such as elevated levels of inflammation and oxidative stress.(15,17) Dysfunctional adipocytes also have higher rates of lipolysis, with fatty acids being released into the circulation bound to albumin that can cause pathologic disruption of non-adipose tissues such as the liver, pancreas, blood vessels, and muscle.(16) In this respect, it is hypothesized that insulin resistance in skeletal muscle of those who are obese is caused by accumulation of *excess* intramyocellular lipids.(15) The inverse association between muscle density and inflammatory mediators demonstrated in our study provide further support for this hypothesis.

While sarcopenia is historically defined as the loss of lean muscle mass and strength with aging,(18) recent evidence suggests the quality of muscle tissue is more functionally relevant than its quantity. (13) In this regard, a study examining skeletal muscle attenuation and strength in the elderly found that skeletal muscle density decreases with age and higher muscle density is associated with greater strength, independent of muscle cross sectional area.(19) Such results indicate that lipid accumulation within muscle may hinder muscle function.(13) Furthermore, it is hypothesized that a greater abundance of adipocytes within muscle increases local concentrations of inflammatory cytokines,(10) which may contribute to sarcopenia and functional declines of aging through catabolic effects on muscle.(20) Even healthy aging results in increases of circulating inflammatory markers.(20) Indeed, higher levels of IL-6 and TNF-α are associated with lower muscle mass and strength in elderly adults(21) and experimental studies have shown that administration of IL-6 or TNF-α in rats causes muscle catabolism.(22)

It is also important to consider the protective role that muscle itself may play against inflammation. In support of this hypothesis, previous authors have suggested that, like fat, muscle is an endocrine organ.(14, 23) For instance, Pedersen et al described peptides and cytokines produced and released by muscle fibers as “myokines”, which target end organs via the circulation and act on muscle in paracrine fashion.(14, 23) As such, exercise may have salutary effects among those with chronic disease, or aging in general, from reduction of systemic inflammation.(24,25) In addition to exercise induced decreases in adiposity, it is hypothesized that anti-inflammatory myokines secreted by contracting muscle play a key role.(14, 24)

The results of our study may have implications for the prevention of CVD. Specifically, IL-6 and resistin have previously been associated with cardiovascular disease. For example, there was a strong association observed between increasing resistin levels and incident cardiovascular disease, coronary heart disease, and heart failure independent of cardiovascular risk factors, obesity, and other markers of inflammation/ insulin resistance. (26) Similarly, prolonged moderate increases in IL-6 levels were found to be associated with risk of coronary heart disease as strongly as several major established risk factors, including blood pressure and blood cholesterol levels.(27)

Strengths of this study include a very well characterized, large, multi-ethnic cohort that allowed for comparison of associations across race/ethnicity. Also, most studies on body

composition have focused on the effects of discrete measures of adiposity (i.e. visceral and subcutaneous fat). As such, our report expands the current literature by providing results on both muscle area and density. Moreover, we examined four different adiposity associated inflammatory mediators, as well as contemporary measures of abdominal muscle area and density from CT scans, and categorized the abdominal muscle by functional properties. A limitation of our study is the cross sectional study design, which precludes excluding the possibility of reverse causality (i.e. inflammation resulting in changes in muscle mass). The population from this study was healthy at baseline and the race/ethnic distribution is not representative of the general population. Therefore, the generalizability of the findings should be made with caution.

In conclusion, abdominal muscle density, but not muscle area, is independently and inversely associated with IL-6 and resistin levels. As such, interventions aimed at improving abdominal muscle density, such as high repetition strength training, may result in lower levels of these adiposity associated inflammatory mediators and, thereby, contribute to the prevention of inflammation-linked chronic diseases such as CVD.

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Figure 1.

