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Research Article

Intramyocellular Lipid and Impaired Myofiber Contraction in Normal Weight and Obese Older Adults

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Abstract

Background. Evidence implicates the amount and location of fat in aging-related loss of muscle function; however, whether intramyocellular lipids affect muscle contractile capacity is unknown.

Methods. We compared both in vivo knee extensor muscle strength, power, and quality and in vitro mechanical properties of vastus lateralis single-muscle fibers between normal weight (NW) and obese older adults and determined the relationship between muscle lipid content (both intramuscular adipose tissue and intramyocellular lipids) and in vivo and in vitro muscle function in NW and obese individuals.

Results. The obese group had a greater percentage of type-I fibers compared to the NW group. The cross-sectional area of type-I fibers was greater in obese compared to NW; however, maximal shortening velocity of type-I fibers in the obese was slower compared to NW. Type-I and type-IIa fibers from obese group produced lower specific force than that of type-I and type-IIa fibers from the NW group. Normalized power was also substantially lower (~50%) in type-I fibers from obese adults. The intramyocellular lipids data showed that total lipid droplet area, number of lipid droplets, and area fraction were about twofold greater in type-I fibers from the obese compared to the NW group. Interestingly, a significant inverse relationship between average number of lipid droplets and single-fiber unloaded shortening velocity, maximal velocity, and specific power was observed in obese participants. Additionally, muscle echointensity correlated with single-fiber specific force.

Conclusions. These data indicate that greater intramyocellular lipids are associated with slower myofiber contraction, force, and power development in obese older adults.

Key Words: Muscle—Obesity—Sarcopenia

Aging is associated with impaired skeletal muscle function, including a reduced capacity to generate force and power by whole muscle (1), and a decline in individual muscle fiber contraction velocity and force generation (2). Combined with muscle atrophy, these changes lead to reduced muscle strength and quality (force per unit of muscle) and loss of physical function with age (3). Clinically, muscle quality may be a better indicator of overall functional capacity than absolute muscle strength (4); thus, identifying the mechanisms underlying aging-related loss of myocyte force production is of high relevance for prevention and/or treatment of functional impairment with aging. In this study, we examined whether lipotoxicity (excess lipid storage within muscle)

may be another factor that contributes to impaired single-fiber contractility.

Both the absolute and relative amount of body fat increases with age (5), and greater fat mass is associated with lower muscle strength, power, and quality in older adults, even in those with a normal amount of muscle mass (6). Importantly, higher body fat in older adults partially contributes to the rate of decline in muscle mass and quality, and physical function with age (7). Advancing age also results in a redistribution of fat in the body; the amount of intermuscular adipose tissue, intramuscular (fat within muscle but between fibers), and intramyocellular lipid (IMCL) tends to increase, whereas the amount of subcutaneous fat declines with age (8). Greater fat infiltration into muscle is associated with lower muscle strength and power in older men and women (9,10), and it is a very strong predictor of functional decline in older adults (11).

Despite this strong evidence implicating the amount and location of fat in aging-related loss of muscle function, how fat or lipid stores affect muscle contractile capacity (force) and velocity (power) is not known. An isolated single-muscle fiber segment is an ideal model for examining the relationship between lipid accumulation and contractile force and power to advance knowledge of the mechanisms by which adiposity and muscle lipotoxicity may contribute to aging-related declines in muscle function. Thus, the main purpose of this study was to compare both in vivo knee extensor muscle strength, power, and quality and in vitro mechanical properties of vastus lateralis single-muscle fibers between normal weight (NW) and obese older adults matched on age and sex and to determine the association between muscle lipid content (both intermuscular adipose tissue and IMCL) and in vivo and in vitro muscle function.

Methods

Detailed methods are included in Supplemental Material.

Participant Characteristics and In Vivo and In Vitro Measurements

Older (age 65–80 years) men and women (13 NW and 21 obese) were included in the study, which was approved by the Wake Forest School of Medicine Institutional Review Board. All participants provided written informed consent to participate. Procedures for vastus lateralis muscle biopsy and methods to measure body composition, thigh composition, and in vivo knee extensor strength, power, and quality have been described (12,13). Single-muscle fiber experimental setup and solutions have been described (2,14).

