Muscle Endurance in Elderly Nursing Home Residents Is Related to Fatigue Perception, Mobility, and Circulating Tumor Necrosis Factor-Alpha, Interleukin-6, and Heat Shock Protein 70

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(See editorial comments by Drs. Hermes Florez and Bruce R. Troen, pp 558–560)

OBJECTIVES: To explore the relationships between muscle endurance and circulating interleukin (IL)-6, tumor necrosis factor alpha (TNF-α), and heat shock protein (Hsp)70 in nursing home residents and to assess how muscle endurance relates to self-perceived fatigue and mobility.

DESIGN: Exploratory study.

SETTING: Three nursing homes of the Foundation for Psychogeriatrics (Brussels, Belgium).

PARTICIPANTS: Seventy-seven residents (53 female and 24 male, mean age 81 ± 8).

MEASUREMENTS: Participants were assessed for muscle endurance (fatigue resistance and grip work); perceived fatigue (visual analogue scale for fatigue); fatigue during daily activities (Mobility-Tiredness Scale); effect of fatigue on quality of life (World Health Organization Quality Of Life questionnaire); mobility (Tinetti Test & Elderly Mobility Scale (EMS)); and circulating IL-6, TNF-α, and Hsp70.

RESULTS: Residents with better fatigue resistance reported less self-perceived tiredness ($P < .05$). Similar trends were observed for fatigue during daily activities and for the extent to which fatigue bothered subjects. Higher grip work was associated with less self-perceived fatigue on all fatigue scales ($P < .01$). Fatigue resistance and grip work were positively related to balance and basic mobility (all $P < .01$; trend for relationship between fatigue resistance and EMS). Subjects with high IL-6 and Hsp70 showed significantly worse fatigue resistance ($P = .007$) and muscle work ($P = .045$) than those with high IL-6 and low Hsp70. In male residents, higher TNF-α was related to worse fatigue resistance and grip work ($P < .05$).

CONCLUSION: Elderly nursing home residents complaining of fatigue need to be taken seriously, because they show worse muscle endurance, which is related to poorer mobility. Inflammatory processes involving TNF-α and the interaction between IL-6 and Hsp70 are related to poorer muscle endurance in these patients. **J Am Geriatr Soc 56:389–396, 2008.**

Key words: heat shock protein; cytokines; muscle endurance; nursing homes; elderly

Muscle weakness, fatigue, loss of mobility, and low-grade inflammation are typical characteristics of frailty in geriatric patients.[1,2] All elderly nursing home residents, given their dependency, present some degree of frailty, with a high risk for progression. This might explain, at least partly, why fatigue, observed in 98% of the residents,[3] is such a common complaint in this population. It is not clear whether the reported sensation of fatigue in these patients correlates with impaired muscle endurance. Surprisingly, resistance to fatigue is not commonly evaluated in nursing home residents. This might be because frail elderly persons are often unable to perform the classic endurance tests[4] or are not mobile enough to participate in tests involving large mechanical devices. An easy and reliable method to evaluate resistance to muscle fatigue in frail elderly subjects has been previously described.[5–7] During the test, subjects are instructed to sustain maximal handgrip effort as long as possible, and fatigue resistance is expressed as the time during which grip strength drops to 50% of its maximum. Fatigue resistance allows the calculation of grip work, a supplementary parameter for muscle endurance that has been previously described[8] and reflects the work output delivered by the muscles during the fatigue resistance test.

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In elderly persons, muscle endurance appears to be related to inflammatory status. Inflammatory cytokines, whose actions include the activation of immune cells, the release of acute phase proteins, and the induction of fever, are the main orchestrators of inflammation.[9,10] In addition to the regulation of the immune reaction against external aggression, several cytokines are involved in the catabolic processes associated with inflammation. Tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β, and IL-6 are particularly known to have cytotoxic and proteolytic properties.[9] High concentrations of these cytokines in the blood circulation during inflammatory pathology are related to severe muscle wasting and cachexia.[11,12] Cytokines are also involved in the healing process and the downregulation of the acute phase in the resolution of inflammation,[13] and it has been suggested that IL-6 can exert inflammatory and antiinflammatory signaling.[14] It is also well documented that physical exercise provokes an inflammatory reaction, with the release of inflammatory cytokines, especially IL-6, into the blood circulation.[15] In this context, IL-6 is mainly released from the contracting muscles and would exert another signaling function with beneficial effects on general health and muscle performance.[16] In community-dwelling elderly men without any clinically relevant inflammation, circulating levels of IL-6 were found to be positively related to fatigue resistance and grip work.[8] Also, muscle endurance, as measured according to grip work, related well to self-perceived fatigue and physical functioning,[8] although in studies with hospitalized geriatric patients, IL-6 and circulating C-reactive protein were negatively related to fatigue resistance.[5,7] Fatigue resistance was also significantly responsive to rapid changes in clinical condition[5] and improved upon selective antiinflammatory therapy in hospitalized geriatric patients with acute infections.[7]