Multivariable Associations between Quartiles of Muscle Density and Interleukin-6

Q2 = Quartile 2, Q3 = Quartile 3, Q4 = Quartile 4

Adjusted for: age, gender, race, dyslipidemia, diabetes, hypertension, eGFR, CAC, physical activity, sedentary behavior, leptin, adiponectin, resistin, CRP, TNF-α, abdominal subcutaneous and visceral fat, and muscle area

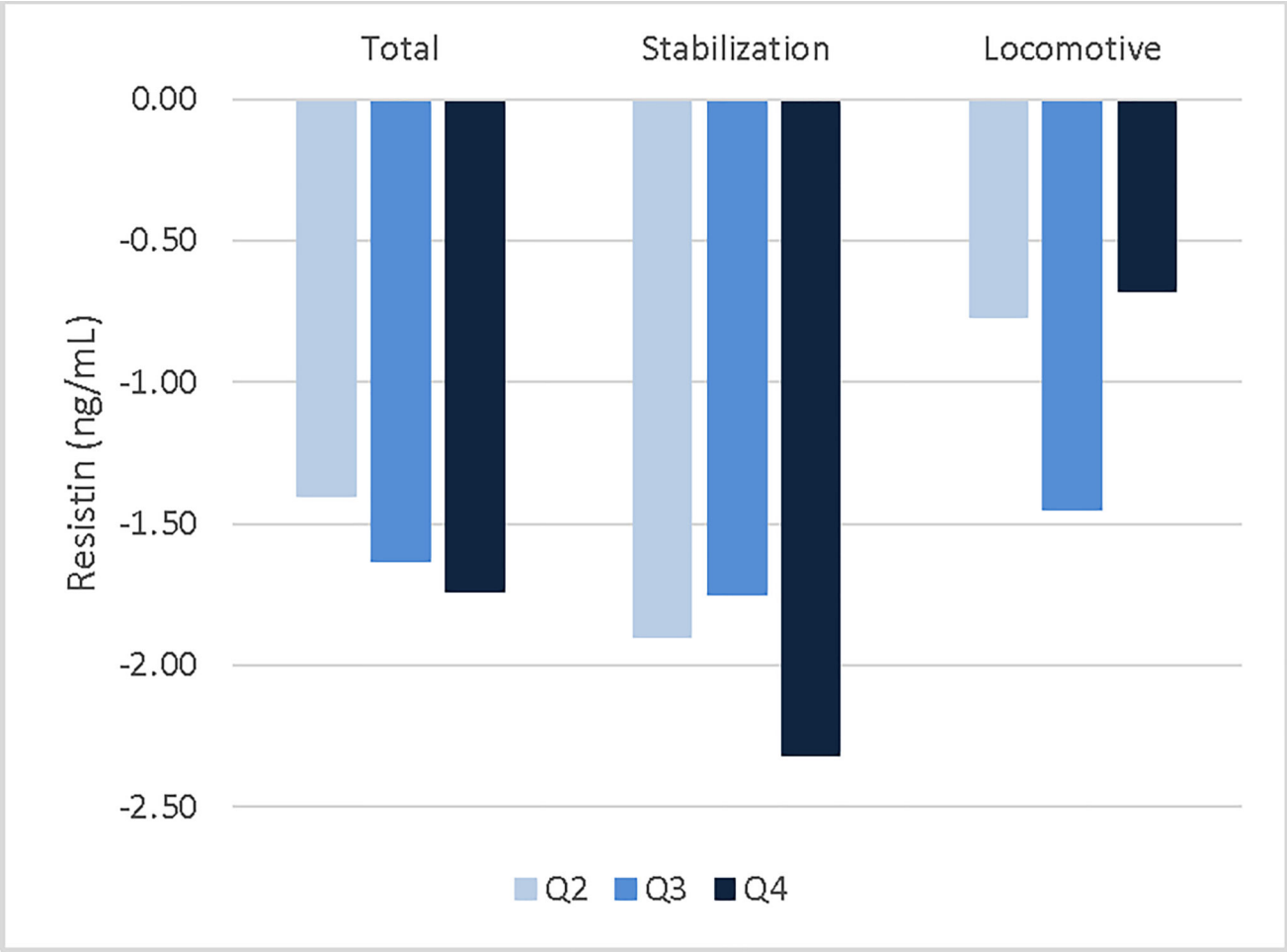

Figure 2.

