Muscle Attenuation Is Associated With Newly Developed Hypertension in Men of African Ancestry

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Abstract—Increased ectopic adipose tissue infiltration in skeletal muscle is associated with insulin resistance and diabetes mellitus. We evaluated whether change in skeletal muscle adiposity predicts subsequent development of hypertension in men of African ancestry, a population sample understudied in previous studies. In the Tobago Health Study, a prospective longitudinal study among men of African ancestry (age range 40–91 years), calf intermuscular adipose tissue, and skeletal muscle attenuation were measured with computed tomography. Hypertension was defined as a systolic blood pressure ≥140 mm Hg, or a diastolic blood pressure ≥90 mm Hg, or receiving antihypertensive medications. Logistic regression was performed with adjustment for age, insulin resistance, baseline and 6-year change in body mass index, baseline and 6-year change in waist circumference, and other potential confounding factors. Among 746 normotensive men at baseline, 321 (43%) developed hypertension during the mean 6.2 years of follow-up. Decreased skeletal muscle attenuation was associated with newly developed hypertension after adjustment for baseline and 6-year change of body mass index (odds ratio [95% confidence interval] per SD, 1.3 [1.0–1.6]) or baseline and 6-year change of waist circumference (odds ratio [95% confidence interval] per SD, 1.3 [1.0–1.6]). No association was observed between increased intermuscular adipose tissue and hypertension. Our novel findings show that decreased muscle attenuation is associated with newly developed hypertension among men of African ancestry, independent of general and central adiposity and insulin resistance. Further studies are needed to adjust for inflammation, visceral and other ectopic adipose tissue depots, and to confirm our findings in other population samples. (***Hypertension*****. 2017;69:00-00. DOI: 10.1161/HYPERTENSIONAHA.116.08415.)**
● **Online Data Supplement**

Key Words: adipose tissue ■ African continental ancestry group ■ hypertension ■ male, aging ■ muscle, skeletal ■ obesity

Storage of adipose tissue around and within nonadipose tissue organs (known as ectopic adipose tissue) is now recognized as a risk factor for type 2 diabetes mellitus (T2D) and cardiovascular disease, independent of general adiposity.[1–8] Compared with abdominal visceral adipose tissue, adipose tissue infiltration within and around muscles is understudied, but has recently become a focus of research on obesity. Skeletal muscle accounts for ≤80% of glucose disposal. Thus, excess adipose tissue infiltration in muscles may impair muscle function and, subsequently, drive cardiometabolic diseases.

Skeletal muscles adiposity can be divided into 2 subtypes: intermuscular adipose tissue (IMAT, visible adipose tissue beneath the fascia lata) and intramuscular adipose tissue (adiposity within the muscle cells). Lower skeletal muscle attenuation is indicative of greater intramuscular adipose tissue content.[9,10] Skeletal muscle attenuation is mainly influenced by lipid, water, and glycogen. Peripheral quantitative computed tomography (pQCT) is performed to quantify tissue area, volume, and attenuation. It is unlikely to be biased by the change of water and glycogen contents and, therefore, is thought to mainly reflect lipid infiltration.[11]

Compared with whites, African ancestry individuals have greater burden of T2D[12] and hypertension[13] and have greater ectopic adipose tissue infiltration in the skeletal muscle.[14,15] However, they also have less general[16] and visceral adipose tissue.[17] This suggests that skeletal muscle adiposity may be a key adipose tissue depot contributing to the disproportionally greater risk of cardiometabolic diseases in African ancestry populations.

Despite the fact that skeletal muscle adiposity has been linked to insulin resistance[18] and T2D,[19] the studies on the association between skeletal muscle adiposity and hypertension are sparse, inconclusive, and cross-sectional in design. To date, no study has focused on African ancestry individuals who are at high risk for hypertension. Therefore, our objective was to prospectively evaluate the relationship between skeletal muscles adiposity and newly developed hypertension among middle-aged and elderly men of African ancestry,

Received September 9, 2016; first decision October 4, 2016; revision accepted February 5, 2017.

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The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.116.08415/-/DC1.

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while accounting for potential confounding factors, including total and central adiposity and insulin resistance. We hypothesized that greater skeletal adiposity would be associated with the development of hypertension and that the association would be independent of general and central adiposity and insulin resistance.

Methods

Tobago Health Study

The first Tobago Health Study visit was conducted between 1997 and 2003 on the Caribbean island of Tobago, with the original purpose of providing prostate cancer screening. To be eligible, men had to be ambulatory, noninstitutionalized, and not terminally ill. Three thousand three hundred and seventy-six men (aged ≥40 years) were recruited regardless of their health status via flyers, public service announcements, posters, informing healthcare workers at local hospital and health centers, and word of mouth. The sample was representative of the population with low admixture, including 94% African, 4.6% European, and <1.4% Native American participants.[20]

