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Association of Interleukin-6 with Lower Extremity Function Following Hip Fracture – The role of Muscle Mass and Strength

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Abstract

Objectives—Determine whether the association of interleukin 6 (IL-6) with lower-extremity function in the year after hip fracture is explained by an effect on muscle mass or strength.

Design—Analysis on data from a longitudinal cohort study.

Setting—Two Baltimore area hospitals.

Participants—Community-dwelling women aged ≥65 years, admitted to one of two hospitals in Baltimore with a new, non-pathological fracture of the proximal femur between 1992 and 1995.

Measurements—At 2, 6 and 12 months post fracture, serum IL-6, appendicular lean muscle mass (aLM), and grip strength were measured and the Lower Extremity Gain Scale (LEGS), a summary measure of performance of 9 lower extremity tasks was calculated. Generalized estimating equations (GEE) were used to model the longitudinal relationship between IL-6 tertile and LEGS. We examined whether muscle mass or strength explained the relationship between IL6 and LEGS by adding measures aLM, grip strength or both into the model.

Results—Subjects in the lowest IL-6 group performed better on the LEGS than those in the highest tertile by 4.51 (95% CI: 1.50, 7.52) points at 12 months post fracture. Adjusting for aLM, and grip strength this difference was 4.28 points (95% CI: 1.14, 7.43) and 3.81 points (95% CI: 0.63, 7.00) respectively. Adjusting for both aLM and grip strength the mean difference in LEGS score was 3.88 points (95% CI: 0.63, 7.13).

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Conclusions—In older women after hip fracture, the diminished recovery of lower extremity function observed with higher levels of the inflammatory marker IL-6 is better explained by reduced muscle strength, rather than reduced muscle mass.

Introduction

Low muscle mass or sarcopenia is an important factor in the development of functional disability in older adults. Recent studies have suggested that loss of muscle mass does not fully explain the decreased muscle strength seen with advanced age;^{1, 2} and changes in muscle strength, in disproportion to changes in muscle mass, have been observed.

Serum markers of chronic inflammation have been associated with sarcopenia, and decreased muscle strength;^{3–7} and inflammation is believed to contribute to muscle weakness by both accelerated protein loss and contractile dysfunction.⁸

We have found that in older women recovering from hip fracture, the serum level of the inflammatory cytokine interleukin 6 (IL-6) is associated with functional recovery in the 12 months post fracture.⁹ Although a substantial loss of muscle mass (5 to 6%) occurs in women during the year after hip fracture,^{10, 11} there is evidence to suggest that a decline in muscle strength to a greater degree than a decline in muscle mass is associated with worse recovery of lower extremity function.^{12–14} Whether the association of IL-6 level with lower extremity function in the year post hip fracture is explained by an effect on muscle mass or strength is not known.

We examined a cohort of women admitted to two Baltimore area hospitals between 1992 and 1995 who were enrolled in the Baltimore Hip Studies. Women 65 years and older were followed for a year post hip fracture, in order to evaluate whether the association of IL-6 levels with lower extremity function in the year post hip fracture is explained by an effect on muscle mass or strength.

Methods

Subjects were drawn from the third cohort in the Baltimore Hip Studies (BHS-3). Between 1992 and 1995, 205 Caucasian women, aged at least 65 years and community dwelling, admitted to one of two hospitals in Baltimore with a new, non-pathological fracture of the proximal femur, agreed to participate in a prospective study. Subjects were evaluated at 3 or 10 days (baseline) and at 2, 6, and 12 months post hospitalization for fracture (follow-up). The study protocol was approved by the Institutional Review Boards of both hospitals, and of the University of Maryland Baltimore. A more detailed description of this cohort may be found elsewhere.^{9, 10}