Multivariable Associations between Quartiles of Muscle Density and Resistin

Q2 = Quartile 2, Q3 = Quartile 3, Q4 = Quartile 4

Adjusted for: age, gender, race, dyslipidemia, diabetes, hypertension, eGFR, CAC, physical activity, sedentary behavior, leptin, adiponectin, IL-6, CRP, TNF-α, abdominal subcutaneous and visceral fat, and muscle area

TABLE 1

COHORT CHARACTERISTICS

Characteristic	Mean (SD)/Median or Frequency (Percent)	Min – Max
Age (years)	64.7 (9.6)/64	46 – 88
Female	961 (49%)	
Non- Hispanic White	785 (40%)	
Hispanic American	501 (26%)	
African American	407 (21%)	
Chinese American	251 (13%)	
Waist to hip ratio	0.94 (0.07)/0.94	0.67 – 1.19
BMI (kg/m^2)	28.0 (5.1)/27.3	15.8 – 55.9
Obese (BMI> 30)	570 (30%)	
Creatinine (mg/dl)	0.94 (0.27)/0.90	0.38 – 5.4
eGFR by CKD-epi eqn ($ml/min/1.73m^2$)	79.2 (17.4)/79.9	10.2 – 147.0
Moderate to vigorous physical activity (Met-min/week)	4937 (4746)/3577	0 – 36900
Sedentary behavior (Met-min/ week)	1678 (1093)/1470	0 – 6300
Ever Smoked	874 (46%)	
Dyslipidemia	732 (39%)	
Diabetes	271 (14%)	
Hypertension	889 (47%)	
Coronary Calcium Score	178.3 (436.4)/8.8	0 – 4136
Leptin (ng/ml)	20.6 (22.0)/13.2	0.02 – 224.94
Adiponectin (μg/ml)	20.8 (13.3)/17.5	2.4 – 110.7
IL6 (pg/ml)	2.4 (1.8)/1.9	0.3 – 11.9
Resistin (ng/ml)	16.4 (8.4)/15.0	2.4 – 230.4
CRP (mg/L)	3.2 (7.0)/1.5	0.16 – 161
TNF-α (pg/ml)	5.8 (9.7)/4.6	0.7 – 269.8
Subcutaneous fat area (cm^2)	253.7 (117.7)/236.1	6.1 – 780
Visceral fat area (cm^2)	146.6 (68.4)/136.3	16.4 – 469.6
Total abdominal muscle area (cm^2)	98.3 (27.6)/94.7	34.9 – 226.9
Stabilization abdominal muscle area (cm^2)	74.6 (21.8)/72.1	27.8 – 187.8
Locomotive abdominal muscle area (cm^2)	23.7 (7.4)/22.6	3.0 – 51.5
Total abdominal muscle density (HU)	42.2 (5.5)/42.7	25.9 – 56.8
Stabilization abdominal muscle density (HU)	39.5 (6.1)/40.0	20.7 – 55.1
Locomotive abdominal muscle density (HU)	50.2 (5.2)/50.9	26.6 – 63.4

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TABLE 2

MEAN ABDOMINAL MUSCLE AREAS (CM^2) AND DENSITIES (HU) BY INFLAMMATORY MEDIATOR QUARTILES

Abdominal Muscle Variable	Interleukin - 6 Quartile (pg/ml)				P-value
	Q1 (<1.2)	Q2 (1.2 – 1.9)	Q3 (1.9 – 2.9)	Q4 (> 2.9)	
Total area	102.6	99.0	97.0	95.8	0.69
Stabilization area	77.4	75.0	73.7	73.2	0.63
Locomotive area	25.2	24.0	23.2	22.5	<0.01
Total density	44.7	42.8	41.4	40.1	<0.01
Stabilization density	42.2	40.1	38.6	37.3	<0.01
Locomotive density	52.2	50.7	49.5	48.5	<0.01

Abdominal Muscle Variable	Resistin Quartile (ng/ml)				P-value
	Q1 (<11.9)	Q2 (11.9 – 15.0)	Q3 (15.0 – 19.1)	Q4 (>19.1)	
Total area	99.7	100.8	98.0	95.6	0.86
Stabilization area	75.7	76.4	74.4	72.7	0.70
Locomotive area	24.0	24.4	23.6	22.9	0.58
Total density	43.2	42.6	41.9	41.3	0.02
Stabilization density	40.6	40	39.2	38.5	0.03
Locomotive density	50.9	50.4	49.9	49.6	0.11