Between 2003 and 2007, 2173 men from the original cohort were invited via telephone for a calf skeletal muscle composition scan using pQCT, which served as the baseline visit for these analyses. From 2010 to 2013, we invited these men to return for repeat pQCT scans of calf skeletal muscle composition. A total of 1614 men completed the follow-up assessment (80% of survivors). Both the baseline and follow-up visits followed the same procedures for questionnaire interviews, biospecimen collection, and pQCT scans.[21] Hypertension was defined as a systolic blood pressure ≥140 mm Hg, or a diastolic blood pressure ≥90 mm Hg, or currently taking antihypertensive medications. Men with hypertension or a history of cardiovascular disease at baseline were excluded; however, men with other metabolic disorders, such as diabetes mellitus, were included. A total of 746 initially normotensive men were included in the final analyses (Figure 1). Compared with 868 excluded men, the included men were younger and with a healthier metabolic profile, including lower body mass index (BMI), waist circumference (WC), and homeostasis model assessment of insulin resistance (HOMA-IR), less likely to be former smoker, but more likely to be current smoker (all P value <0.05).

The Institutional Review Boards of the University of Pittsburgh and the Tobago Division of Health and Social Services approved this study, and all participants provided written informed consent before data collection.

pQCT Quantification of Skeletal Muscle Adiposity

Studies use pQCT scans for measuring either intermuscular adipose tissue or muscle attenuation. In our study, both types of measures were obtained by pQCT scans of the calf performed using the Stratec XCT-2000. The scanner is calibrated daily to the European Forearm Phantom, which contains 4 volumetric density bone mineral inserts of 0, 50, 100, and 200 mg/cm^3 and operated at a fixed peak kilovoltage. The accurate check of machine stability was performed with manufacturer-supplied quality assurance phantom, which contains density inserts of a known density and cross-sectional area that must be correctly determined before clinical scans.

At both study visits, 2.2 mm cross-sectional images of the calf skeletal muscle composition were obtained at 66% of the tibia length, proximal to the terminal end of the tibia, because this is the region with the largest circumference of the calf and the least variability between individuals.[22] The scanned position was determined while men were seated comfortably with their lower leg positioned in the pQCT gantry such that the tibia was parallel to the floor with the limb supported at the distal thigh and foot.[23] Standardized protocols for participant positioning are performed for all scans.[24] All images were analyzed with STRATEC analysis software version 5.5D (Orthometrix, Inc, White Plains, NY) by a trained investigator unaware of the participants' disease status.

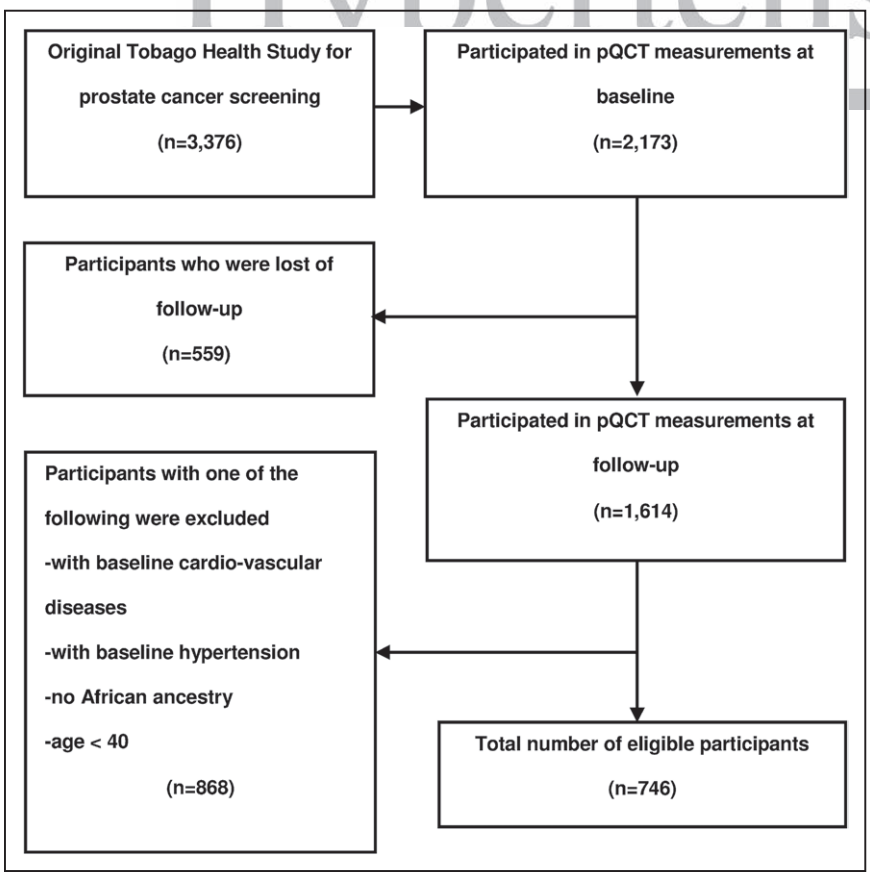

Figure 1. Flow Chart of Tobago Health Study. pQCT indicates peripheral quantitative computed tomography.