Measure of Function

At the 2, 6 and 12 month evaluations, timed performance of 9 lower extremity tasks was assessed at each evaluation: [1] reach for an item on the ground from a sitting position; [2] put a sock on the fractured-side foot; [3] put a shoe on the fractured-side foot; [4] rise from an armless chair; [5] walk ten feet; [6] step up four steps; [7] step down four steps; [8] get on the toilet; and [9] get off the toilet. Performance of these tasks was scored on a scale of 0 to 4 to create a summary score of lower extremity function, the Lower Extremity Gain Scale (LEGS).¹⁵ This score ranges from 0–36 with higher scores indicating better performance. It has been shown to be a reliable measure and the domains that it assesses have been identified by hip fracture patients and their caregivers as important aspects of functioning. A difference of approximately 2 points on this scale is believed to be clinically meaningful.¹⁶

IL-6 measurement

The methods for collection and storage of serum samples have been described in detail elsewhere.¹⁷ Briefly, sera obtained at the 2, 6 and 12 month time points were stored at -70°C . When stored at these temperatures IL-6 is believed to remain stable in serum for many years.¹⁸ IL-6 levels were measured in serum that had not been previously thawed by a two-antibody ELISA using biotin-streptavidin-peroxidase detection, and commercially available human antibodies (Pierce/Endogen, Rockford, IL). Samples from these time points were analyzed in the same batch to minimize laboratory variability. The linear range for the IL-6 assay was 1.5 to 100 pg/ml. The inter-assay CV was 3.6% and the intra-assay CV% was 8%. Cytokine measurements above the upper detection limit of 100 pg/ml were converted to the highest level of the assay and measurements below the lower detection limit of 1.5 pg/ml were scored as zero. At the 2-month, 6-month and 12-month examinations 7%, 5% and 5% respectively of the IL-6 measurements were above the assay limit and 1%, 3% and 5% were below the detection limit for the assay.

Measures of Body Composition

At the 2, 6 and 12 month evaluations, dual-energy x-ray absorptiometry (DXA) (Hologic, Inc., Waltham, MA) was used to measure whole and regional body composition, using a method described in detail elsewhere.¹⁰ Since the presence of post-operative swelling and metallic implants may affect DXA readings,¹⁹ appendicular lean mass (aLM) was calculated as the sum of the lean mass in the arms and twice the lean mass in the unfractured leg, as has been done in other studies of hip fracture patients.¹⁴ Total body fat was calculated similarly and percent body fat was calculated based on the DXA results at each of the 2, 6 and 12-month evaluations.

Measure of Strength

Due to the proximity of the hip fracture event, measures of proximal lower extremity strength were not obtained in this cohort. Grip strength, which has been shown to be a strong predictor of lower extremity function^{20, 21} was measured at each of the 2, 6 and 12-month evaluations using a handheld dynamometer (Jamar, Clifton, NJ). The maximum strength results (in kilograms) of four grip strength trials (two in each arm) with patients seated were used.

Covariates

Age, the type of surgical repair (internal fixation, hemi-arthroplasty or arthroplasty), and the presence or absence of 20 non-infectious and 3 infectious in-hospital complications were collected from the hospital record at baseline. Since infection is associated with elevated inflammatory cytokine levels,²² infectious and non-infectious in-hospital complications were tabulated separately. The list of potential complications appears in detail elsewhere.⁹ The presence, prior to the fracture, of osteoarthritis, coronary artery disease (history of either angina pectoris, cardiovascular disease or myocardial infarction), congestive heart failure, stroke, dementia, diabetes, chronic obstructive pulmonary disease, and peripheral vascular disease was also collected at baseline from the hospital record. These conditions were chosen because they have been observed to be associated with an adverse effect on functional recovery in elders.²³ Details on physical therapy treatment was assessed by a review of the medical record at the acute inpatient, rehabilitation center and outpatient settings and the number of physical therapy sessions received by the participants was tabulated. At each of the 2, 6 and 12-month evaluations, mental Status was assessed using the Mini-Mental State Examination (MMSE).²⁴ At the baseline evaluation, subjects reported on their pre-fracture limitations with eleven activities of Daily Living requiring lower extremity functioning (LE-ADLs). A score of LE-ADL function was calculated as the count of the number of activities in which the person was impaired (required either human or equipment assistance or both or completely unable to