Intramyocellular Lipid

Analyses were conducted on at least 80 fibers per participant (8–10 contiguous fibers/field: 40 type-I and 40 type-IIa fibers). Specifically, we measured individual myofiber cross-sectional area (CSA), the number of lipid droplets per cell, the total area of lipid droplets, the average droplet size, and the area fraction occupied by lipid droplets. We averaged these values for all the type-I and type-IIa fibers for each participant.

Skeletal Muscle Ultrasound

A subset of the obese adults (n = 12, age 68 ± 3 years, 66% male, body mass index = 31 ± 2 kg/m^2) within this study underwent skeletal muscle ultrasound at the time of the muscle biopsy. Transverse ultrasound images of the quadriceps femoris were obtained with a B-mode ultrasound imaging device using a Sonosite (Bothell, WA) transducer. In all images, the gain, compression, and sonographic settings remained constant between participants. Imaging was obtained in a supine position with the leg supported in passive extension and neutral rotation. The transducer was positioned perpendicular to the longitudinal axis of the quadriceps femoris at the midpoint between the anterior superior iliac spine and the proximal end of the patella. Pressure on the transducer was kept to a minimum to avoid distortion of skin and subcutaneous tissues with a generous amount of gel and visualization of real-time ultrasound images. The hydration status was controlled for each participant.

Muscle echointensity was measured using the gray scale analysis histogram feature on Image J (Bethesda, MD). The selected region of interest included as much of the bulk quadriceps femoris but avoided the surrounding fascia. The mean and standard deviation (SD) echointensity values of the region were expressed as a value between 0 (black) and 255 (white) (15).

Statistical Analysis

Sigma Stat 11.0 (Systat Software, San Jose, CA) was used for all statistical analyses. The alpha level was set at $p < .05$ for all tests. All data are presented as mean ± SEM. Differences in continuous variables between the NW and obese groups were analyzed with one-way analysis of variance. Group differences in muscle fiber type were analyzed using chi-square analysis. Pearson correlation analysis was used to identify relationships between IMCL and fiber CSA and between single-fiber contractile properties and IMCL.

Results

Participant Demographics and Body Composition

Demographic characteristics and body composition in 13 NW and 21 obese older adults are shown in Table 1. There were no differences in age or height between the two groups, but the obese group was approximately 32% heavier and had 61% more total fat mass and 18% more total lean mass than the NW group ($p < .05$, Table 1).

Thigh Composition, Peak Knee Extensor Torque, and Muscle Quality

Thigh composition, peak knee extensor torque, and muscle quality (peak torque normalized to thigh muscle volume) are

Table 1. Demographic Characteristics and Total Body Composition of NW and Obese Groups

	NW (n = 13)	Obese (n = 21)
Age (y)	70 ± 2	69 ± 2
Body mass (kg)	65 ± 3.0	85 ± 3.1*
Height (cm)	172 ± 2.8	168 ± 2.2
BMI (kg/m^2)	22 ± 0.52	30 ± 0.43*
Fat mass (kg)	20 ± 1.1	33 ± 1.2*
Lean mass (kg)	44 ± 2.8	52 ± 2.6*
% body fat	32 ± 1.7	39 ± 1.2*

Notes: BMI = body mass index; NW = normal weight. Data are mean ± SE. The NW and obese groups include 6 males and 7 females and 10 males and 11 females, respectively.

*$p < .05$ between groups.

presented in Table 2. The obese group had greater total thigh volume (37%) and thigh fat volume (50%) compared to the NW group ($p < .05$). Despite greater muscle volume (19%) and absolute peak knee extensor torque (20%) for both the legs in the obese group compared to the NW group, the ratio of normalized knee extensor peak torque to thigh muscle volume (muscle quality) was greater (26%) for both the legs in the NW group compared to the obese group. Also, normalized knew extensor peak torque to body weight was significantly different between groups (Table 2).

