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Asymmetry in CT Scan Measures of Thigh Muscle 2 Months After Hip Fracture: The Baltimore Hip Studies

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Abstract

Background. Hip fracture is an important problem for older adults with significant functional consequences. After hip fracture, reduced muscle loading can result in muscle atrophy.

Methods. We compared thigh muscle characteristics in the fractured leg with those in the nonfractured leg in participants from the Baltimore Hip Studies 7th cohort using computed tomography (CT) scan imaging.

Results. At 2 months postfracture, a single 10-mm axial CT scan was obtained at the midthigh level in 47 participants (26 men and 21 women) with a mean age of 80.4 years (range 65–96), and thigh muscle cross-sectional area (CSA), CSA of intermuscular adipose tissue (IMAT), as well as mean radiological attenuation were measured. Total thigh muscle CSA was less on the side of the fracture by 9.2 cm^2 (95% CI: 5.9, 12.4 cm^2), whereas the CSA of IMAT was greater by 2.8 cm^2 (95% CI: 1.9, 3.8 cm^2) on the fractured side. Mean muscle attenuation was lower on the side of the fracture by 3.61 HU (95% CI: 2.99, 4.24 HU).

Conclusions. The observed asymmetry is consistent with the effect of disuse and inflammation in the affected limb along with training effects in the unaffected limb due to the favoring of this leg with ambulation during the postfracture period.

Key Words: Hip fracture—Muscle composition—Computed tomography—aged.

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Hip fracture is a major public health problem that results in significant burden to the health care system. More than 340,000 persons aged older than 65 years fracture a hip in the United States annually (1), and this number is expected to double by 2040 (2). Therefore, hip fracture is and will continue to be a significant burden on the health care system (3). A hip fracture event also has significant

consequences for older patients and their families and often heralds a period of increased functional decline and disability (4,5).

Following a hip fracture, there is a sudden loss of physical function (as measured by ability to walk independently and walking speed) followed by a period of recovery that can continue for a year or more depending on the area of function examined (4). By the end of a year, half of those who were able to walk independently before their fracture are still not able to walk independently (4,6). The duration of disability extends beyond that required for fracture healing, implying that the hip fracture event may trigger other adverse consequences that result in disability.

After hip fracture, reduced muscle loading secondary to pain and functional loss can result in muscle atrophy. Additionally, the increased energy demand due to the stress of surgery and healing, coupled with catabolism caused by the postinjury pro-inflammatory state, further increases the risk of muscle protein loss (7–9). Loss of muscle mass and declines in muscle quality may be important mechanisms that impede functional recovery after hip fracture and negatively affect function long after the fracture event. One study found that total body lean mass decreased by 6% in the first 2 months after a hip fracture, whereas fat mass increased by 3.6% in the year following fracture (10). However, little research has examined how specific muscles are affected. Recent work has suggested that loss of muscle mass does not fully explain the decreased muscle strength seen with advanced age (11), with disproportionally larger declines seen in muscle strength than in loss of muscle mass (12). Measures of lower extremity muscle composition may provide greater insights into the pathways through which hip fracture results in functional decline.

Computed tomography (CT) has been used extensively to characterize both the size and composition of skeletal muscle. The extent of radiological attenuation or "radiodensity" is generally considered to result from lipid accumulation and has been extensively used as a radiological proxy for muscle composition characteristics, including intramuscular fat infiltration (13,14). Indeed, higher muscle attenuation on CT scan imaging correlates with lower intramuscular fat content and greater muscle strength, independent of muscle mass (13).

We compared thigh muscle characteristics in the fractured leg with those in the nonfractured leg in older men and women, 2 months following hip fracture, in a cohort from the Baltimore Hip Studies (BHS). We hypothesized that compared with the nonfractured leg, there would be lower muscle cross-sectional area (CSA) and greater fat infiltration in the thigh musculature on the side of the fracture.

Methods

Parent Study

Study data were obtained from the BHS 7th cohort (BHS-7), a prospective cohort study that is being carried out in eight hospitals that participate in the BHS hospital network. Details of this study can be found elsewhere (15). Briefly, the goal of the parent BHS-7 study is to examine the metabolic, physiological, neuromuscular, functional, and clinical consequences of hip fracture in both men and women.