perform). The eleven activities included were Walking ten feet or across a room; Walking one block on a level sidewalk; Climbing five stairs; Getting into a car; Getting into and out of bed; Rising from an armless chair; Putting on pants; Putting socks and shoes on both feet; Getting in/out of a bath or shower; Taking a bath, shower, or sponge bath; and Getting on and off the toilet. The scale thus ranges from zero to eleven with higher scores representing greater pre-fracture dependency. Height was collected by self report at the baseline examination. Proxy data were used whenever patient data were unavailable or the patient was cognitively impaired (MMSE score less than 17). At each visit, participants were asked about pain symptoms and the use of medications during the previous week. The presence of pain was defined as a positive response to the question “within the past week have you had any pain or discomfort whatsoever.” Use of pain reliever/anti-inflammatory agents was defined as the report of use during the previous week of aspirin, non-aspirin based pain relievers or corticosteroids.

Statistical Analyses

Due to the proximity of the baseline evaluation to the hip fracture surgery, only 56 participants attempted the LEGS measurements at baseline (data not shown). Also, the serum levels of IL-6 at the baseline evaluation are more likely to reflect a normal physiological response to the trauma of hip fracture and subsequent surgical repair, and not a prolonged inflammatory process.^{25, 26} Consistent with our previous work,⁹ we therefore restricted the current analyses to the 2, 6 and 12 month follow-up time points. Subjects were divided into groups based on their serum IL-6 levels over the 2, 6 and 12 month time points of the follow-up period (low group: $IL-6 \leq 5.63$, middle group $5.63 < IL-6 \leq 14.30$, and high group $IL-6 > 14.30$ pg/ml). These cut-points represent the IL-6 tertile levels of all the observations over the 2 to 12 month follow-up period, therefore ensuring that approximately equal numbers of observations are included in each IL-6 group over the follow-up period.

Generalized estimating equations (GEE)²⁷ were used to model the longitudinal relationship between IL-6 category at the 2, 6 and 12 month follow-up evaluations and grip strength and aLM, using a normal working model and robust standard errors in order to account for correlations across time within individuals. Generalized F tests were used to compare grip strength and aLM trajectories between those in the mid-level and high IL-6 categories to the lowest (reference) IL-6 group. The models were adjusted for age, comorbidity, and percent body fat.

Generalized estimating equations (GEE)²⁷ were similarly used to model the longitudinal relationship between IL-6 category at the 2, 6 and 12 month follow-up evaluations and LEGS. Again, generalized F tests were used to compare LEGS trajectories between those in the mid-level and high IL-6 categories to the lowest (reference) IL-6 group, and time-specific t-tests were performed to compare IL-6 group scores at each time point. The models were adjusted for age, comorbidity, the type of surgical repair (internal fixation versus arthroplasty repairs), post-surgical complications, the number of physical therapy sessions received by 2 months post-fracture, percent body fat, pre-fracture LE-ADL score, MMSE score, height, pain and medication use.

We examined whether muscle mass, muscle strength or both mediated (according to the definition of Baron and Kenny²⁸), in part, the relationship between serum IL6 levels and lower extremity function by adding the measures of aLM, grip strength or both into the model. We examined differing effects of muscle mass and strength over time by including time-by-predictor interaction terms into the models. We also examined for interaction between muscle mass and strength through the inclusion of interaction terms in the model.

The validity of GEE results are contingent on missing data being missing completely at random (MCAR) as defined by Rubin.²⁹ A sensitivity analysis of the MCAR assumption using

weighted estimating equations (WEE) was performed.³⁰ The weights were calculated by performing a logistic regression of observing both IL-6 and LEGS (yes/no) on the covariates used in the analysis model for each visit.

