Higher Inflammatory Marker Levels in Older Persons: Associations With 5-Year Change in Muscle Mass and Muscle Strength

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Background. There is growing evidence that higher levels of inflammatory markers are associated with physical decline in older persons, possibly through the catabolic effects of inflammatory markers on muscle. The aim of this study was to investigate the association between serum levels of inflammatory markers and loss of muscle mass and strength in older persons.

Methods. Using data on 2,177 men and women in the Health, Aging, and Body Composition Study, we examined 5-year change in thigh muscle area estimated by computed tomography and grip and knee extensor strength in relation to serum levels of interleukin-6 (IL-6), C-reactive protein, tumor necrosis factor-alpha (TNF-α), and soluble receptors (measured in a subsample) at baseline.

Results. Higher levels of inflammatory markers were generally associated with greater 5-year decline in thigh muscle area. Most associations, with the exception of soluble receptors, were attenuated by adjustment for 5-year change in weight. Higher TNF-α and interleukin-6 soluble receptor levels remained associated with greater decline in grip strength in men. Analyses in a subgroup of weight-stable persons showed that higher levels of TNF-α and its soluble receptors were associated with 5-year decline in thigh muscle area and that higher levels of TNF-α were associated with decline in grip strength.

Conclusions. TNF-α and its soluble receptors showed the most consistent associations with decline in muscle mass and strength. The results suggest a weight-associated pathway for inflammation in sarcopenia.

Key Words: Muscle—Inflammatory markers—Aging—Weight.

CIRCULATING levels of inflammatory markers such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) are often elevated in older persons and have been shown to be associated with increased morbidity (1–6) and mortality (7). In addition, there is growing evidence that levels of these inflammatory markers are associated with poorer physical performance and (incident) disability (8–13).

The association between elevated levels of inflammatory markers and physical decline may be explained by a direct causal role of inflammatory markers in the age-related decline in muscle mass and strength (14). Cross-sectional studies have demonstrated that higher levels of inflammatory markers are associated with lower muscle mass and strength (10,15). However, only two prospective studies have examined the relationship between inflammatory markers and sarcopenia with inconsistent results (16,17). A limitation of both these studies is the assessment of muscle mass by dual-energy x-ray absorptiometry (DXA). DXA may overestimate muscle mass because (increases in) muscle hydration or intramuscular fat deposition will be detected as (an increase in) lean tissue. Computed tomography (CT), however, allows calculation of volume measures of skin, skeletal muscle, and adipose tissue (with its attendant nonfat components). A second limitation is the use of only serum levels of inflammatory markers. There is evidence that higher levels of soluble receptors may represent a more prolonged or severe underlying inflammatory state (18,19) and might be

more reliable markers of chronic inflammation (20). Finally, cytokines (2,21) and muscle mass loss (22) have been linked with weight change, and earlier studies did not account for the possibility that weight change could modify the association of inflammation with change in lean mass.

The aim of the present study was to examine whether high serum levels of inflammatory markers and soluble receptors are associated with 5-year change in muscle mass, assessed by CT, and with 5-year change in muscle strength, measured as isometric grip strength and isokinetic quadriceps strength, in a large sample of well-functioning older men and women.

METHODS

Study Sample

Data were used from the Health, Aging, and Body Composition Study, a prospective cohort study on the interrelationship of changes in body composition and health conditions on physiological and functional changes in older persons. The study sample includes 3,075 black and white men and women, aged 70–79 years at baseline. Whites were recruited from a random sample of Medicare beneficiaries residing in zip codes form the metropolitan areas surrounding Pittsburgh, Pennsylvania and Memphis, Tennessee. Blacks were recruited from all age-eligible residents in these geographic areas. Potential participants received a mailing, followed by a telephone eligibility screen. Eligibility criteria included age 70–79 years in the recruitment period from March 1997 to July 1998; self-report of no difficulty walking one quarter of a mile or climbing 10 steps without resting; no difficulty performing basic activities of daily living; no reported use of a cane, walker, crutches, or other special equipment to get around; no history of active treatment for cancer in the prior 3 years; and no plan to move out of the area in the next 3 years.

Only participants with complete data on the inflammatory markers (IL-6, CRP, and/or TNF-α) at baseline and with complete data on 5-year change in muscle mass and/or muscle strength were included in the study ($n = 2,177$). Most of the persons with missing data were deceased (83%). Compared with the 2,177 participants included in the analyses, those who dropped out were older, more often male, more often black, had a lower knee extensor strength, had higher levels of inflammatory markers (IL-6, CRP, and TNF-α), were less physically active, and more often had one or more chronic diseases (all *p* values < .05).

The study was reviewed and approved by the Institutional Review Boards at the University of Tennessee and the University of Pittsburgh. All participants provided informed consent before participating in the study.