The mineral equivalent density of adipose tissue, muscle, and cortical bone differ from 0, 80, 1200 mg/cm^3, respectively, based on the calibration of the scanner. Automatic threshold-based iterative edge detection–guided segmentation of muscle from bone followed a density threshold of 280 mg/cm^3 with contour mode 1 and peel mode 2 (bone area and mass). Segmentation of muscle from subcutaneous adipose tissue followed a threshold of 40 mg/cm^3 with contour mode 3 and peel mode 1 (total muscle+bone area and mass).[23] Muscle cross-sectional area was determined by subtracting bone area from total bone+muscle area. IMAT (mm^2) was determined by a shift of mineral equivalent density from 80 (muscle) to 0 (adipose tissue) in mg/cm^3. Muscle attenuation was calculated as the ratio of muscle mass (mg/cm) and muscle area (cm^2).[25]

The coefficients of variation for total, subcutaneous, and IMAT, muscle area, and muscle density, respectively, were 1.0%, 1.5%, 7.6%, 0.9%, and 1.1%, which were determined by repeat pQCT scanning in 15 individuals.

General Adiposity Measures

Height was measured to the nearest 0.1 cm with a wall-mounted stadiometer. Weight was measured to the nearest 0.1 kg on a balance beam scale. BMI was calculated as the ratio of weight and squared height (kg/m^2). WC was measured to the nearest 0.1 cm at the narrowest point of waist or at the umbilicus if the narrowest point could not be identified.

Medical Conditions

Blood pressure was measured using an automated blood pressure cuff 3 times during each clinic visit after 10 minutes rest. The average of the second and third reading were used to define hypertension status. Men were instructed to bring all prescription medications taken in the past 30 days to the clinic visit and were recorded by interviewers. Taking antihypertensive medication was defined using the ATC/DDD drug classification system (the Anatomical, Therapeutic, Chemical classification system with Defined Daily Doses).[26] Hypertension was defined as a systolic blood pressure ≥140 mm Hg, or a diastolic blood pressure ≥90 mm Hg, or currently taking antihypertensive medications. The HOMA-IR was calculated as (glucose×insulin)/22.5.[27] Other comorbidities, including prevalent cardiovascular disease, renal disease, stroke, and myocardial infarction, were self-reported as yes/no using an interviewer-administered questionnaire.

Other Measurements

Standardized interviewer-administered questionnaires were used to collect demographic information and other factors known to be related to hypertension. Education level was dichotomized into high school and higher versus lower than high school. Marital status was defined as married or living with a spouse versus other. Former smokers were defined as men who smoked >100 cigarettes but did not currently smoke, and current smokers were defined as men who had smoked >100 cigarettes and currently smoked. Alcohol consumption was defined as having ≥4 drinks per week in the past 12 months. As walking is the predominant form of physical activity in Tobago, whether a participant reported walking for exercise, to work, the store, or to church ≥4 times in the past 7 days was collected as a measure of physical activity. Sedentary lifestyle was assessed as the hours of television watched, with the cutoff point of ≥21 hours per week considered sedentary. Self-reported overall health status compared with men of their own age was dichotomized as good/excellent versus fair/poor/very poor. The information from the questionnaires and anthropometric measurements were obtained on the same day as the pQCT scans.

Statistical Analysis

The absolute 6-year change in adiposity measure of interest, including calf muscle attenuation, calf IMAT, BMI, and WC, were calculated for each individual as the difference between follow-up visit and baseline visit. We performed histogram and scatter plot analyses on continuous variables to inspect the distribution and to assess potential outliers, defined as any value outside the interval of Q3+3×interquartile range and Q1–3×interquartile range. The distributions of IMAT and muscle attenuation were skewed with outliers, and after excluding outlier (20 for baseline IMAT and 19 for 6-year absolute increase in IMAT, and 1 for baseline muscle attenuation and 2 for 6-year absolute decrease in muscle attenuation), the distributions of the measures were approximately normal. The difference in variables between individuals with newly developed hypertension and those with normal blood pressure at follow-up are presented as mean±standard deviation (SD), median (interquartile range), or N (frequency) and were analyzed with Student's t test, Wilcoxon test, or χ^2 test, respectively. Sensitivity analyses were performed with and without outliers included.

Logistic regression was first performed for association between overall (BMI) or central (WC) adiposity change measures and newly developed hypertension in separate models. Calf IMAT or skeletal muscle attenuation were further added to the models separately because these 2 measures were highly correlated. All fully adjusted models included age, marriage status, education level, smoking status, alcohol consumption, physical activity, sedentary lifestyle, HOMA-IR, calf muscle area, and follow-up years. We included adjustment for calf muscle area because of its known decrease with aging and its possible association with muscle adipose tissue infiltration. Odds ratios (ORs) and 95% confidence interval (CI) are presented per SD change in adiposity measure for BMI, WC, and calf IMAT and skeletal muscle attenuation. Multicollinearity was tested, and all variance inflation factors were found to be <10. To understand whether different definitions of hypertension would alter this association, we further stratified the hypertensive group by the use of antihypertensive medication. ORs of the adiposity measurements were presented with the nonhypertensive subgroup as the reference and compared between medically treated and untreated subgroups using multinomial logistic regression.