Results

Characteristics of the study sample are summarized in Table 1. Mean (SD) age was 79.66 (7.83) years. All subjects were white. At the 2, 6 and 12 month evaluations, serum was collected and analyzed for IL-6 levels on 91, 96 and 77 participants, grip strength was measured on 85, 91 and 73 participants, DXA evaluations for body composition were performed on 78, 82 and 70 participants, and the LEGS test was completed by 62, 75 and 54 participants, respectively. Of these subjects, 51, 63 and 51 subjects had complete information required for the analyses presented here at 2, 6 and 12 months, respectively and 68 subjects were included at least once in the primary analyses. Subjects who were included in the 2 month analyses, but had incomplete information at either the 6 or 12 month evaluations did not differ significantly with respect to age, comorbidity, post-fracture surgical complications, or the number of physical therapy sessions received, but they reported limitations with a greater number of lower extremity tasks pre-fracture (4.59 versus 1.67, $p < 0.001$).

In longitudinal analyses, subjects in the low IL-6 group displayed greater aLM ($p = 0.07$) and grip strength ($p = 0.12$) during the follow-up period. At 12 months post fracture those in the low IL-6 group had, on average 0.56 kg (95% CI: 0.07 kg, 1.1 kg) greater aLM and 2.4 kg greater grip strength (95% CI: 0.14 kg, 4.7 kg) compared to those in the highest group. (Figure 1).

Subjects in the low IL-6 group performed better on the LEGS than those in the high group over the 2, 6 and 12 months evaluations ($p = 0.007$ in longitudinal analyses). Performance on the LEGS did not differ significantly between the middle and high IL-6 groups. The difference in LEGS score between the high and low groups was greatest at 12 months post-fracture when, adjusted for covariates only, on average those in the highest IL-6 group scored 4.51 (95% CI: 1.50, 7.52) points worse on the LEGS measure (Figure 2, panel A). Adjusting for covariates and aLM (Figure 2, panel B), the difference in LEGS scores at 12 months was 4.28 points (95% CI: 1.14, 7.43); adjusting for covariates and grip strength (Figure 2, panel C) the difference at 12 months was 3.81 points (95% CI: 0.63, 7.00). Adjusting for covariates and both aLM and grip strength (Figure 2, panel D) resulted in little change of the 12-month effect estimate over adjustment for covariates and grip strength alone; the mean difference at 12 months between the low and high groups of IL6 in this model was 3.88 points (95% CI: 0.63, 7.13).

Adjusted for covariates, and IL-6 group, for each standard deviation (SD) difference in aLM (SD=2.6 kg), LEGS scores differed by on average 0.3 points ($p = 0.62$) while for each SD difference in grip strength (SD = 4.8 kg), LEGS scores differed by 2.3 points ($p = 0.005$). With both aLM and grip strength in the model, for each SD difference in grip strength, LEGS scores differed by 2.4 points ($p = 0.007$).

The sensitivity analysis yielded similar results and the same conclusions as the GEE analysis (data not shown).

Discussion

We previously reported that serum IL-6 levels are adversely associated with lower extremity function in the year following hip fracture.⁹ In the current analyses, we explored whether muscle mass, strength or both explained this association. We found that although the overall interpretation of the longitudinal association between IL-6 group and LEGS changed little with the different models, adjustment for muscle mass attenuated the 12-month effect estimate by 5%, from 4.51 to 4.28 points whereas adjustment for muscle strength resulted in a 16%

attenuation of the 12-month estimated effect from 4.51 to 3.81 points. Adjustment for both muscle mass and strength did not alter the effect estimate substantially over adjustment for strength alone. These results would suggest that the association of IL-6 with lower extremity function following hip fracture is explained by muscle strength in disproportion to muscle mass.