Morphological and Contractile Characteristics of Single-Muscle Fibers

The composition of fiber types by sodium dodecyl sulfate–polyacrylamide gel electrophoresis was derived from a total of 166 single-muscle fibers in the NW group and 322 in the obese group. The obese group had a greater percentage (76% vs 66%) of type-I myosin heavy chain isoforms (and lower percentage [24% vs 34%] of type-IIa myosin heavy chain isoforms) compared to the NW group ($X^2 = 5.197$, $p < .05$). The prevalence of hybrid muscle fibers was 3.2% for both obese and NW participants.

The CSA of type-I fibers was 9.2% greater in the obese group compared to the NW group ($p < .05$) as shown in Figure 1A; there was no group difference in CSA of type-IIa fibers. Type-I fibers were larger than type-IIa fibers in both the obese (~12% difference) and NW (~5% difference) groups ($p < .05$; Figure 1A). Maximal shortening velocity of type-I fibers in the obese group was ~25% slower compared to the NW group ($p < .05$), whereas shorting velocity of type-IIa fibers was faster than type-I fibers, regardless of group status (Figure 1B). Type-I and type-IIa fibers from the obese produced ~22% and ~24% lower absolute force (mN), respectively, compared to the NW group ($p < .05$; Figure 1C). Likewise, specific force (kN/m^2; calculated by force [mN]/fiber CSA) was also lower in the obese compared to the NW group, ~28 and ~25% for type-I and type-IIa fibers, respectively ($p < .05$; Figure 1D). The number of fibers used for these analyses is that reported above for myosin heavy chain classification. In summary, single-muscle fibers, especially type-1 fibers, from the obese older adults were larger but generated less force and contracted more slowly compared to fibers from the NW older adults.

Table 2. Thigh Muscle Composition, Isokinetic Strength, and Quality of Knee Extensor of NW and Obese Older Adults

	NW ($n = 13$)	Obese ($n = 21$)
Total thigh volume (cm^3)	1103 ± 45	1513 ± 40*
Thigh fat volume (cm^3)	488 ± 52	732 ± 51*
Thigh muscle volume (cm^3)	551 ± 35	658 ± 36*
Intermuscular fat volume (cm^3)	10 ± 1.3	32 ± 3.3*
Right peak torque (Nm)	100 ± 8.6	118 ± 9.0*
Right peak torque/thigh muscle volume (Nm/cm^3)	0.29 ± 0.02	0.19 ± 0.01*
Left peak torque (Nm)	99 ± 8.7	120 ± 8.6*
Left peak torque/thigh muscle volume (Nm/cm^3)	0.28 ± 0.02	0.19 ± 0.01*
Right peak torque/body weight (Nm/kg)	1.66 ± 0.1	1.36 ± 0.1*
Left peak torque/body weight (Nm/kg)	1.61 ± 0.1	1.39 ± 0.1*

Notes: NW = normal weight. Data are mean ± *SE*.
*$p < .05$ between groups.

Power-Generating Capacity of Single-Muscle Fibers

Figure 2 shows absolute and normalized power of single-muscle fibers from all participants. Absolute and normalized power were greater in type-IIa compared to type-I fibers in both groups ($p < .05$; Figure 2A and B). Absolute power (μN·FL/s) of type-I fibers from the obese group was substantially lower (~46%) compared to the NW group ($p < .05$; Figure 2A). Normalized power (W/L) was also substantially lower (~50%) in type-I fibers from the obese group, compared to the NW group ($p < .05$; Figure 2B). These lower power outputs may result from ~25% lower force and ~25% slower shortening velocity because the a/P_o ratio did not differ between groups (NW: 0.04 ± 0.001; obese: 0.04 ± 0.002). Interestingly, the power output of type-IIa fibers did not differ between groups.

Intramyocellular Lipid

IMCL data were obtained in 10 participants (5 NW, 5 obese), and a total of 1,075 fibers (481 NW, 594 obese) were identified by their lipid droplet characteristics and fiber type, determined by Oil-red-O and adenosine triphosphatase staining, respectively (Figure 3). As shown in Table 3, type-I fibers had greater total lipid droplet area and more lipid droplets ($p < .05$) than type-IIa fibers in both groups, but this difference was more pronounced in the obese group. Total lipid droplet area, number of lipid droplets, and area fraction were about twofold greater in type-I fibers from the obese group compared to the NW group ($p < .05$). Additionally, the obese group had a greater number of lipid droplets in type-IIa fibers compared to the NW group ($p < .01$), but total droplet area and area fraction of type-IIa fibers did not differ between the groups (Table 3). In summary, fibers from the obese group showed about a twofold greater area of lipid droplet than fibers from the NW group, especially in the type-I fibers.