All analyses were performed using SAS statistical software version 9.3 (SAS Institute Inc, Cary, NC).

Results

Baseline Characteristics

Of the 746 men without hypertension or cardiovascular disease at the baseline, 321 developed hypertension over the follow-up time (median [interquartile range] 6.2 years [5.9–6.5 years]; Table 1). Men who developed hypertension were older, more likely to be sedentary, and had higher HOMA-IR at baseline (all P<0.05). Moreover, men who developed hypertension tended to have greater unadjusted baseline BMI, WC, calf IMAT, and lower baseline calf muscle attenuation (all P<0.05).

Association of 6-Year Absolute Change in Overall, Central, and Skeletal Muscle Adiposity Measures With Newly Developed Hypertension

There was no association between absolute change in overall adiposity, as measured by BMI, and odds of newly developed hypertension after adjusting for baseline BMI, age, demographic characteristics, lifestyle factors, and HOMA-IR (OR, 1.0; 95% CI, 0.9–1.2; Table 2). In a model containing all covariates, baseline BMI, change in BMI, baseline muscle attenuation, and change in muscle attenuation, a 1 SD (2.9 mg/cm^3) incremental decrease in muscle attenuation was associated with increased odds of newly developed hypertension (OR, 1.3; 95% CI, 1.0–1.6; Table 2), while change in overall adiposity remained insignificant in the model (P=0.55). In models including BMI adjustment for overall adiposity, there

Table 1. Baseline Characteristics by Newly Developed Hypertension Status

Baseline Characteristics	Follow-Up Hypertension Status			
	Hypertensive (N=321)	Nonhypertensive (N=425)	Crude OR* (95% CI)	*P* Value†
Age, y	56.1±8.0	52.9±7.5	1.1 (1.0–1.1)	<0.001
Education level, n (%)				
High school and above	40 (12.6)	46 (11.0)	1.2 (0.7–1.8)	0.51
Marital status, n (%)				
Married or live with a spouse	238 (74.8)	296 (70.0)	1.3 (0.9–1.8)	0.14
Current smoker, n (%)	37 (11.5)	62 (14.6)	0.8 (0.5–1.2)	0.16
Former smoker, n (%)	66 (20.6)	74 (11.4)	1.2 (0.8–1.7)	0.16
Alcohol consumption, n (%)				
>3 drinks per week	28 (8.7)	43 (10.1)	0.8 (0.5–1.4)	0.51
Physical activity, n (%)				
>3 times per week	159 (49.5)	218 (51.3)	0.9 (0.7–1.2)	0.63
Sedentary lifestyle, n (%)				
≥21 h per week	61 (19.1)	60 (14.2)	1.4 (1.0–2.1)	0.07
HOMA-IR	3.2±1.9	2.5±1.7	1.5 (1.3–1.8)	<0.001
Fasting blood glucose, (mg/dL‡	95 (22.5)	87 (14)	1.6 (1.4–1.9)	<0.001
BMI, kg/m^2	27.1±4.3	25.9±4.1	1.3 (1.2–1.6)	<0.001
WC, cm	92.0±10.6	88.0±10.3	1.5 (1.3–1.7)	<0.001
Calf subcutaneous adipose tissue, mm^2	1362.5±629.8	1292.3±670.9	1.1 (1.0–1.3)	0.15
Calf IMAT, mm^2	211.1±173.3	175.8±144.8	1.2 (1.1–1.4)	0.01
Calf muscle attenuation, mg/cm^3§	77.0±3.1	77.8±2.7	1.3 (1.1–1.5)	<0.001

BMI indicates body mass index; CI, confidence interval; HOMA-IR, homeostasis model assessment of insulin resistance; IMAT, intermuscular adipose tissue; OR, odds ratio; and WC, waist circumference.

†*P* values for comparisons between the hypertensive and nonhypertensive subjects from 2-sample T tests or Wilcoxon tests or χ^2 tests or Fisher's exact test.

*Per SD change for continuous variables except for age (per year).

‡Median (IQR).

§Per SD decrease.

was null association of 6-year absolute increase in calf IMAT and odds of newly developed hypertension (*P*=0.88; Table 2).

However, there was a significant association between absolute change in central adiposity, as measured by WC, and odds of newly developed hypertension when adjusting for baseline WC, age, demographic characteristics, lifestyle factors, and HOMA-IR (OR per SD change in WC, 1.2; 95% CI, 1.0–1.4; Table 2). In a model containing all covariates, baseline WC, change in WC, baseline muscle attenuation, and change in muscle attenuation, a 1 SD (2.9 mg/cm^3) decrease in muscle attenuation was associated with increased odds of newly developed hypertension (OR, 1.3; 95% CI, 1.0–1.6; Table 2), and the association with change in central adiposity was attenuated (*P*=0.11; Table 2). Again, in models including WC adjustment for central adiposity, there was null association of 6-year absolute increase in calf IMAT and odds of newly developed hypertension (*P*=0.90; Table 2).