Muscle Mass

Muscle mass was assessed as mid-thigh cross-sectional muscle area by CT. Axial CT scans at the mid-thigh level were obtained during the baseline examination and after a 5-year follow-up. CT images were acquired in Pittsburgh (9800 Advantage; General Electric, Milwaukee, WI) or in Memphis (Somatom Plus 4; Siemens, Erlangen, Germany and PQ 2000S; Marconi Medical Systems, Cleveland, OH). All images were transferred electronically to a central reading center and analyzed by a single observer on a SUN workstation (SPARC station II; Sun Microsystems, Mountain View, CA) using IDL development software (RSI Systems, Boulder, CO). The procedures are described in detail elsewhere (23). The total area of nonadipose, nonbone tissue within the deep fascial plane was used as a measure of muscle area. Reproducibility of muscle area was assessed by reanalyzing a 5% convenience sample of the study cohort and showed a coefficient of variation (CV) less than 5%. We used data from persons in whom the same leg was scanned at baseline and at 5-year follow-up in whom the slice location on the femur was within 20 mm of the baseline location (mean difference +3.9 mm [*SD* 6.0]). All persons included in this study met these criteria.

Muscle Strength

Handgrip strength (kg) was measured using a hand-held dynamometer (Jamar; TEC, Clifton, NJ). The dynamometer was adjusted for hand size for each participant, and two trials were performed on each hand. The maximum values of the right and the left hand were summed (24).

Isokinetic strength of the knee extensors was measured by a Kin-Com 125 AP Dynamometer (Chattanooga, TN) at 60 degrees per second and was calculated from the average of three reproducible and acceptable trials out of a maximum of six trials. Due to strict criteria for safety reasons, knee extensor strength was assessed in 87% ($n = 2,674$) of the original cohort of 3,075 persons.

Inflammatory Markers

Levels of IL-6, TNF-α, CRP and the soluble receptors of IL-2 (IL-2 soluble receptor [IL-2sR], $n = 498$), IL-6 (IL-6 soluble receptor [IL-6sR], $n = 499$), and TNF-α (TNFsR1, $n = 496$ and TNFsR2, $n = 486$, randomly selected from the original total sample of 3,075 persons) were assessed in duplicate from frozen-stored serum collected after an overnight fast at baseline. Cytokines and soluble cytokine receptor levels were measured using enzyme-linked immunosorbent assay kits (R&D Systems, Minneapolis, MN) and CRP levels using enzyme-linked immunosorbent assay based on purified protein and polyclonal anti-CRP antibodies (Calbiochem, San Diego, CA). The detectible limits are described elsewhere (12). The CRP assay was standardized according to the World Health Organization First International Reference Standard with a sensitivity of 0.08 µg/mL. Assays of blind duplicates collected for 150 participants yielded an average interassay CV of 10.3% for IL-6, 8.0% for CRP, and 15.8% for TNF-α.

Potential Confounders

Covariates included age, sex, race, study site, chronic diseases, physical activity, steroid use, estrogen use, anti-inflammatory drug use, statin use, and weight change. Physical activity of the past 7 days and the intensity level at which each activity was performed were assessed by questionnaire. Based on the metabolic equivalent of each activity and body weight, an overall activity score in kilocalorie per week was created. Steroid use, estrogen use, anti-inflammatory drug use, and statin use were determined from drug data coded using the Iowa Drug Information System code (25). Chronic diseases were assessed by self-report, medication use, and clinical data and included pulmonary disease, cardiac disease, diabetes mellitus, arthritis, cerebrovascular diseases, peripheral atherosclerosis, and cancer. Weight (total mass) was assessed by DXA at baseline and at 5-year follow-up.

Statistical Analyses

Changes in muscle characteristics and body weight were calculated as 5-year follow-up value minus baseline value. Serum levels of inflammatory markers that were not normally distributed were log (ln) transformed. Multiple linear regression analyses were used to identify regression coefficients per standard deviation in (ln) serum inflammatory markers for change in muscle characteristics. Analyses were adjusted for the baseline measure of the outcome variable, age, sex, race, study site, chronic diseases, physical activity, and medication use. In a second model, analyses were additionally adjusted for 5-year change in weight. Potential sex and race differences in the associations under study were tested ($p < .10$) using Sex × Inflammatory markers and Race × Inflammatory markers product terms. The analyses were repeated in subgroups of weight-stable persons (weight change <3%).

RESULTS

Baseline characteristics of the study sample are shown in Table 1. The mean 5-year change in mid-thigh muscle area was -13.5 cm^2 $\pm$ *SD* 19.1 (-5.1%) in men and -6.3 cm^2 $\pm$ *SD* 14.5 (-3.4%) in women. The mean change in grip strength was -7.2 kg $\pm$ *SD* 12.5 (-9.2%) in men and -3.6 kg $\pm$ *SD* 9.0 (-7.6%) in women. The mean change in knee extensor strength was -24.9 Nm $\pm$ *SD* 27.8 (-18.4%) in men and -13.2 Nm $\pm$ *SD* 18.3 (-16.0%) in women. Baseline characteristics of the subsample with data on soluble receptors are also shown in Table 1.