Abdominal Muscle Variable	CRP Quartile (mg/L)				P-value
	Q1 (<0.7)	Q2 (0.7 – 1.5)	Q3 (1.5 – 3.3)	Q4 (>3.3)	
Total area	101.3	100.2	98.3	94.1	0.75
Stabilization area	76.5	75.8	74.7	72.1	0.79
Locomotive area	24.8	24.4	23.5	22.0	0.01
Total density	43.8	42.6	41.7	40.7	<0.01
Stabilization density	41.2	39.9	39.0	37.9	<0.01
Locomotive density	51.5	50.4	49.8	49.0	<0.01

Abdominal Muscle Variable	TNF – α Quartile (pg/ml)				P-value
	Q1 (<3.4)	Q2 (3.4 – 4.6)	Q3 (4.6 – 6.3)	Q4 (<6.3)	
Total area	97.0	98.2	101.8	97.2	0.06
Stabilization area	73.5	74.5	77.2	74.0	0.03
Locomotive area	23.5	23.6	24.6	23.2	0.65
Total density	42.8	42.5	42.4	41.3	0.06
Stabilization density	40.1	39.8	39.8	38.5	0.08
Locomotive density	50.7	50.4	50.2	49.5	0.07

TABLE 3

MULTIVARIABLE LINEAR REGRESSION OF CONTINUOUS ABDOMINAL MUSCLE AREAS AND DENSITIES FOR THE INFLAMMATORY MEDIATORS

Interleukin-6 $^{\gamma}$			
Abdominal Muscle Variable	Model 1	Model 2	Model 3
	β	β	β
Total area	−0.042	−0.039	−0.035
Stabilization area	−0.012	−0.020	−0.021
Locomotive area	−0.138***	−0.089***	−0.061
Total density	−0.285***	−0.209***	−0.153***
Stabilization density	−0.276***	−0.210***	−0.148***
Locomotive density	−0.190***	−0.116***	−0.088***
Resistin $^{\varphi}$			
Abdominal Muscle Variable	Model 1	Model 2	Model 3
	β	β	β
Total area	−0.079**	−0.074**	−0.083**
Stabilization area	−0.057*	−0.056*	−0.064*
Locomotive area	−0.092**	−0.074*	−0.092**
Total density	−0.104***	−0.077***	−0.111***
Stabilization density	−0.097***	−0.071**	−0.107***
Locomotive density	−0.075***	−0.054**	−0.069**
CRP $^{\gamma}$			
Abdominal Muscle Variable	Model 1	Model 2	Model 3
	β	β	β
Total area	−0.005	−0.0005	−0.033
Stabilization area	0.008	0.002	−0.026
Locomotive area	−0.061	−0.016	−0.035
Total density	−0.176***	−0.085***	−0.038
Stabilization density	−0.174***	−0.083***	−0.034
Locomotive density	−0.111***	−0.051**	−0.026

Model 1 - CVD Risk Factors: age, gender, race, dyslipidemia, diabetes, hypertension, eGFR, CAC, physical activity, sedentary behavior
Model 2- Model 1 + leptin, adiponectin, IL6, resistin, CRP, TNF-α
Model 3 – Model 2 + Abdominal subcutaneous and visceral fat