Relationship Between IMCL and Fiber CSA

There were positive relationships between IMCL and CSA of type-I and type-IIa fibers in both groups. Specifically, larger type-I (Figure 4A) and type-IIa (Figure 4D) fibers had greater total lipid droplet area in both the obese ($p < .01$) and NW ($p < .05$) groups, and larger type-I (Figure 4B) and type-IIa (Figure 4E) fibers had a greater number of lipid droplets in both obese ($p < .01$) and NW ($p < .01$) older adults. However, the average droplet area did not show any relationship with CSA in either group for type-I fibers (Figure 4C). This relationship was significant for obese ($p < .05$), but not NW adults for type-IIa fibers (Figure 4F). Thus, the greater IMCL with increased fiber CSA mainly resulted from increased number of lipid droplets, rather than an increase in the size of individual lipid droplets.

Relationship Between IMCL and Single-Fiber Contraction Velocity, Force, and Power

A significant inverse relationship between average number of lipid droplets and single unloaded shortening velocity (V_o), maximal velocity (V_{max}), the curvature of the force–velocity relationship (a/P_o), and specific power was observed in obese,

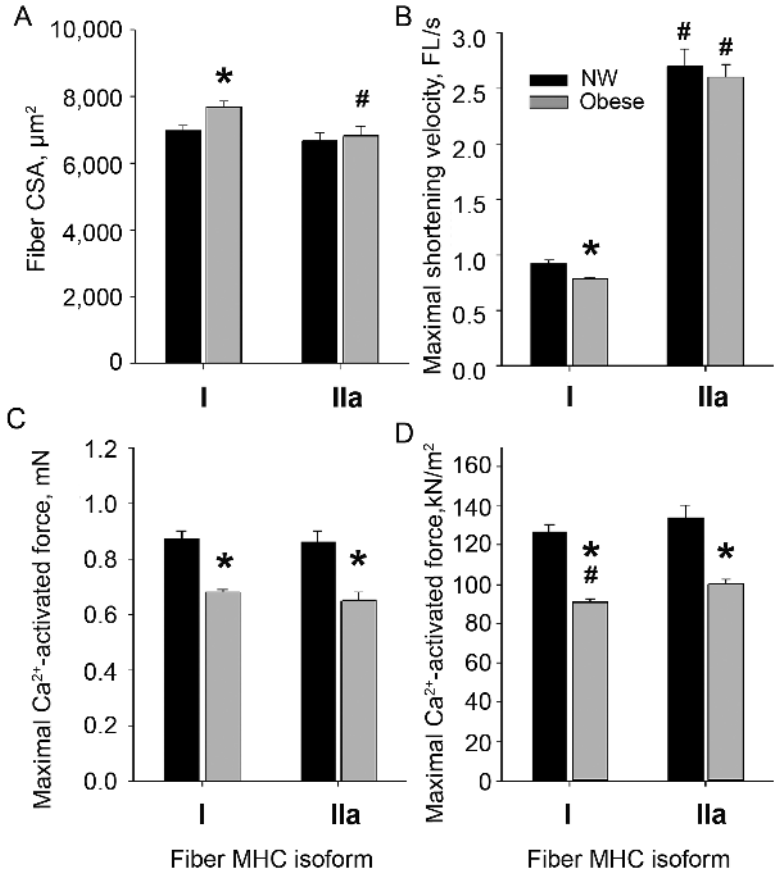

Figure 1. Functional characteristics of single-muscle fibers. Type-I and type-IIa fiber cross-sectional area (CSA) (**A**), maximal shortening velocity (**B**), absolute maximal Ca^{2+}-activated force (**C**), and specific maximal Ca^{2+}-activated force relative to CSA (**D**) in normal weight (NW; black) and obese (gray) groups. *Significant difference between groups within fiber type; #significant difference between fiber types within group.