Spearman correlations between cytokines and soluble receptors were calculated (Table 2). The strongest correlation existed between IL-6 and CRP ($r = .47$). There were also significant correlations between IL-6 and TNF-α ($r = .27$) and between CRP and TNF-α ($r = .13$). TNFsR1 and TNFsR2 showed a strong intercorrelation ($r = .79$), and both were highly correlated with IL-2sR ($r = .59$ and $r = .61$, respectively) and TNF-α ($r = .49$ and $r = .57$, respectively). Overall, IL-6sR showed the weakest correlations with the cytokines and soluble receptors. The correlation between IL-6 and IL-6sR was .06.

Persons with higher levels of IL-6, CRP, and TNF-α experienced a greater loss of thigh muscle area (Table 3, model 1). However, after additional adjustment for 5-year change in weight (model 2), the associations were no longer significant. Of the soluble receptors, lower levels of IL-6sR were associated with decline in thigh muscle area, whereas higher levels of TNFsR1 were associated with decline in thigh muscle area. These associations remained significant after additional adjustment for change in weight.

Table 4 shows the result of multiple linear regression analyses of inflammatory markers with 5-year change in grip strength and knee extensor strength. A higher level of TNF-α was associated with a greater decline in grip strength and knee extensor strength, and these associations remained significant after adjustment for change in weight ($p = .13$ for knee extensor strength). No associations were observed for IL-6 or CRP.

The associations between the soluble receptors (IL-2sR, IL-6sR, TNFsR1, and TNFsR2) and the 5-year change in grip strength and knee extensor strength are shown in Table 5. Only higher levels of IL-6sR were associated with greater decline in grip strength. Additional adjustment for change in weight did not markedly change this association. There were no associations between the soluble receptors and knee extensor strength.

To further eliminate the influence of weight change, we performed additional analyses in weight-stable persons only (weight loss or gain <3%). Higher levels of TNF-α were associated with a decline in thigh muscle area ($p = .02$; Figure 1) and a decline in grip strength ($p = .03$). Of the soluble receptors, lower levels of IL-6sR were associated with a decline in thigh muscle area ($p = .003$) and higher levels of TNFsR1 and TNFsR2 were associated with decline in thigh muscle area ($p = .01$ and $p = .001$, respectively).

No interactions were found between inflammatory markers and sex or race for any of the associations ($p > .10$).

DISCUSSION

To our knowledge, this is the first study investigating the association between inflammatory markers and 5-year change in muscle mass and muscle strength. We were able to measure thigh muscle area by CT and we used two measures of muscle strength (grip strength and knee extensor strength). Moreover, we used data on serum levels of inflammatory markers as well as soluble receptors.

A remarkable finding was the consistent association between TNF-α and decline in muscle mass and strength. These associations were attenuated when adjusting for weight change, and the results were confirmed in the subgroup of weight-stable persons. TNF-α is known to be an important cytokine in skeletal muscle wasting and reduced muscle function (26). Muscle catabolism has been attributed to TNF-α in inflammatory diseases including cancer (27),