The associations of overall and central adiposity with newly developed hypertension differed by medication use, such that baseline and changes in adiposity were only associated with untreated hypertension (treatment effect *P* value <0.01 for all; Table S2 in the online-only Data Supplement). However, the association of 6-year absolute decrease in muscle attenuation with newly developed hypertension did not differ significantly by treatment status (*P* value >0.20; Table S2). No significant difference by treatment status was seen for models of calf IMAT.

Figure 2 demonstrates the relationship between 6-year decrease in muscle attenuation and odds of newly developed hypertension by quartile (linear-trend *P* value =0.04). The quartile with the greatest reduction in muscle attenuation was associated with elevated risk of developing hypertension (OR, 1.7; 95% CI, 1.0–2.8).

Discussion

In this study, we found a novel association between decreased skeletal muscle attenuation, a surrogate measure of greater intramuscular adipose tissue, and increased odds of newly developed hypertension after 6 years of follow-up in men of African ancestry. These results were independent of and stronger predictors than general and central adiposity. Therefore, our findings support the hypothesis that muscle attenuation may be a more important risk factor for hypertension than general or central adiposity, particularly in men of African ancestry.

Table 2. Multivariable Adjusted Odds Ratios for Newly Developed Hypertension per SD Difference in Absolute Baseline and Longitudinal Skeletal Muscle Adiposity Measures

Adiposity Measures	OR (95% CI)*	*P* Value
Multivariable effects adjusted for overall adiposity (BMI)†		
Model with BMI only		
6-year increase in BMI	1.0 (0.9–1.2)	0.76
Baseline BMI	1.2 (1.0–1.5)	0.02
Model with BMI and calf muscle attenuation		
6-year decrease in muscle attenuation	1.3 (1.0–1.6)	0.02
6-year increase in BMI	1.1 (0.9–1.3)	0.55
Baseline muscle attenuation	1.3 (1.0–1.6)	0.04
Baseline BMI	1.1 (0.9–1.4)	0.50
Model with BMI and Calf IMAT		
6-year increase in IMAT	1.0 (0.8–1.2)	0.88
6-year increase in BMI	1.0 (0.9–1.2)	0.86
Baseline IMAT	1.0 (0.8–1.3)	0.77
Baseline BMI	1.2 (1.0–1.5)	0.11
Multivariable effects adjusted for central adiposity (WC)*		
Model with WC only		
6-year increase in WC	1.2 (1.0–1.4)	0.03
Baseline WC	1.3 (1.1–1.6)	0.002
Model with WC and Calf muscle attenuation		
6-year decrease in muscle attenuation	1.3 (1.0–1.6)	0.02
6-year increase in WC	1.2 (1.0–1.4)	0.11
Baseline muscle attenuation	1.2 (1.0–1.5)	0.09
Baseline WC	1.2 (0.9–1.5)	0.25
Model with WC and Calf IMAT		
6-year increase in IMAT	1.0 (0.8–1.2)	0.89
6-year increase in WC	1.2 (1.0–1.4)	0.05
Baseline IMAT	1.0 (0.8–1.2)	0.90
Baseline WC	1.3 (1.1–1.6)	0.02

BMI indicates body mass index; CI, confidence interval; IMAT, intermuscular adipose tissue; HOMA-IR, homeostasis model assessment of insulin resistance; OR, odds ratio; and WC, waist circumference.

*Per SD incremental increase for baseline characteristics, except for muscle attenuation (per SD incremental decrease).

†All models are additionally adjusted for age, education, marriage status, alcohol consumption, physical activity, current smoker, former smoker, sedentary lifestyle, baseline HOMA-IR, 6-year change in calf muscle area, and follow-up years.

To our knowledge, this is the first longitudinal study on the impact of muscle attenuation on hypertension. The few existing cross-sectional studies linking hypertension to skeletal muscle adiposity have been inconclusive. The Health ABC study (Health, Aging and Body Composition) reported that cross-sectional thigh IMAT was associated with prevalent hypertension in elderly men and women of African ancestry but not in elderly whites. However, in the same study, there was no association with thigh muscle attenuation and prevalent hypertension.[28] In a report by the Framingham Study in 2949 middle-aged participants, there was an association between paraspinous muscle attenuation and prevalent hypertension, though the association was attenuated after further adjustment for visceral adipose tissue or BMI.[29] The discrepancy in results between the previous studies and ours may signify that there are muscle-specific associations,[18] that the previous results were specific to cross-sectional data, and that the duration of hypertension should be taken into consideration as it may alter the subsequent accumulation of muscle adipose tissue. In addition, our study found that antihypertensive medication use had no impact on the association between muscle attenuation and hypertension.