In studies of older adults, including adults post hip fracture, muscle strength, in disproportion to muscle mass, has been associated with poor function.^{12–14, 31} Our results are consistent with previous studies that have found that, in older adults, levels of inflammatory markers are more strongly associated with muscle strength than muscle mass³² and that changes in muscle strength may explain the association between IL-6 with functional loss.³³ To our knowledge, however, this is the first study to examine these associations longitudinally in a cohort of frail older adults recovering from a traumatic and disabling event, hip fracture.

In a less disabled cohort of older adults, inflammatory cytokine levels have been found to be associated with low levels of muscle mass³² and, in turn, low muscle mass was associated with poor lower extremity function.³⁴ In contrast, in this and other cohorts of elders post hip fracture, an association between aLM and lower extremity function was not found.^{12, 14} Although aLM is considered a measure of sarcopenia, its utility may be limited in the study of frail elders such as those recovering from hip fracture, where many may have low muscle mass. For example, in the cohort studied here, the mean (SD) aLM at the baseline examination was 13.9 (3.0) kg compared to published values of 16.1 (2.5) kg in older white women from the Health Aging and Body Composition (Health ABC) Study.³² Previously published analyses from the BHS-3 cohort have demonstrated that lean body mass decreases rapidly post hip fracture with, compared to the immediately post-fracture measurement, a decline of 6.4% noted by 2 months post fracture and a persistent decrease of 6.0% noted at one year. In contrast, fat mass was found to decrease by only 1.6% by 2 months and increase by 3.6% by 12 months post fracture, suggesting that the loss of lean tissue exceeds that of overall body mass.¹⁰ Low muscle mass is believed to be central to the frailty syndrome³⁵ and therefore in frail elders, such as those who suffer hip fracture, changes in muscle mass may be small. Processes intrinsic to the muscle itself, however, such as alterations of contractile protein structure with resulting changes in muscle contractile properties may explain the observed declines in strength that are associated with inflammation.

Although the specific mechanisms that explain declines in muscle strength in older adults are not completely understood, factors such as age-associated decreases in the proportion of myosin heavy chain type II fibers,³⁶ increased connective tissue, fatty infiltration,³⁷ altered muscle metabolism,³⁸ and changes to the muscle spindle³⁹ are believed to play a role. Single muscle fibers taken from older subjects have been found to have significantly lower maximal force compared with similar fibers from younger individuals, suggesting that the intrinsic ability of muscle fibers to generate force is lower in older subjects.⁴⁰ Although single muscle fibers from old subjects are frequently smaller in cross sectional area (CSA) than those taken from younger individuals,³⁷ the decline in force observed with aging exceeds this decrease in CSA.⁴¹ This may be explained, in part, by myosin concentration levels in muscle fibers from older and younger individuals as myosin concentration has been found to have a linear relationship with specific force (force/CSA) generation in single muscle fibers and these concentrations are lower in fibers taken from the skeletal muscle of older, compared to younger subjects.⁴¹ Inflammation can also affect muscle contractile properties. In addition to the catabolic effect of chronic inflammatory states,^{42, 43} tumor necrosis factor alpha (TNF- α) is believed to depress contractile force at the myofilament level, by a mechanism mediated by reactive oxygen species (ROS) and nitric oxide (NO) derivative generation.⁴⁴

These results must be viewed with the following limitations in mind. As we have previously reported, a proportion of study subjects had cytokine levels beyond the range of the assays employed and, due to selective forces, serum samples at later evaluations were obtained from younger women with less comorbidity, compared to the cohort as a whole at baseline.⁹ Also, all of the subjects included in these analyses were white women and thus we are unable to assess whether similar associations exist in men or in women of other ethnicities. Finally, the association of IL-6 with both muscle strength and muscle mass observed here explained 19% of the relationship between this inflammatory cytokine and recovery of lower extremity function post hip fracture. This would suggest that these associations, although interesting, represent but one piece of a more complex mechanism and other processes, beyond the scope of study of these analyses, are also likely to be involved.