Table 1. Characteristics of the Study Sample

	Study Sample		Subsample With Soluble Receptors	
	Men ($n = 1,023$)	Women ($n = 1,154$)	Men ($n = 162$)	Women ($n = 177$)
Age, $M \pm SD$	73.6 ± 2.8	73.3 ± 2.8	73.7 ± 2.8	73.4 ± 2.9
Study site, %				
Pittsburgh	50.3	48.2	53.1	49.2
Memphis	49.7	51.8	47.5	50.8
Race, %				
Black	31.5	42.3	56.2	53.1
White	68.5	57.7	43.8	46.9
Current	9.0	7.8	9.9	10.2
Physical activity (kcal/wk), median (IQR)	5581.1 (3121.1–9232.2)	5002.1 (2802.4–7808.6)	5224.3 (3034.4–8039.2)	4733.9 (2766.5–7247.3)
Body mass index	27.2 ± 3.8	27.6 ± 5.4	26.9 ± 3.8	28.0 ± 5.3
Weight, $M \pm SD$	81.8 ± 13.1	70.5 ± 14.5	80.2 ± 12.6	71.4 ± 14.2
5-y change in weight, $M \pm SD$	−1.7 ± 5.2	−1.5 ± 5.4	−1.7 ± 5.4	−2.0 ± 5.6
Chronic diseases, %				
Cancer, excl skin cancer	18.3	15.1	17.9	15.9
Cardiovascular disease	30.5	20.0	34.0	20.7
Peripheral arterial disease	5.1	3.4	7.7	5.8
Diabetes mellitus	24.5	18.9	23.9	19.8
Symptomatic osteoarthritis	5.9	14.0	4.3	15.3
Osteoporosis	3.2	25.7	1.9	25.4
Lung disease	9.9	11.2	13.0	14.8
Congestive heart failure	2.6	1.6	2.5	2.3
Anti-inflammatory drug use, %	52.2	53.8	53.1	56.5
Oral steroid use, %	1.3	2.7	1.2	1.7
Oral estrogen use, %	—	24.4	—	22.6
Statin use, %	12.5	13.1	12.3	11.9
IL-6 (pg/mL), median (IQR)	1.80 (1.27–2.67)	1.66 (1.14–2.57)	1.84 (1.30–2.81)	1.73 (1.24–2.75)
CRP (mg/l), median (IQR)	1.39 (0.91–2.47)	1.92 (1.06–3.48)	1.53 (0.89–2.61)	2.04 (1.22–3.83)
TNF-α (pg/mL), median (IQR)	3.21 (2.43–4.07)	3.04 (2.35–3.84)	3.26 (2.40–4.11)	2.96 (2.42–3.85)
IL-2sR (mg/mL), median (IQR)	—	—	1.26 (0.99–1.56)	1.17 (0.91–1.58)
IL-6sR (mg/mL), median (IQR)	—	—	3.24 (2.75–3.97)	3.49 (3.00–4.16)
TNFsR1 (mg/mL), median (IQR)	—	—	1.52 (1.31–1.85)	1.51 (1.24–1.78)
TNFsR2 (mg/mL), median (IQR)	—	—	3.44 (3.02–3.97)	3.29 (2.79–3.91)
Baseline thigh muscle area (cm²), $M \pm SD$	264.7 ± 42.5	184.8 ± 34.2	265.4 ± 46.7	186.3 ± 34.6
5-y change thigh muscle area, $M \pm SD$	−13.5 ± 19.1	−6.3 ± 14.5	−16.4 ± 19.3	−6.5 ± 14.9
Baseline grip strength (kg), $M \pm SD$	78.0 ± 16.4	47.5 ± 11.4	77.9 ± 16.2	48.4 ± 11.1
5-y change grip strength, $M \pm SD$	−7.2 ± 12.5	−3.6 ± 9.0	−7.7 ± 13.4	−5.0 ± 8.8
Baseline knee extensor strength (Nm), $M \pm SD$	135.3 ± 34.9	82.7 ± 22.2	133.5 ± 33.2	83.0 ± 22.8
5-y change knee extensor strength, $M \pm SD$	−24.9 ± 27.8	−13.2 ± 18.3	−26.5 ± 24.9	−13.3 ± 17.2

Notes: CRP = C-reactive protein; IL-6 = interleukin-6; IL-2sR = interleukin-2 soluble receptor; IL-6sR = interleukin-6 soluble receptor; IQR = interquartile range; TNF-α = tumor necrosis factor-alpha; TNFsR1 = tumor necrosis factor soluble receptor 1; TNFsR2 = tumor necrosis factor soluble receptor 2.

congestive heart failure (28), AIDS (29), and chronic obstructive pulmonary disease (30). There are at least two different mechanisms by which TNF-α may compromise muscle function. First, it has been shown that TNF-α can

Table 2. Correlation* Between Inflammatory Markers

	IL-6	CRP	TNF-α	IL-2sR	IL-6sR	TNFsR1	TNFsR2
IL-6	—	.47	.27	.21	.06	.31	.28
CRP	—	—	.13	.12	−.01	.25	.21
TNF-α	—	—	—	.44	.21	.49	.57
IL-2sR	—	—	—	—	.28	.59	.61
IL-6sR	—	—	—	—	—	.31	.27
TNFsR1	—	—	—	—	—	—	.79

Notes: CRP = C-reactive protein; IL-6 = interleukin-6; IL-2sR = interleukin-2 soluble receptor; IL-6sR = interleukin-6 soluble receptor; TNF-α = tumor necrosis factor-alpha; TNFsR1 = tumor necrosis factor soluble receptor 1; TNFsR2 = tumor necrosis factor soluble receptor 2.

* Spearman correlation coefficients.

directly stimulate protein loss in muscle cells (31,32). Second, experimental studies have indicated that TNF-α can induce alterations of muscle proteins independent of protein loss, resulting in diminished force production (33). This is supported by the results of our study in which we found associations of TNF-α with decline in grip strength.

Because weight change has been linked with inflammatory markers (2,21) and muscle mass (22), we investigated whether change in weight could explain (part of) the association between inflammatory markers and change in muscle mass. Indeed, many associations between inflammatory markers and change in muscle mass were reduced after adjustment for weight change, suggesting a mediating role for weight change in the associations under study. However, when we performed additional analyses in subgroups of weight-stable persons, we still found significant associations

Table 3. Linear Regression Analysis of Inflammatory Markers With Absolute Change in Muscle Mass by Computed Tomography (per SD^* change in marker)

		Model 1		Model 2	
	N	B (SE)	p Value	B (SE)	p Value
IL-6	1,494	−1.30 (0.45)	.004	−0.14 (0.37)	.71
CRP	1,538	−1.32 (0.45)	.004	−0.48 (0.37)	.19
TNF-α	1,449	−1.34 (0.45)	.003	−0.37 (0.37)	.32
IL-2sR	228	−2.16 (1.34)	.11	−1.08 (1.08)	.32
IL-6sR	228	1.52 (0.76)	.05	2.03 (0.60)	.001
TNFsR1	228	−3.73 (1.36)	.007	−2.23 (1.11)	.05
TNFsR2	225	−1.63 (0.98)	.10	−0.78 (0.79)	.33