The mechanisms that link muscle attenuation and increased risk of newly developed hypertension are not yet understood. Insulin resistance seems to be a direct regulator of the complex cross talk of skeletal muscle adiposity and hypertension,[30] although other indirect mechanisms, such as inflammation[30,31] or oxidative stress,[30,32] may also be involved. Pathophysiology studies have suggested that hypertension per se is a status of insulin resistance because several reports have described an interaction between insulin signaling and the renin–angiotensin systems (RAAS).[30,33] Angiotensin II inhibits insulin signaling and insulin-induced nitric oxide production and leads to elevated insulin level.[31] In addition, inhibition of the RAAS improves insulin sensitivity and slows the progression of T2D.[31] Furthermore, insulin resistance–induced hyperinsulinemia leads to hyperfiltration, causes structural changes in the kidney (glomerular hypertrophy and focal segmental glomerulosclerosis), and substantially lowers glomerular filtration rate and increases arterial pressure.[30] However, in our study, the association between muscle attenuation and hypertension persisted even after adjusting for HOMA-IR, suggesting that this adipose tissue depot may be an important risk factor for hypertension independent of insulin resistance. Other potential mechanisms of effects in addition to insulin resistance include inflammation and oxidative stress. Ectopic adipose tissues become inflamed and infiltrated with

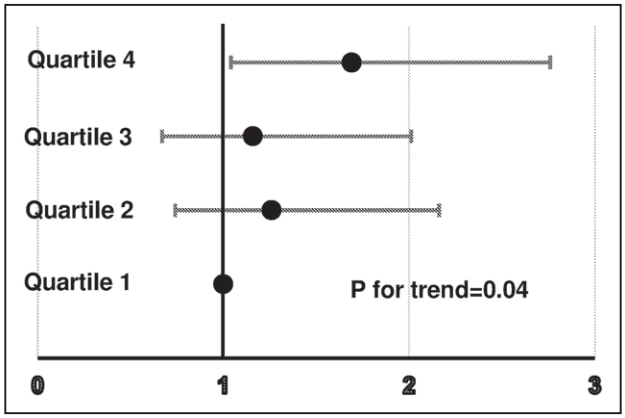

Figure 2. Odds of newly developed hypertension with 6-year absolute decrease of muscle attenuation after adjustment for central adiposity. All models are additionally adjusted for age, education, marriage status, alcohol consumption, physical activity, current smoker, former smoker, sedentary lifestyle, baseline homeostasis model assessment of insulin resistance (HOMA-IR), and 6-year change in muscle area, baseline waist circumference (WC), and 6-year increase of WC.

macrophages that secrete proinflammatory cytokines, such as interleukin-6 and tumor necrosis factor-α, which can trigger activation of the RAAS.[34] Also, the accumulation of lipid in muscle cells increases tricarboxylic acid cycle activity and generates excess lipid intermediates,[35] resulting in oxidative stress, which may be associated with activation of the RAAS.[36]

In our study, IMAT was not associated with newly developed hypertension in any model, despite the fact that we have previously reported an association between IMAT and risk of incident T2D in this population.[37] This indicates that inter- and intramuscular adipose tissue may have different impacts on the development of cardiometabolic complications; however, the underlying mechanisms are unknown. The different locations of IMAT (visible adipose tissue beneath the fascia lata) and intramuscular adipose tissue (adiposity infiltration within muscle fibers and muscle cells) may suggest that there could be different ways for ectopic adipose tissue accumulation to trigger metabolic changes. The accumulation of intramuscular adipose tissue may have a negative impact on insulin action and insulin diffusion capacity via reducing nutritive blood flow to muscles,[38] whereas the accumulation of IMAT may induce insulin resistance via impaired insulin signaling,[39] thereby leading to future hypertension.

Ours is the first longitudinal study to focus on ectopic skeletal muscle adiposity and hypertension and provides a novel perspective in understanding the pathophysiology of hypertension and the heterogeneity of obesity. A major strength of our study is the use of longitudinal data to assess newly developed hypertension instead of prevalent hypertension, which minimizes the prevalence–incidence bias, a bias induced by identifying factors related to the duration and prognosis of the disease rather than the disease itself. Moreover, we included a wide age range, which enabled us to detect longitudinal changes in skeletal adiposity throughout the aging process.

Our study also has some limitations. Although we used a prospective study design, our study was not designed to definitively establish a causal relationship between skeletal adiposity and hypertension. Second, although we excluded men with hypertension at baseline, the possibility that the measured change in muscle attenuation occurred after the onset of hypertension cannot be completely eliminated. Thus, we were still not able to precisely discern the temporal sequence of change in skeletal muscle adiposity and the onset of hypertension. Third, we focused on men of African ancestry living in the Caribbean region, which limits the generalizability of our findings to women and other race/ethnic populations in other geographic regions. Fourth, the participants were healthier and with greater muscle attenuation at baseline, compared with those who were loss-of-follow-up, which may bias our results to null. However, we are still able to detect a significant association between muscle attenuation and newly developed hypertension, indicating that our findings are robust. Fifth, the impact of other ectopic adipose tissue depots, such as visceral, liver, heart, perivascular, and kidney, could not be examined in our data. Sixth, muscle attenuation reflects both extra- (lipid storage in interstitial adipose tissue) and intramyocellular adipose tissue (lipid droplets storage in muscle cells), which may have different biological impact on cardiometabolic disorders, but cannot be distinguished with the computed tomography imaging used in our study.