Patients were eligible if they were ≥65 years and admitted to one of the study hospitals during the study period with a diagnosis of hip fracture (ICD-9 codes 820.00–820.9). Patients were excluded if they had a pathological fracture, were not community dwelling at the time of the fracture, were non-English speaking, were bedbound during the 6 months prior to the fracture, required human

assistance with ambulation prior to the fracture, resided more than 70 miles from the hospital, weighed more than 300 pounds, did not undergo surgical repair, or had any hardware in the contralateral hip (either due to hip fracture or hip replacement), thereby leaving no unaffected hip for bone density scanning purposes. Participants were assessed at baseline (within 22 days of hospital admission) and 2 months postadmission. The study protocol was approved by the Institutional Review Board (IRB) at the University of Maryland, Baltimore, as well as by each of the study hospitals' respective IRBs.

Baseline Measures

Information regarding prefracture medical comorbidities, fracture type, and surgical repair was obtained by review of medical charts. Prefracture comorbid disease information was used to calculate the Charlson comorbidity index (16).

At the baseline visit, weight was measured using the same standard scale in all participants. Knee height was measured to the nearest 0.1 cm in the left leg using a sliding caliper, and stature was estimated from the knee height measurement using the method of Chumlea and colleagues (17). Information on participant demographics was obtained at the baseline evaluation by patient self-report or proxy interviews.

CT Scan Measures

As part of an ancillary study to BHS-7, CT scans of the midthigh are being obtained at 2 months postfracture. All participants who were enrolled in the parent study and who had not died, dropped out, or been lost to follow-up by the 2-month follow-up visit were eligible for enrollment in the ancillary study. Participants were excluded if they were unable to lie supine for the CT scan or had cognitive impairment preventing them from being left alone during the CT scan. One hundred and thirty five participants in the BHS-7 study were screened for participation in the ancillary study; of these, 67 (49.6%) were determined to be eligible and 50 of whom (74.6% of eligible participants) agreed to participate in the ancillary study. Two participants later withdrew from the ancillary study, and one participant withdrew from both the parent and the ancillary study, leaving the final sample of 47 participants who provided CT scan data.

A single 10-mm axial CT scan (Philips Brilliance 64 CT scanner, Phillips Electronics N.V. Eindhoven, The Netherlands) was obtained at the midthigh level on each participant at the time of the 2-month evaluation (18). All images were analyzed by one person. Thigh muscle CSA was quantified using SliceOmatic software version 3 (Tomovision, Montréal, Canada). Intermuscular adipose tissue (IMAT) was distinguished from the subcutaneous adipose tissue by manually drawing a line along the deep fascial plane surrounding the thigh muscles. Once the adipose tissue was segmented from the images, individual muscles were identified. Skeletal muscle attenuation was measured for each muscle as the mean attenuation value between 0 and 100 HU as a marker of skeletal muscle lipid content (13,18). Muscle CSA and muscle attenuation were quantified for all the muscles of the thigh, a majority of which are the quadriceps and hamstring muscles.

Analyses

Study participant data are presented as the mean and range. Paired sample *t* tests were performed to compare the fractured to the nonfractured legs. All analyses were performed using the statistical package SAS (SAS Institute, Cary, NC).

Results

Data on 47 participants (26 men and 21 women) at 2 months after hip fracture are presented. Participant characteristics are presented in Table 1. Mean age was 80.4 years (range 65–96). The majority of participants (*n* = 37) were either married or widowed. Seventeen participants (37.0%) had a high school diploma, whereas 20 (43.5%) had more than 12 years of formal education, and 9 individuals (19.6%) had less. Mean prefracture Charlson comorbidity index score was 2.4 (range 0.0–8.0), suggesting a moderate comorbid disease burden.

At 2 months postfracture (Table 2), on the side of the fracture, the thigh CSA was smaller by 9.2 cm^2 (95% CI: 5.9, 12.4 cm^2), the CSA of IMAT was greater by 2.8 cm^2 (95% CI: 1.9, 3.8 cm^2), and the overall muscle attenuation was lower by 3.61 HU (95% CI: 2.99, 4.24 HU).