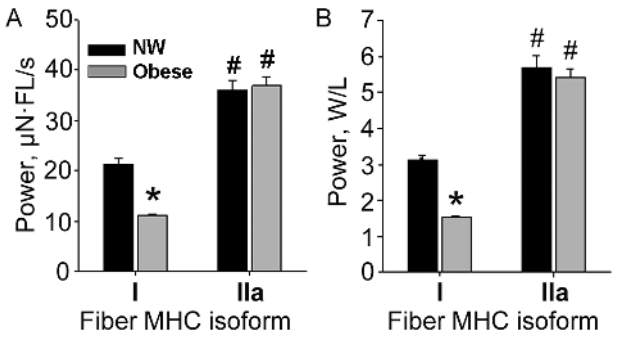

Figure 2. Power-generating capacity of single-muscle fibers. Type-I and type-IIa muscle fiber absolute power (**A**) and power normalized to fiber size (**B**) in normal weight (NW; black) and obese (gray) participants. *Significant difference between groups within fiber type; #significant difference between fiber types within group.

but not in NW participants (Table 4). Similarly, average total droplet area, average droplet area, and fractional area strongly and inversely correlated with these single-fiber contraction parameters except for the average droplet area–a/P_o relationship. These data indicate that greater fat infiltration was associated with slower myofiber contraction velocity and power in obese older adults.

Muscle Ultrasound Echointensity Is Associated With Single-Fiber Contractile Force and IMCL

We performed skeletal muscle ultrasound on a subset of the obese patients at the time of skeletal muscle biopsy. Quadriceps *SD* echointensity values demonstrated a strong positive correlation with the IMCL average area fraction in type-I myofibers (Figure 5A). Quadriceps mean and *SD* echointensity values were moderately negatively correlated with the mean Ca^{2+}-activated specific force values for both type-I and type-IIa fibers (Figure 5B and C). Figure 5D shows a representative ultrasound image used for this analysis.

Discussion

The association between fat infiltration and deranged skeletal muscle metabolism and function has been extensively examined and characterized (16,17); however, a nexus between IMCL and muscle fiber mechanical properties has not been clearly established. This is the first study that shows there is a strong and inverse relationship between number and size of myofiber lipid droplets and loss in contraction speed and power generation capacity of single-muscle fibers in obese older adults. Our results also demonstrate that muscle fibers from obese older adults generate less force and power and contract more slowly, despite having a larger CSA, than muscle fibers from NW older adults.

The present study examined the contribution of variation in lipid stores to in vivo thigh muscle isokinetic strength and muscle

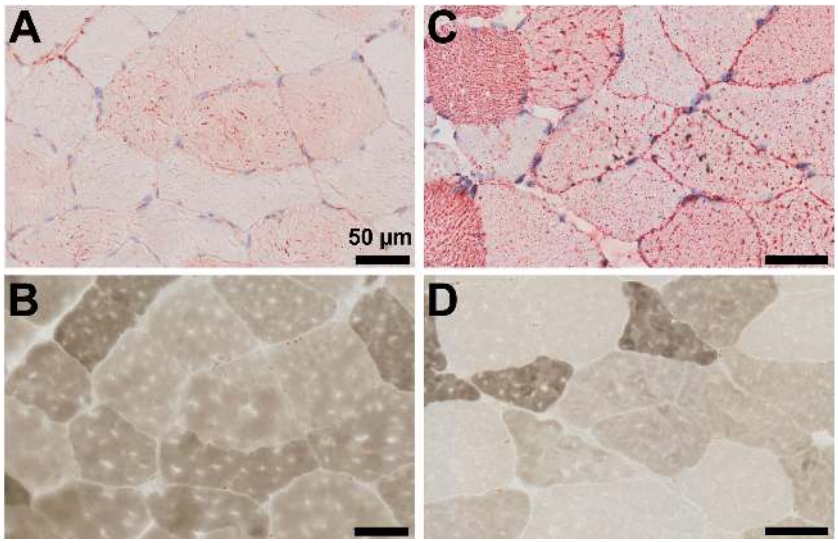

Figure 3. Oil-red-O (**A–C**) and adenosine triphosphatase (**B–D**) staining of muscle cross-sections from a representative normal weight (**A–B**) and obese (**C–D**) study participant.