Perspectives

In summary, this study reports a previously unidentified adverse association of decreased muscle attenuation on the development of hypertension, independent of general or central adiposity among high-risk men of African ancestry. Our findings also suggest that decreases in muscle attenuation may be more important than increases in general or central adiposity in driving metabolic disorders in these men. This may be a partial explanation for the cardiometabolic resilience in the population of African ancestry, who are at high risk for cardiometabolic disease, despite having less whole-body and visceral adipose tissue. In these men, decreased muscle attenuation may be a novel and modifiable risk factor that is important for the prevention of cardiometabolic disorders and for healthy aging. Our results should be replicated in other racial and ethnic groups and among women. Future studies are also needed to delineate whether the decreased muscle attenuation is a marker or the cause of the development of hypertension, to test for potential mediation effects of insulin resistance, inflammation, and the RAAS system, to identify the possible biological mechanisms underlying this relationship, and to evaluate whether our observed association is independent of sarcopenia, an important skeletal muscle abnormality of aging-related muscle loss that is more prevalent in hypertensive versus normotensive adults.

Acknowledgment

We thank the coauthors for their efforts in study design and article preparation. We are also grateful for the important work by all staff members of the Tobago Health Studies Office.

Source of Funding

This research was supported by grant R01-AR049747 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases and grants R01-DK097084 and K01-DK083029 from the National Institute of Diabetes and Digestive and Kidney Diseases.

Disclosures

None.

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Novelty and Significance

What Is New

- There were no previous longitudinal studies examining the association between ectopic skeletal muscle adiposity and hypertension.
- Decreased skeletal muscle attenuation is associated with increased odds of newly developed hypertension independent of general and central adiposity after 6 years of follow-up in men of African ancestry.
- A decrease in muscle attenuation may be a more important risk factor for hypertension than general or central adiposity.

What Is Relevant?

- The greater decrease of muscle attenuation may explain the excess risk of developing hypertension among the population of African ancestry who have relatively less whole-body and visceral adipose tissue than among the whites.
- The association between muscle attenuation and hypertension may be muscle location specific.

Summary

A decrease of muscle attenuation over 6 years of follow-up was associated with 30% increased odds of newly developed hypertension among men of African ancestry.

Muscle Attenuation Is Associated With Newly Developed Hypertension in Men of African Ancestry

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Hypertension. published online March 6, 2017;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563

Supplementary Tables: Muscle attenuation Is Associated with Newly Developed Hypertension in Men of African Ancestry

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Short title: Muscle attenuation and hypertension

Word Count of Manuscript: 5857

Word Count of Abstract: 249

Total Number of Tables: 2

Total Number of Figures: 2

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Table S1. Multivariable adjusted odds ratios for newly developed hypertension per SD difference in absolute baseline and longitudinal skeletal muscle adiposity measures, with outliers included

Adiposity Measures	OR (95% CI)	P value
Multivariable Effects Adjusted for Overall Adiposity (BMI)*		
Model with BMI and Calf Muscle Attenuation		
6-year decrease in Muscle attenuation	**1.3 (1.1, 1.7)**	**0.02**
6-year increase in BMI	1.1 (0.9, 1.3)	0.53
Baseline Muscle attenuation†	1.3 (1.0, 1.6)	0.05
Baseline BMI	1.1 (0.9,1.4)	0.41
Model with BMI and Calf IMAT		
6-year increase in IMAT	1.1 (1.0, 1.4)	0.16
6-year increase in BMI	1.0 (0.8, 1.2)	0.96
Baseline IMAT	1.1 (0.9, 1.3)	0.63
Baseline BMI	1.2 (1.0, 1.5)	0.08
Multivariable Effects Adjusted for Central Adiposity (WC)*		
Model with WC and Calf Muscle Attenuation		
6-year decrease in Muscle attenuation	**1.3 (1.1, 1.6)**	**0.02**

6-year increase in WC	1.2 (1.0, 1.4)	0.10
Baseline Muscle attenuation[†]	1.2 (1.0, 1.5)	0.11
Baseline WC	1.2 (0.9, 1.5)	0.21
Model with WC and Calf IMAT		
6-year increase in IMAT	1.1 (0.9, 1.3)	0.32
6-year increase in WC	1.2 (1.0, 1.4)	0.06
Baseline IMAT	1.0 (0.8, 1.2)	0.84
Baseline WC	**1.3 (1.1, 1.6)**	**0.01**

[*]All models are additionally adjusted for: age, education, marriage status, alcohol consumption, physical activity, current smoker, former smoker, sedentary lifestyle, baseline HOMA-IR, 6-year change in calf muscle area and follow-up years.