$^{\gamma}$Results are expressed as fractions

$^{\varphi}$Results are expressed as ng/ml

*** $p \leq 0.01$,

** $p \leq 0.05$,

* $p \leq 0.10$

TABLE 4

MULTIVARIABLE LINEAR REGRESSION OF QUARTILES OF ABDOMINAL MUSCLE AREAS AND DENSITIES FOR THE INFLAMMATORY MEDIATORS

Interleukin-6 [γ]				
Abdominal Muscle Variable		**Model 1**	**Model 2**	**Model 3**
		β	**β**	**β**
Total area	Q2	0.013	−0.004	0.011
	Q3	−0.010	−0.032	−0.034
	Q4	−0.031	−0.040	−0.027
Stabilization area	Q2	0.018	0.023	0.025
	Q3	−0.013	−0.024	−0.030
	Q4	−0.017	−0.030	−0.033
Locomotive area	Q2	−0.033	−0.007	−0.008
	Q3	−0.085	−0.047	−0.034
	Q4	−0.177***	−0.101*	−0.076
Total density	Q2	−0.085**	−0.034	0.001
	Q3	−0.274***	−0.190***	−0.133***
	Q4	−0.426***	−0.295***	−0.189***
Stabilization density	Q2	−0.154***	−0.090**	−0.058
	Q3	−0.307***	−0.236***	−0.179***
	Q4	−0.452***	−0.327***	−0.228***
Locomotive density	Q2	−0.128***	−0.040	−0.041
	Q3	−0.223***	−0.131***	−0.089**
	Q4	−0.314***	−0.192***	−0.154***

Resistin [φ]				
Abdominal Muscle Variable		**Model 1**	**Model 2**	**Model 3**
		β	**β**	**β**
Total area	Q2	−0.300	−0.581	−0.742
	Q3	−1.056	−1.143*	−1.248*
	Q4	−1.512*	−1.585**	−1.815**
Stabilization area	Q2	−0.919	−0.873	−1.003
	Q3	−0.523	−0.735	−0.721
	Q4	−1.638**	−1.485**	−1.690**

Resistin [9]				
Abdominal Muscle Variable		**Model 1**	**Model 2**	**Model 3**
		β	**β**	**β**
Locomotive area	Q2	−1.050 *	−1.107 **	−1.294 **
	Q3	−1.812 ***	−1.611 **	−1.934 **
	Q4	−2.060 **	−1.798 **	−2.098 **
Total density	Q2	−1.640 ***	−1.443 ***	−1.531 **
	Q3	−2.080 ***	−1.581 ***	−1.856 ***
	Q4	−2.118 ***	−1.466 **	−2.091 ***
Stabilization density	Q2	−1.977 ***	−1.558 ***	−2.010 ***
	Q3	−2.025 ***	−1.515 **	−1.923 ***
	Q4	−2.476 ***	−1.710 **	−2.588 ***
Locomotive density	Q2	−0.856	−0.550	−0.947
	Q3	−1.446 ***	−1.134 **	−1.730 ***
	Q4	−0.806	−0.374	−1.009

CRP [7]				
Abdominal Muscle Variable		**Model 1**	**Model 2**	**Model 3**
		β	**β**	**β**
Total area	Q2	0.048	0.001	−0.022
	Q3	0.033	0.045	0.028
	Q4	0.061	0.023	−0.040
Stabilization area	Q2	−0.045	−0.061	−0.084
	Q3	0.039	0.035	0.034
	Q4	−0.010	−0.006	−0.059
Locomotive area	Q2	−0.014	0.002	−0.016
	Q3	−0.081	0.001	−0.041
	Q4	−0.114	−0.010	−0.076
Total density	Q2	−0.099	−0.021	0.014
	Q3	−0.285 ***	−0.081	−0.023
	Q4	−0.426 ***	−0.186 **	−0.074
Stabilization density	Q2	−0.168 **	−0.033	0.029
	Q3	−0.288 ***	−0.069	−0.003
	Q4	−0.460 ***	−0.196 ***	−0.075

CRP [γ]				
Abdominal Muscle Variable		**Model 1**	**Model 2**	**Model 3**
		β	**β**	**β**
Locomotive density	Q2	−0.165 **	−0.030	0.041
	Q3	−0.188 ***	−0.051	−0.003
	Q4	−0.290 ***	−0.137 **	−0.035

Model 1 - CVD Risk Factors: age, gender, race, dyslipidemia, diabetes, hypertension, eGFR, CAC, physical activity, sedentary behavior
Model 2- Model 1 + leptin, adiponectin, IL6, resistin, CRP, TNF-α
Model 3 – Model 2 + Abdominal subcutaneous and visceral fat

[γ] Results are expressed as fractions

[φ] Results are expressed as ng/ml

*** $p \leq 0.01$,

** $p \leq 0.05$,

* $p \leq 0.10$