Discussion

Atrophy and replacement of muscle with adipose tissue is a well-described phenomenon of aging, and CT scan–based measures of thigh muscle composition have previously been examined in non-disabled older men and women (19,20). Compared with the data from these studies in nondisabled elderly patients, hip fracture patients appear to have lower mean thigh muscle CSA, in either leg, than nondisabled elderly patients, with similar muscle attenuation (19,20). Although muscle atrophy and replacement of muscle by adipose tissue may occur with aging, such changes may be accelerated by the decreased loading of thigh muscles resulting from pain and disability that occurs early on in hip fracture recovery. Results of the current analysis demonstrate lower muscle area, lower mean muscle

Table 1. Baseline Characteristics of the Study Sample (N = 47)

	Mean (range) or N (%)
Age	80.4 (65–96)
Mean (Range)	
Male	26 (55.3)
N (%)	
BMI (Kg/m^2)	26.0 (20.4 – 38.2)
Charlson Comorbidity Index	2.4 (0.0 – 8.0)
Mean (range)	
Marital status*	
Never married	5 (10.9)
Married	21 (45.7)
Widowed	16 (34.8)
Divorced	4 (8.7)
Ethnicity	
White	41 (89.1)
African American	4 (8.7)
Other	2 (4.3)
Education*	
≤12 years	9 (19.6)
12 years	17 (37.0)
>12 years	20 (43.5)
Fracture type*	
Subcapital	14 (29.8)
Trochanteric	27 (57.5)
Surgical repair*	
Hemiarthroplasty/arthroplasty	17 (36.2)
Internal fixation	29 (61.7)

* Totals may be less than 47 due to the missing data.

attenuation, and greater intermuscular fat in the fractured compared with the nonfractured legs. To our knowledge, this is the first study to examine thigh muscle composition in hip fracture patients using CT scanning and the first study to demonstrate asymmetry in measures of thigh muscle between the fractured and nonfractured leg.

In addition to decline in the lean mass that has been seen following hip fracture (10), changes in muscle composition may also have important functional consequences in this frail population of older adults and may help to further explain the profound functional declines seen following hip fracture (5). Greater muscle attenuation on CT scan imaging reflects lower intramuscular fat content and is positively associated with muscle strength, independent of muscle mass (13). It is muscle strength rather than muscle mass that is believed to be important for function in older adults, including those recovering from hip fracture (20–22). Thus, the changes in muscle composition observed here of decreased lean muscle mass and increased fat in and around the muscle in the fractured leg may explain some of these adverse functional consequences in this population.

The differences in the fractured and nonfractured legs may be explained by the physiological response to the initial injury of hip fracture and surgical repair, as well as postfracture disuse of the affected leg due to functional loss and pain (23,24). Following trauma such as hip fracture and hip fracture surgery, there is an inflammatory response in order to initiate healing through the recruitment of immune and inflammatory cells to the site of injury (25). These cells are instrumental in the orchestration of cell movement necessary for wound repair. Tumor necrosis factor alpha, a key cytokine in this process (26), also induces muscle catabolism and cachexia (8). The inflammatory response following injury may therefore contribute to the observed asymmetry between the affected and the unaffected limbs (27). Inflammation following surgical trauma and hip fracture has been observed to be associated with an adverse effect on recovery (7,28). Pain, which is also mediated by inflammatory cytokines, is an important aspect of postinjury recovery (29).

The decreased weight bearing resulting from favoring the unaffected leg in ambulation during the post–hip fracture period may also explain the differences between the affected and the unaffected leg that we observed at 2 months post–hip fracture repair because muscle disuse resulting from the removal of weight bearing can lead to decreased protein synthesis and increased protein degradation (30). In contrast, the favoring of the unaffected leg in ambulation could lead to an increase in muscle volume and a decrease in adipose tissue content, due to a training effect, further increasing the asymmetry between the two limbs (31). Asymmetrical lower limb loading may persist beyond the 2-month time point examined here. In one cross-sectional study, distal leg loading, knee extension strength, and calf muscle CSA were found to be lower on the fractured leg in older adults who were on average 3.5 years post–hip fracture in one cross-sectional study (32). If measures of lower extremity muscle composition are associated with function in older adults, then this persistent asymmetry in lower limb musculature may help to explain the functional declines seen in hip fracture patients (5). A longitudinal analysis of thigh musculature using the CT scan data from the BHS-7 cohort may help identify factors associated with a persistence of thigh muscle asymmetry in hip fracture patients and the importance of this asymmetry to postfracture recovery.