BMI: body mass index; IMAT: intermuscular adipose tissue: WC: waist circumference

[†]per SD incremental decrease

Table S2. Multivariable adjusted odds ratios for hypertension with and without medication per SD difference in absolute baseline and longitudinal skeletal muscle adiposity measures

Adiposity Measures	Hypertensive with medication	Hypertensive without medication	Treatment effect P value
Multivariable Effects Adjusted for Overall Adiposity (BMI)*			
Model with BMI only			
6-year increase in BMI	**0.8 (0.6, 1.0)**	**1.5 (1.2, 1.9)**	**<0.01**
Baseline BMI	1.1 (0.9, 1.4)	**1.4 (1.1, 1.8)**	0.13
Model with BMI and Muscle attenuation			
6-year decrease in Muscle attenuation	**1.4 (1.1, 1.7)**	1.2 (0.9, 1.5)	0.34
6-year increase in BMI	0.8 (0.6, 1.1)	**1.5 (1.1, 2.0)**	**<0.01**
Baseline Muscle attenuation†	**1.3 (1.0, 1.7)**	1.1 (0.8, 1.5)	0.27
Baseline BMI	0.9 (0.6, 1.2)	**1.5 (1.1, 2.1)**	**<0.01**
Model with BMI and Calf IMAT			
6-year increase in IMAT	1.0 (0.8, 1.3)	1.0 (0.8, 1.3)	0.96
6-year increase in BMI	**0.8 (0.6, 1.0)**	**1.5 (1.2, 1.9)**	**<0.01**
Baseline IMAT	1.0 (0.8, 1.3)	1.1 (0.8, 1.4)	0.54
Baseline BMI	1.0 (0.8, 1.4)	**1.4 (1.0, 1.8)**	0.09
Multivariable Effects Adjusted for Central Adiposity (WC)*			
Model with WC only			
6-year increase in WC	1.0 (0.9, 1.3)	**1.6 (1.2, 2.0)**	**0.004**
Baseline WC	**1.2 (1.0, 1.5)**	**1.5 (1.2, 1.9)**	0.15

Model with WC and Muscle attenuation			
6-year decrease in Muscle attenuation	**1.3 (1.0, 1.7)**	1.2 (0.9, 1.6)	0.49
6-year increase in WC	1.0 (0.8, 1.2)	**1.7 (1.2, 2.3)**	**0.002**
Baseline Muscle attenuation[†]	**1.3 (1.0, 1.6)**	1.1 (0.8, 1.5)	0.50
Baseline WC	1.0 (0.7, 1.3)	**1.5 (1.1, 2.1)**	**0.02**
Model with WC and Calf IMAT			
6-year increase in IMAT	1.0 (0.8, 1.2)	1.0 (0.8, 1.3)	0.81
6-year increase in WC	1.0 (0.8, 1.3)	**1.6 (1.2, 2.0)**	**0.01**
Baseline IMAT	1.0 (0.8, 1.2)	1.1 (0.8, 1.4)	0.58
Baseline WC	1.2 (0.9, 1.5)	**1.6 (1.2, 2.1)**	**0.05**

[*]All models are additionally adjusted for: age, education, marriage status, alcohol consumption, physical activity, current smoker, former smoker, sedentary lifestyle, baseline HOMA-IR, 6-year change in calf muscle area and follow-up years.

BMI: body mass index; IMAT: intermuscular adipose tissue: WC: waist circumference

[†]per SD incremental decrease

Table S3. Baseline characteristics by follow-up status

Baseline Characteristics	Follow-up status		
	Participants† (N=747)	Loss-of-follow-ups (N=195)	P-value
Age (year)	54.3 ± 7.8	61.8 ± 11.4	<0.001
Education level, n (%)			
High school and above	86 (11.7)	22 (11.6)	0.96
Marital status, n (%)			
Married or live with a spouse	535 (72.1)	124 (64.3)	0.03
Current smoker, n (%)	99 (13.3)	36 (18.5)	0.06
Former smoker, n (%)	140 (18.7)	43 (22.1)	0.30
Alcohol consumption, n (%)			
>3 drinks per week	71 (9.5)	21 (10.8)	0.60
Physical activity, n (%)			
>3 times per week	377 (50.5)	88 (45.1)	0.18
Sedentary lifestyle, n (%)			
>21 hours per week	121 (16.2)	31 (15.9)	0.91
HOMA-IR	2.6 ± 1.4	2.7 ± 1.4	0.04
BMI (kg/m^2)	26.4 ± 4.2	26.4 ± 5.1	0.98
WC (cm)	89.7 ± 10.6	90.8 ± 12.7	0.24
Calf subcutaneous fat (mm^2)	1322.9 ± 653.7	1360.6 ± 762.0	0.49
Calf IMAT (mm^2)	197.7 ± 171.5	255.4 ± 214.6	0.0001
Calf muscle attenuation (mg/cm^3)	77.5 ± 2.9	75.8 ± 3.9	<0.001

[*] *P*-values for comparisons between the hypertensive and non-hypertensive subjects from two-sample T-tests or Chi-square tests or Fisher's Exact Test

[†] 1 of the participants was excluded in the following analyses for missing value on hypertension status at the follow-up

BMI: body mass index; IMAT: intermuscular adipose tissue: WC: waist circumference