Notes: Model 1: adjusted for baseline muscle mass, age, sex, race, study site, chronic diseases, physical activity, anti-inflammatory drug use, statin use, estrogen use, and steroid use; model 2: additionally adjusted for 5-year change in weight. CRP = C-reactive protein; IL-6 = interleukin-6; IL-2sR = interleukin-2 soluble receptor; IL-6sR = interleukin-6 soluble receptor; IQR = interquartile range; TNF-α = tumor necrosis factor-alpha; TNFsR1 = tumor necrosis factor soluble receptor 1; TNFsR2 = tumor necrosis factor soluble receptor 2.

* *SD* 0.66 for IL-6, 0.85 for CRP, 0.41 for TNF-α, 0.42 for IL-2sR, 0.32 for IL-6sR, 0.29 for TNFsR1, and 0.29 for TNFsR2.

Table 4. Linear Regression Analysis of Inflammatory Markers With Absolute Change in Grip Strength and Knee Extensor Strength (per SD^* change in marker)

		Model 1		Model 2	
	N	B (SE)	p Value	B (SE)	p Value
5-y change in grip strength (kg)					
IL-6	1,913	−0.30 (0.24)	.22	−0.20 (0.24)	.41
CRP	1,970	−0.25 (0.25)	.32	−0.20 (0.25)	.44
TNF-α	1,856	−0.62 (0.24)	.01	−0.53 (0.24)	.03
5-y change in knee extensor strength (Nm)					
IL-6	1,649	−0.55 (0.53)	.30	−0.25 (0.53)	.63
CRP	1,696	0.23 (0.54)	.68	0.36 (0.54)	.50
TNF-α	1,599	−1.02 (0.52)	.05	−0.79 (0.52)	.13

Notes: Model 1: adjusted for baseline grip strength or knee extensor strength, age, sex, race, study site, chronic diseases, physical activity, anti-inflammatory drug use, statin use, estrogen use, and steroid use; model 2: additionally adjusted for 5-year change in weight. CRP = C-reactive protein; IL-6 = interleukin-6; TNF-α = tumor necrosis factor-alpha.

* *SD* 0.66 for IL-6, 0.85 for CRP, 0.41 for TNF-α.

of TNF-α and its soluble receptors with change in thigh muscle area, suggesting that weight change does not completely explain the associations between inflammatory markers and change in muscle mass. More research on the (possibly mediating) role for weight change is warranted.

Contrary to all other inflammatory markers under study, we found a positive association of IL-6sR with change in thigh muscle area. IL-6sRs appear to facilitate and enhance IL-6 activity (34). IL-6 has been classified as both a pro-inflammatory and anti-inflammatory cytokine. IL-6 is tightly linked to TNF-α; TNF-α induces production of IL-6, whereas IL-6 inhibits TNF gene expression. The complex of IL-6sR and IL-6 can act as a very strong inhibitor of TNF-α (35). Higher levels of IL-6sR may therefore indicate a tight regulation of TNF-α, preventing the loss of muscle mass. On the other hand, IL-6sR showed a negative association with change in muscle strength. Other biological studies are needed to further investigate the role of IL-6sR in sarcopenia and loss of strength.

This study did not show any statistically significant associations between inflammatory markers and change in knee extensor strength. Due to the stringent exclusion criteria of the knee extensor strength test, 13% of the persons in the original cohort were excluded from that test. These persons were older, had lower grip strength, lower thigh muscle area, and higher levels of inflammatory markers. These frailer persons were, however, included in the grip strength test. This may explain the differences in associations between inflammatory markers and grip strength compared with knee extensor strength.

This study has a few limitations. First, the study sample consisted of well-functioning men and women without any self-reported physical limitations at baseline. Therefore, persons with low muscle mass and strength were more

likely to be excluded from the study. However, the association of inflammation status with decline in muscle mass and strength can be well studied in healthy nondisabled persons who are gradually losing health and function. Second, because there was a relatively long follow-up of 5 years, many respondents were excluded from the analyses. The main reason for this loss to follow-up was death, which is an important issue in cohort studies of older persons. Therefore, we should be careful with the generalizability of our results. Compared with the participants included in the analyses,

Table 5. Linear Regression Analysis of Soluble Receptors With Absolute Change in Grip Strength and Knee Extensor Strength (per SD^* change in marker)