Although these results are interesting, they should be viewed with the following limitations in mind. The analyses presented here are cross-sectional, and therefore we are unable to determine the direction of the association. Although we have speculated that disuse of

Table 2. Thigh Muscle Characteristics (N = 47)*

	Fractured Leg	Nonfractured Leg	Difference†
CSA (cm^2)	74.45 (69.18, 79.73)	83.61 (77.14, 90.07)	−9.15 (−12.37, −5.93)
IMAT (cm^2) 11.95 (10.66, 13.24)	14.78 (13.09, 16.47)	11.95 (10.66, 13.24)	2.84 (1.86, 3.81)
Attenuation (Hu)	36.08 (34.80, 37.37)	39.70 (38.35, 41.04)	−3.61 (−4.24, −2.99)

*Mean (95% CI). CSA – total thigh cross sectional area, IMAT – cross sectional area of intermuscular adipose tissue.

†Values in the fractured leg minus those in the non-fractured leg.

the affected limb following hip fracture may explain the observed association, due to the cross-sectional nature of the analyses, we are unable to exclude that the observed asymmetry did not exist prior to the fracture, perhaps resulting from gait asymmetry that may have contributed to a fall and hip fracture.

In conclusion, at 2 months post–hip fracture repair, older men and women demonstrated lower muscle attenuation and greater intermuscular fat in the fractured compared with the nonfractured legs, on CT scan imaging. These changes are consistent with atrophy and replacement of muscle with fatty tissue and may be a result of decreased muscle use, inflammation, or both in the year postfracture. Future studies will better evaluate the processes that explain these changes and their influence on recovery of lower extremity function in the year following hip fracture. A better understanding of these processes may have implications not only for the care of hip fracture patients but may also aid in the understanding of the processes that underlie functional decline in frail and sarcopenic older adults in general.