Table 3. IMCL Lipid Characteristics in NW and Obese Older Adults

	NW		Obese	
	Type-I (263 Fibers)	Type-IIa (218 Fibers)	Type-I (220 Fibers)	Type-IIa (374 Fibers)
Total droplet area (µm²)	221 ± 10.3*	103 ± 7.8	496 ± 33*,†	130 ± 5.9
Number of lipid droplets	167 ± 6.6*	69 ± 4.0	293 ± 12*,†	101 ± 4.2†
Average of each droplet area (µm²)	1.4 ± 0.04	1.4 ± 0.05	1.6 ± 0.06*,†	1.2 ± 0.03†
Area fraction (%)	5.5 ± 0.24*	2.8 ± 0.19	9.4 ± 0.52*,†	3.3 ± 0.14

Notes: IMCL = intramyocellular lipid; NW = normal weight. Data are mean ± *SE*. Total number of muscle fibers analyzed: 1,075.
*Significantly different than type-IIa fiber type within group.
†Significantly different than corresponding fiber type of NW group.

quality and to in vitro mechanical properties of single-muscle fibers from vastus lateralis muscle in obese and NW older adults. In vivo measurements revealed that obese older adults had greater muscle mass and volume, and higher absolute peak torque but lower peak knee extensor torque normalized to thigh muscle volume than NW adults. Our data also showed that the obese group had 2.4-fold more intermuscular fat than the NW group, which is a similar to a previous report (18). This is consistent with the concept that muscle fat may have a negative impact on muscles important for locomotion (19,20).

Adiposity and Muscle Function With Aging

Many cross-sectional studies show a higher prevalence of disability, and lower muscle strength, quality, and power, in older persons with higher body mass index and fat mass, even in those with a normal amount of lean mass (21). Longitudinal studies also support a greater decline in physical function and earlier onset of disability in older adults with greater adiposity (22). In addition to evidence implicating total fat mass as a predictor of functional decline, fat infiltration into skeletal muscle has been associated with less muscle power (23), lower isokinetic and specific torque (24), slower walking speed and chair rise times (10), and higher risk of mobility limitation (11). Because these associations between adiposity and function are not entirely explained by age, physical activity, chronic disease, or lower muscle mass, there must be effects of fat itself on molecular, morphologic, or metabolic properties of muscle that lead to loss of function. Yet, there have been limited advances in identifying relevant mechanisms underlying the interaction of adipose tissue and skeletal muscle, especially those with implications for aging-related disability. Using isolated muscle fibers, this study extends prior findings of in vivo associations between amount and location of fat with muscle function (6,25) to confirm that this link is also observed at the cellular level. This work sets the stage for further research designed to identify the molecular, metabolic, and/or structural mechanisms by which excess lipid affects the contractile capacity of muscle. Future research should also examine not only the role of the amount of stored lipid but also the type of fatty acids that are stored on muscle contractile properties.

Impairment of In Vitro Muscle Mechanics in Obese Compared to NW Older Adults

Myofibers contract in vitro under standardized experimental conditions of temperature, ionic strength, and Ca^{2+} concentration. Because IMCL is also measured at the cellular level, this controlled setting is ideal to determine the contribution of variation in amount of cellular lipid (IMCL) to single-fiber contractility. Differential mechanical properties between fibers from obese and NW older adults may result from myofiber lipid droplet accumulation, and/or differential cross-bridge properties during muscle contraction. As previously proposed, the lower intrinsic force-generating ability of fibers from