		Model 1		Model 2	
	N	B (SE)	p Value	B (SE)	p Value
5-y change in grip strength (kg)					
IL-2sR	309	−1.14 (0.71)	.11	−1.04 (0.71)	.15
IL-6sR	309	−1.05 (0.47)	.03	−1.01 (0.47)	.03
TNFsR1	306	−0.38 (0.85)	.66	−0.27 (0.86)	.75
TNFsR2	305	0.05 (0.51)	.93	0.09 (0.51)	.85
5-y change in knee extensor strength (Nm)					
IL-2sR	256	−1.83 (1.48)	.22	−1.68 (1.47)	.25
IL-6sR	256	−1.44 (0.93)	.13	−1.20 (0.94)	.20
TNFsR1	255	−2.24 (1.59)	.16	−1.86 (1.59)	.25
TNFsR2	253	−1.54 (1.00)	.13	−1.44 (1.00)	.15

Notes: Model 1: adjusted for baseline grip strength or knee extensor strength, age, sex, race, study site, chronic diseases, physical activity, anti-inflammatory drug use, statin use, estrogen use, and steroid use; model 2: additionally adjusted for 5-year change in weight. CRP = C-reactive protein; IL-6 = interleukin-6; IL-2sR = interleukin-2 soluble receptor; IL-6sR = interleukin-6 soluble receptor; IQR = interquartile range; TNF-α = tumor necrosis factor-alpha; TNFsR1 = tumor necrosis factor soluble receptor 1; TNFsR2 = tumor necrosis factor soluble receptor 2.

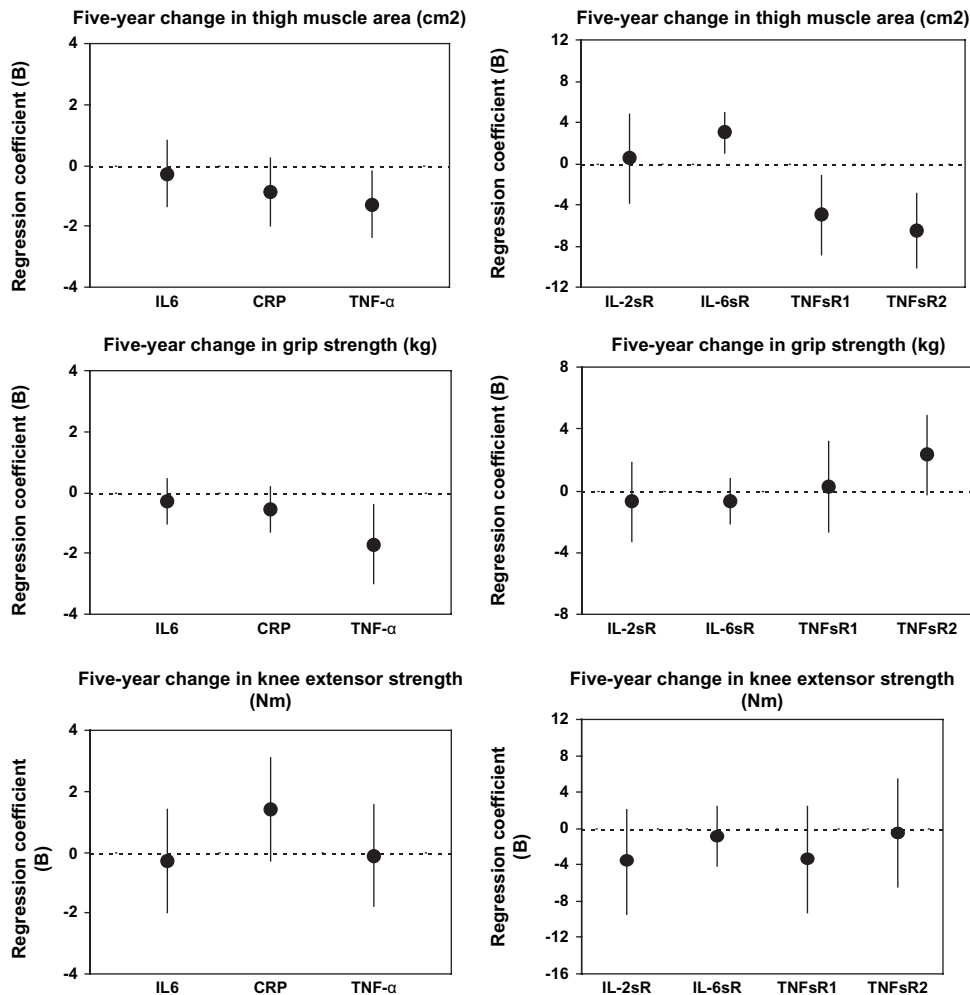* *SD* 0.42 for IL-2sR, 0.32 for IL-6sR, 0.29 for TNFsR1 and 0.29 for TNFsR2.