Funding

References

1. Agency for Health Care Policy and Research.*Hospital Inpatient Statistics, 1996*.Washington, DC:US Department of Health and Human Services;1999.
2. Schneider EL,Guralnik JM.The aging of America—impact on health care costs*JAMA*.1990;263:2335–2340.
3. Braithwaite RS,Col NF,Wong JB.Estimating hip fracture morbidity, mortality and costs*J Am Geriatr Soc*.2003;51:364–370.
4. Magaziner J,Hawkes W,Hebel JRRecovery from hip fracture in eight areas of function*J Gerontol Med Sci*.2000;55A:M498–M507.
5. Magaziner J,Fredman L,Hawkes WChanges in functional status attributable to hip fracture: a comparison of hip fracture patients to community-dwelling aged*Am J Epidemiol*.2003;157:1023–1031.
6. Michel JP,Hoffmeyer P,Klopfenstein C,Bruchez M,Grab B,d'Epinay CL.Prognosis of functional recovery 1 year after hip fracture: typical patient profiles through cluster analysis*J Gerontol A Biol Sci Med Sci*.2000;55:M508–M515.
7. Miller RR,Cappola AR,Shardell MDPersistent changes in interleukin-6 and lower extremity function following hip fracture*J Gerontol A Biol Sci Med Sci*.2006;61:1053–1058.
8. Reid MB,Li YP.Tumor necrosis factor-alpha and muscle wasting: a cellular perspective*Respir Res*.2001;2:269–272.
9. Paddon-Jones D,Sheffield-Moore M,Cree MGAtrophy and impaired muscle protein synthesis during prolonged inactivity and stress*J Clin Endocrinol Metab*.2006;91:4836–4841.
10. Fox KM,Magaziner J,Hawkes WGLoss of bone density and lean body mass after hip fracture*Osteoporos Int*.2000;11:31–35.
11. Newman AB,Haggerty CL,Goodpaster BStrength and muscle quality in a well-functioning cohort of older adults: The Health, Aging and Body Composition Study*J Am Geriatr Soc*.2003;51:323–330.
12. Goodpaster BH,Park SW,Harris TBThe loss of skeletal muscle strength, mass, and quality in older adults: The Health, Aging and Body Composition Study*J Gerontol A Biol Sci Med Sci*.2006;61:1059–1064.
13. Goodpaster BH,Kelley DE,Thaete FL,He J,Ross R.Skeletal muscle attenuation determined by computed tomography is associated with skeletal muscle lipid content*J Appl Physiol*.2000;89:104–110.
14. Kelley DE,Slasky BS,Janosky J.Skeletal muscle density: effects of obesity and non-insulin-dependent diabetes mellitus*Am J Clin Nutr*.1991;54:509–515.
15. Orwig D.Men with hip fracture, an increasing problem: how are they different from women who fracture?*Gerontologist*.2009;49:374
16. Charlson M,Szatrowski TP,Peterson J,Gold J.Validation of a combined comorbidity index*J Clin Epidemiol*.1994;47:1245–1251.
17. Chumlea WC,Roche AF,Steinbaugh ML.Estimating stature from knee height for persons 60 to 90 years of age*J Am Geriatr Soc*.1985;33:116–120.
18. Goodpaster BH,Thaete FL,Simoneau J-A,Kelley DE.Subcutaneous abdominal fat and thigh muscle composition predict insulin sensitivity independently of visceral fat*Diabetes*.1997;46:1579–1585.
19. Goodpaster BH,Carlson CL,Visser MAttenuation of skeletal muscle and strength in the elderly: the Health ABC Study*J Appl Physiol*.2001;90:2157–2165.
20. Cawthon PM,Fox KM,Gandra SRDo muscle mass, muscle density, strength, and physical function similarly influence risk of hospitalization in older adults?*J Am Geriatr Soc*.2009;57:1411–1419.
21. Visser M,Harris TB,Fox KMChange in muscle mass and muscle strength after a hip fracture: relationship to mobility recovery*J Gerontol A Biol Sci Med Sci*.2000;55A:M434–M440.
22. Miller RR,Shardell MD,Hicks GEAssociation between interleukin-6 and lower extremity function after hip fracture—the role of muscle mass and strength*J Am Geriatr Soc*.2008;56:1050–1056.
23. Ingemarsson AH,Frandin K,Mellstrom D,Moller M.Walking ability and activity level after hip fracture in the elderly—a follow-up*J Rehabil Med*.2003;35:76–83.
24. Craik RL.Disability following hip fracture*Phys Ther*.1994;74:387–398.
25. Daniel T,Thobe BM,Chaudry IH,Choudhry MA,Hubbard WJ,Schwacha MG.Regulation of the postburn wound inflammatory response by gammadelta T-cells*Shock*.2007;28:278–283.
26. Fu X,Han B,Cai S,Lei Y,Sun T,Sheng Z.Migration of bone marrow-derived mesenchymal stem cells induced by tumor necrosis factor-α and its possible role in wound healing*Wound Repair Regen*.2009;17:185–191.
27. Sato Y,Inose M,Higuchi I,Higuchi F,Kondo I.Changes in the supporting muscles of the fractured hip in elderly women*Bone*.2002;30:325–330.
28. Hall GM,Peerbhoy D,Shenkin A,Parker CJR,Salmon P.Relationship of the functional recovery after hip arthroplasty to the neuroendocrine and inflammatory responses*Br J Anaesth*.2001;87:537–542.
29. Sommer C,Kress M.Recent findings on how proinflammatory cytokines cause pain: peripheral mechanisms in inflammatory and neuropathic hyperalgesia*Neurosci Lett*.2004;361:184–187.
30. Jackman RW,Kandarian SC.The molecular basis of skeletal muscle atrophy*Am J Physiol Cell Physiol*.2004;287:C834–C843.
31. Taaffe D,Henwood T,Nalls M,Walker D,Lang T,Harris T.Alterations in muscle attenuation following detraining and retraining in resistance-trained older adults*Gerontology*.2009;55:217–223.
32. Mikkola T,Sipilä S,Portegijs EImpaired geometric properties of tibia in older women with hip fracture history*Osteoporos Int*.2007;18:1083–1090.