In summary, we have found that muscle strength in disproportion to muscle mass explains the association of serum levels of the inflammatory cytokine IL-6 with lower extremity function in the year after hip fracture. These results should be confirmed in studies where direct measures of muscle composition are available.

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Figure 1.

Association of Grip Strength and Appendicular Lean Mass with Time-Dependent IL-6 Group

—■— Low Group (<5.6 pg/ml) —▲— Middle Group (5.6-14.3 pg/ml) —●— High Group (>14.3 pg/ml)

*Adjusted for age, comorbidity, type of surgical repair, post-surgical complications, percent body fat, pre-fracture LE-ADL score, MMSE score, height, recent pain and recent pain reliever / anti-inflammatory use.

Panel	Test for longitudinal comparison of high vs. low groups	Difference in LEGS score (95% CI) between high vs. low groups at 12 months post fracture
A	P=0.008	-4.51 (-7.52, -1.50)
B	P=0.02	-4.28 (-7.43, -1.14)
C	P=0.05	-3.81 (-7.00, -0.63)
D	P=0.05	-3.88 (-7.13, -0.63)

Figure 2.
Estimated Mean* LEGS Scores by Time-Dependent IL-6 Group

Table 1

Characteristics of the study sample at two months post hip fracture.

IL-6 Group N=68				
Variable	Low (< 5.63 pg/ml) N = 19	Middle (5.63–14.30 pg/ml) N=28	High (> 14.30 pg/ml) N=21	P value
Baseline Age (Years)				
Mean (SD)	78.89 (8.88)	79.35 (7.21)	80.76 (7.88)	0.54
BMI Count (%)				
<18.5 kg/m²	1 (5.3)	4 (14.3)	3 (14.3)	0.22
18.5–24.9 kg/m²	11 (57.9)	14(50.0)	8 (38.1)	
25–29.9 kg/m²	7 (36.8)	4 (14.3)	9 (42.9)	
≥ 30.0 kg/m²	0 (0.0)	6 (21.4)	1 (4.8)	
Baseline Comorbidities Count(%)				
0	7 (36.8)	7 (25.0)	6 (28.6)	0.85
1	6 (31.6)	10 (35.7)	9 (42.9)	
≥ 2	6 (31.6)	11 (39.3)	6 (28.6)	
Type of Surgical Repair Count (%)				
Internal fixation	10 (52.6)	16 (57.1)	17 (85.0)	0.06
Arthroplasty	9 (47.4)	12 (42.9)	3 (15.0)	
In Hospital				
Complications Count (%)				
0	16 (84.2)	22 (78.6)	14 (70.0)	0.56
≥ 1	3 (15.8)	6 (21.4)	6 (30.0)	
Self Report of Pain week prior to the 2-month evaluation Count (%)				
Yes	16 (84.2)	23 (82.1)	16 (76.2)	0.79
No	3 (15.8)	5 (17.9)	5 (23.8)	
Used anti-inflammatory drugs or other pain relievers in the week prior to the 2-month evaluation Count (%)				
Yes	13 (84.6)	21 (75.0)	15 (71.4)	0.88
No	6 (15.4)	7 (25.0)	6 (28.6)	
Pre-fracture limitations in LE-ADL function Mean Number of Limitations (SD)	3.56 (3.05)	4.27 (3.06)	3.36 (2.48)	0.92

Variable	IL-6 Group N=68			P value
	Low (< 5.63 pg/ml)	Middle (5.63–14.30 pg/ml)	High (> 14.30 pg/ml)	
	N = 19	N=28	N=21	
MMSE at 2 months post fracture Mean (SD)	27.43 (2.94)	26.70 (3.73)	25.57 (3.89)	0.12
Number of physical therapy sessions completed by 2 months Mean (SD)	21.95 (13.47)	24.93 (13.37)	27.30 (18.93)	0.60