Figure 1. Association between inflammatory markers and 5-year change in thigh muscle area (cm^2) and grip strength in weight-stable (within 3% change in weight) persons per standard deviation change in marker. *Notes:* Adjusted for baseline measures of the outcome, age, sex, race, study site, chronic diseases, physical activity, anti-inflammatory drug use, statin use, estrogen use, and steroid use. Number of persons in the analyses: 5-year change in thigh muscle area: $n = 617$ for IL-6; $n = 605$ for CRP; $n = 601$ for TNF-α; $n = 85$ for IL-2sR, IL-6sR, and TNFsR1; $n = 84$ for TNFsR2. 5-year change in grip strength: $n = 760$ for IL-6, $n = 779$ for CRP, $n = 739$ for TNF-α, $n = 117$ for IL-2sR and IL-6sR, $n = 115$ for TNFsr1, $n = 116$ for TNFsR2. 5-year change in knee extensor strength: $n = 685$ for IL-6, $n = 702$ for CRP, $n = 667$ for TNF-α, $n = 101$ for IL-2sR and IL-6sR, $n = 100$ for TNFsR1 and TNFsR2. CRP = C-reactive protein; IL-6 = interleukin-6; IL-2sR = interleukin-2 soluble receptor; IL-6sR = interleukin-6 soluble receptor; TNF-α = tumor necrosis factor-alpha; TNFsR1 = tumor necrosis factor soluble receptor 1; TNFsR2 = tumor necrosis factor soluble receptor 2.

those who were excluded were older, more often male, more often black, had a lower knee extensor strength, had higher levels of inflammatory markers (IL-6, CRP, and TNF-α), were less physically active, and more often had one or more chronic diseases. Our results may therefore underestimate the relationship between inflammation and decline in muscle mass and strength. Another limitation is the single assessment of the inflammatory markers at baseline, which makes it impossible to investigate the association between change in inflammatory markers and decline in muscle mass and strength. Third, soluble receptors were measured in a random subsample. Therefore, the numbers used in the analyses with the soluble receptors were small, and the results in the weight-stable subgroup should be interpreted carefully. To increase statistical power, all analyses in the subgroup

of weight-stable persons were repeated, using only those confounders that changed the regression coefficient by 10%. The results were similar to the initial analyses with all confounders (data not shown).

In conclusion, higher levels of IL-6, CRP, TNF-α, IL-6sR, and TNFsR1 were associated with 5-year change in thigh muscle area. After adjustment for 5-year change in weight, these associations (except for IL-6sR) were attenuated. TNF-α was associated with decline in grip strength and borderline associated with decline in knee extensor strength. Overall, TNF-α and its soluble receptors showed the strongest associations and might be important markers of loss of muscle mass and strength. Future studies investigating inflammation-related changes in muscle mass and strength should carefully account for the effects of weight change.