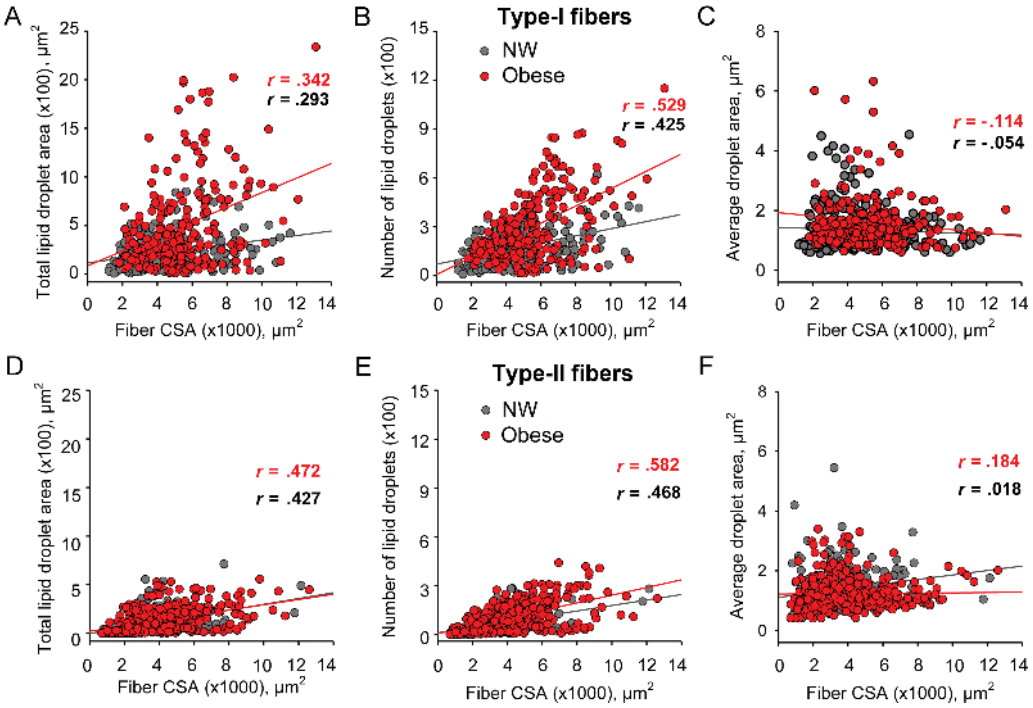

Figure 4. Relationship between intramyocellular lipid and cross-sectional area (CSA) of type-I and type-IIa fibers from normal weight (NW) and obese older adults. Scatterplots of CSA of individual fibers with total lipid droplet area (**A** and **D**), number of lipid droplets (**B** and **E**), and average area of each lipid droplet (**C** and **F**) for individual fibers from NW (gray) and obese (red) participants.

Table 4. Correlation Between IMCL and Single-Fiber Contraction Velocity, Force, and Power in NW and Obese Older Adults

		R Values				
		Specific Force (kN/m²)	V_o (FL/s)	V_{max} (FL/s)	a/P_o	Specific Power (W/L)
Average number of lipid droplets	NW	−0.13	−0.58	−0.48	−0.02	−0.55
	Obese	−0.19	−0.71*	−0.73*	0.80*	−0.69*
Average total droplet area (µm²)	NW	−0.40	−0.45	−0.37	−0.16	−0.63
	Obese	−0.15	−0.72*	−0.75*	0.88*	−0.69*
Average droplet area (µm²)	NW	−0.73*	0.21	−0.18	−0.43	−0.37
	Obese	−0.08	−0.74*	0.76*	0.59	−0.72*
Average area fraction (%)	NW	−0.47	−0.41	−0.38	0.29	−0.53
	Obese	−0.01	−0.79*	−0.81*	0.72*	−0.75*

Notes: a/P_o = unitless parameter describing the curvature of the relationship between obese (n = 9)/NW (n = 10); IMCL = intramyocellular lipids; NW = normal weight; V_{max} = maximal velocity measured as the y intercept of force–velocity relationship; V_o = unloaded shortening velocity.

*Statistically significant.

older, compared to younger, individuals may be due to either a lower number of strongly bound cross-bridges during maximal activation or to a reduced force-generating ability of each cross-bridge (26). Because all types of myofibrils produce similar force (27), we can speculate that fibers from obese adults have less myofibrils than fibers from NW adults (28). The mechanism by which IMCL leads to slower contraction speeds is unknown. Whether IMCL increases internal resistance should be explored (20,29). In our study, type-I fibers from obese adults had about twofold greater total lipid droplet area, number of lipid droplets, and individual lipid droplet area than type-I fibers from NW adults, which results in slower contraction velocity and reduced power generation. Therefore, the lower fiber contractility of myofilament lattice and cytoskeleton of obese participants appear to have an etiological relationship with IMCL content within the fiber.