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REFERENCES

1. Alexandraki K, Piperi C, Kalofoutis C, Singh J, Alaveras A, Kalofoutis A. Inflammatory process in type 2 diabetes: the role of cytokines. *Ann N Y Acad Sci*. 2006;1084:89–117.
2. Kern PA, Saghizadeh M, Ong JM, Bosch RJ, Deem R, Simsolo RB. The expression of tumor necrosis factor in human adipose tissue. Regulation by obesity, weight loss, and relationship to lipoprotein lipase. *J Clin Invest*. 1995;95(5):2111–2119.
3. Blake GJ, Ridker PM. Novel clinical markers of vascular wall inflammation. *Circ Res*. 2001;89(9):763–771.
4. Erren M, Reinecke H, Junker R, et al. Systemic inflammatory parameters in patients with atherosclerosis of the coronary and peripheral arteries. *Arterioscler Thromb Vasc Biol*. 1999;19(10):2355–2363.
5. Vasan RS, Sullivan LM, Roubenoff R, et al. Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: the Framingham Heart Study. *Circulation*. 2003;107(11):1486–1491.
6. Joppa P, Petrasova D, Stancak B, Tkacova R. Systemic inflammation in patients with COPD and pulmonary hypertension. *Chest*. 2006;130(2):326–333.
7. Harris TB, Ferrucci L, Tracy RP, et al. Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. *Am J Med*. 1999;106(5):506–512.
8. Cohen HJ, Pieper CF, Harris T, Rao KM, Currie MS. The association of plasma IL-6 levels with functional disability in community-dwelling elderly. *J Gerontol A Biol Sci Med Sci*. 1997;52(4):M201–M208.
9. Cesari M, Penninx BW, Pahor M, et al. Inflammatory markers and physical performance in older persons: the InCHIANTI study. *J Gerontol A Biol Sci Med Sci*. 2004;59(3):242–248.
10. Taaffe DR, Harris TB, Ferrucci L, Rowe J, Seeman TE. Cross-sectional and prospective relationships of interleukin-6 and C-reactive protein with physical performance in elderly persons: MacArthur studies of successful aging. *J Gerontol A Biol Sci Med Sci*. 2000;55(12):M709–M715.
11. Ferrucci L, Harris TB, Guralnik JM, et al. Serum IL-6 level and the development of disability in older persons. *J Am Geriatr Soc*. 1999;47(6):639–646.
12. Penninx BW, Kritchevsky SB, Newman AB, et al. Inflammatory markers and incident mobility limitation in the elderly. *J Am Geriatr Soc*. 2004;52(7):1105–1113.
13. Hsu FC, Kritchevsky SB, Liu Y, et al. Association between inflammatory components and physical function in the health, aging, and body composition study: a principal component analysis approach. *J Gerontol A Biol Sci Med Sci*. 2009;64(5):581–589.
14. Ferrucci L, Penninx BW, Volpato S, et al. Change in muscle strength explains accelerated decline of physical function in older women with high interleukin-6 serum levels. *J Am Geriatr Soc*. 2002;50(12):1947–1954.
15. Visser M, Pahor M, Taaffe DR, et al. Relationship of interleukin-6 and tumor necrosis factor-alpha with muscle mass and muscle strength in elderly men and women: the Health ABC Study. *J Gerontol A Biol Sci Med Sci*. 2002;57(5):M326–M332.
16. Schaap LA, Pluijm SM, Deeg DJ, Visser M. Inflammatory markers and loss of muscle mass (sarcopenia) and strength. *Am J Med*. 2006;119(6):526.e9–526.e17.
17. Payette H, Roubenoff R, Jacques PF, et al. Insulin-like growth factor-1 and interleukin 6 predict sarcopenia in very old community-living men and women: the Framingham Heart Study. *J Am Geriatr Soc*. 2003;51(9):1237–1243.
18. Van Zee KJ, Kohno T, Fischer E, Rock CS, Moldawer LL, Lowry SF. Tumor necrosis factor soluble receptors circulate during experimental and clinical inflammation and can protect against excessive tumor necrosis factor alpha in vitro and in vivo. *Proc Natl Acad Sci U S A*. 1992;89(11):4845–4849.
19. Honda M, Yamamoto S, Cheng M, et al. Human soluble IL-6 receptor: its detection and enhanced release by HIV infection. *J Immunol*. 1992;148(7):2175–2180.
20. Aderka D, Engelmann H, Shemer-Avni Y, et al. Variation in serum levels of the soluble TNF receptors among healthy individuals. *Lymphokine Cytokine Res*. 1992;11(3):157–159.
21. Cottam DR, Mattar SG, Barinas-Mitchell E, et al. The chronic inflammatory hypothesis for the morbidity associated with morbid obesity: implications and effects of weight loss. *Obes Surg*. 2004;14(5):589–600.
22. Newman AB, Lee JS, Visser M, et al. Weight change and the conservation of lean mass in old age: the Health, Aging and Body Composition Study. *Am J Clin Nutr*. 2005;82(4):872–878.
23. Goodpaster BH, Carlson CL, Visser M, et al. Attenuation of skeletal muscle and strength in the elderly: the Health ABC Study. *J Appl Physiol*. 2001;90(6):2157–2165.
24. Kallman DA, Plato CC, Tobin JD. The role of muscle loss in the age-related decline of grip strength: cross-sectional and longitudinal perspectives. *J Gerontol*. 1990;45(3):82–88.
25. Pahor M, Chrischilles EA, Guralnik JM, Brown SL, Wallace RB, Carbonin P. Drug data coding and analysis in epidemiologic studies. *Eur J Epidemiol*. 1994;10(4):405–411.
26. Reid MB, Li YP. Tumor necrosis factor-alpha and muscle wasting: a cellular perspective. *Respir Res*. 2001;2(5):269–272.
27. Tisdale MJ. Wasting in cancer. *J Nutr*, (suppl 1S) 1999;129:243S–246S.
28. Anker SD, Rauchhaus M. Insights into the pathogenesis of chronic heart failure: immune activation and cachexia. *Curr Opin Cardiol*. 1999;14(3):211–216.
29. Moldawer LL, Sattler FR. Human immunodeficiency virus-associated wasting and mechanisms of cachexia associated with inflammation. *Semin Oncol*, (1 suppl 1) 1998;25:73–81.
30. Farber MO, Mannix ET. Tissue wasting in patients with chronic obstructive pulmonary disease. *Neurol Clin*. 2000;18(1):245–262.
31. Li YP, Reid MB. NF-kappaB mediates the protein loss induced by TNF-alpha in differentiated skeletal muscle myotubes. *Am J Physiol Regul Integr Comp Physiol*. 2000;279(4):R1165–R1170.
32. Li YP, Schwartz RJ, Waddell ID, Holloway BR, Reid MB. Skeletal muscle myocytes undergo protein loss and reactive oxygen-mediated NF-kappaB activation in response to tumor necrosis factor alpha. *FASEB J*. 1998;12(10):871–880.
33. Li X, Moody MR, Engel D, et al. Cardiac-specific overexpression of tumor necrosis factor-alpha causes oxidative stress and contractile dysfunction in mouse diaphragm. *Circulation*. 2000;102(14):1690–1696.
34. Mackiewicz A, Schooltink H, Heinrich PC, Rose-John S. Complex of soluble human IL-6-receptor/IL-6 up-regulates expression of acute-phase proteins. *J Immunol*. 1992;149(6):2021–2027.
35. Igaz P, Horvath A, Horvath B, et al. Soluble interleukin-6 receptor (sIL-6R) makes IL-6R negative T cell line respond to IL-6; it inhibits TNF production. *Immunol Lett*. 2000;71(3):143–148.