Skeletal Muscle Ultrasound, IMCL, and Single-Fiber Contractile Force

Skeletal muscle ultrasound is a noninvasive, low-cost tool that holds potential to inform on skeletal muscle quality. Increased ultrasound echointensity has been attributed to increased intermuscular adipose tissue and intramuscular fat (30) and muscle fibrosis (31) though these data were derived from humans with muscular dystrophy and canines, respectively. Our data suggest that muscle echointensity values in older, obese adults may reflect intermuscular adipose tissue or IMCL content and that muscle ultrasound values correlate with single-fiber specific force.

Limitations

There are some limitations to our study. First, the cross-sectional nature of the study design cannot discern causation or direction of the observed associations. Also, quantification of IMCL and contractile properties were not tested in the same muscle fiber segment, as current techniques do not allow assessing the amount and type of fatty acids in such small fragments of single-muscle fibers. In addition, this study was not large enough to examine sex differences in the relationships among lipid accumulation and single-fiber force and power.

Collectively, our results are consistent and demonstrate that greater fat/lipid content measured with computed tomography, with histology, or with ultrasound shows adverse associations with the ability of muscle to contract with high force and speed. The findings from this study are unique and are the first to show that associations

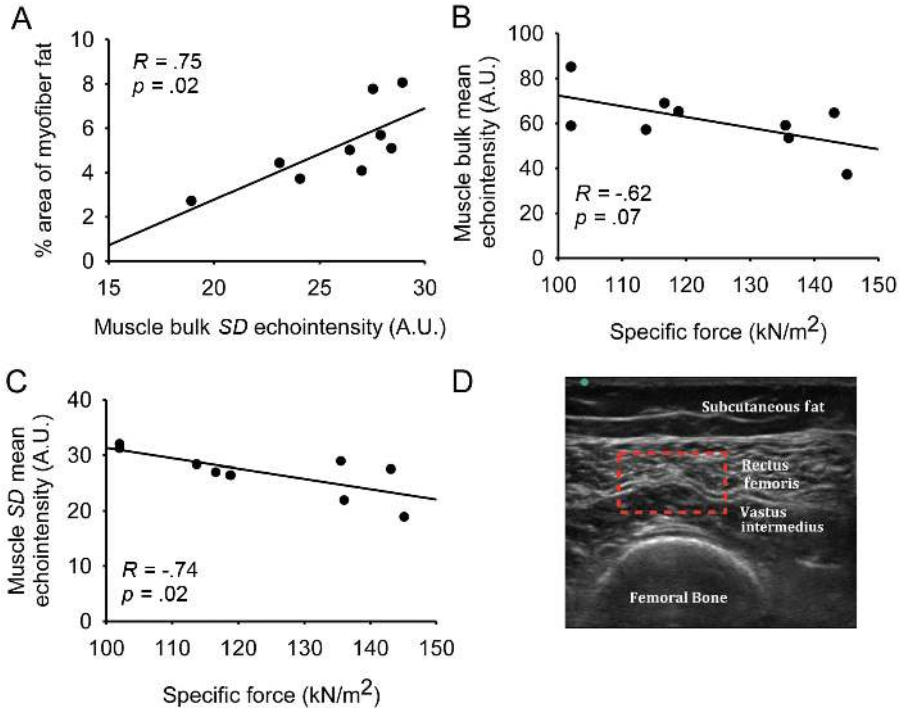

Figure 5. Relationship between ultrasound-derived muscle echointensity and single-fiber specific force and intramyocellular lipid. Scatterplots of muscle bulk standard deviation (*SD*) echointensity with percent area of myofiber fat (**A**), bulk muscle mean (**B**), and *SD* (**C**) values with myofiber specific force. *R*: Pearson correlation coefficient. (**D**) Representative ultrasound image showing subcutaneous fat, rectus femoris, vastus intermedius, and femoral bone.

between fat and muscle function observed in vivo are also observed in vitro at the cellular level.

Supplementary Material

Supplementary material can be found at: http://biomedgerontology.oxfordjournals.org/

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Conflict of Interest

The authors declare that they have no conflict of interest in this study.

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