Depending on the situation in which IL-6 appears in the circulation, its relationship with muscle endurance might be different because of other, interfering processes. During inflammation, heat shock proteins (Hsps) play an important role in cellular protection.[17,18] In particular, the expression of Hsp70, both intracellular[17] and in serum,[18,19] is related to circulating IL-6 and TNF-α. In the skeletal muscle itself, the expression of chaperones belonging to the Hsp70 family is upregulated when exposed to elevated levels of IL-6[20] and physical stress.[21] The role of extracellular Hsp70 is not yet completely understood, although it has been shown that its presence can have a protective effect against necrotic cell death of smooth muscle cells[22] and against apoptosis of motor neurons.[23] From these insights it can be assumed that Hsp70 plays a protective role against conditions related to inflammation, although low serum Hsp70 levels have been reported to be a characteristic of longevity.[24] Although not yet explored, the interaction between Hsp70 and inflammatory processes might be involved in the underlying mechanisms of muscle weakness observed in frail elderly patients.

The aim of this study was to assess how muscle endurance related to self-perceived fatigue and mobility in frail, institutionalized elderly persons. Also, it was hypothesized that relationships would exist with circulating inflammatory markers (IL-6, TNF-α, and Hsp70).

PARTICIPANTS AND METHODS

Participants

Participants were recruited from among the 333 residents of three nursing homes of the Foundation for Psychogeriatrics (Brussels, Belgium). All residents aged 65 and older who were able to understand and to execute the test instructions were eligible. Comorbidity and cognitive decline were not considered as exclusion criteria per se. In pilot studies, the Mini-Mental State Examination (MMSE) was found to be insufficiently useful as a criterion for eligibility. Therefore, the same investigator screened each resident for eligibility in a face-to-face interview during which the study purpose and test procedures were explained. Residents unable to understand or execute the test instructions during the interview were considered to be ineligible. Subjects who had undergone surgery within the previous 6 months or presented any acute medical condition were excluded. Finally, 77 residents (53 female and 24 male) volunteered to participate in the study (Table 1). The local ethical committee approved the study protocol, and all participants gave their written informed consent.

Measurements

Measurement Sequence

First, after overnight fasting, venous blood was drawn from the nondominant arm, and anthropometric measures were taken. Next, the subject completed a questionnaire concerning self-perceived fatigue. Afterwards, handgrip performance and mobility were measured (in all participants by the same investigator, who was unaware of the questionnaire data). Between each assessment, sufficient time was offered to allow full recuperation of the participant. Finally, level of physical dependency,[25] cognitive functioning as measured with the MMSE,[26] comorbidity and medication use were recorded from the subject's medical register. Serum was obtained from the blood and frozen at $-20^{\circ}C$ for determination of circulating cytokines and Hsp70.

Cytokine and Hsp70 Assay

Sera were assayed for IL-6 and TNF-α using enzyme-linked immunosorbent assay (ELISA; Biosource International, Nijvel, Belgium), as reported previously.[27] All determinations were made within one single assay. Intra-assay precision expressed as coefficient of variance (CV) was determined according to the manufacturer's instruction for

Table 1. Inclusion of Participants

Inclusion Criteria	N
Subjects screened for eligibility	333
Subjects excluded	
Aged <65	61
Recent surgery	8
Acute infection	5
Unable to execute or understand test instructions*	163
Refused to participate	19
Subjects included in the study	77

* As screened in face-to-face interview.

low (L), normal (N), and high (H) standards (for IL-6, CV-L = 7.7%, CV-N = 5.7%, and CV-H = 5.1%, detection limit 2.0 ng/L; for TNF-α, CV-L = 5.2%, CV-N = 4.1%, and CV-H = 3.9%, detection limit 1.7 ng/L). Hsp70 in serum was detected as described previously[19] using sandwich ELISA, using a monoclonal antibody to Hsp70 (StressGen, Victoria, Canada); the average intra- and interassay variation were 6% and 9%, respectively, and detection limit of the assay was 10 ng/mL.

Body Composition and Anthropometry

Parameters reflecting obesity, nutritional status, and muscle mass were assessed using anthropometrical measures. Waist–hip index was calculated by dividing the waist perimeter by the hip perimeter. Total body skeletal muscle mass was estimated as described previously[5] with the formula:

$$\text{Muscle Mass (kg)} = \text{Height} \times (0.0553\,TC^2 + 0.0987\,FC^2 + 0.0331\,CC^2) - 2445,$$

with height in cm, *TC* = thigh circumference corrected for the front thigh skinfold thickness (cm), *FC* = uncorrected forearm circumference (cm), and *CC* = calf circumference corrected for the medial calf skinfold thickness (cm).[28]

Self-Perceived Fatigue

Three different instruments were used to measure the sensation of fatigue in participants. Subjects scored their current fatigue level on a visual analogue scale for fatigue (VAS-F). Fatigue after daily-life activities was estimated using the Mobility-Tiredness (Mob-T) Scale, specifically modified to measure tiredness during daily activities in elderly persons (high scores indicate less fatigue).[29] The items from the World Health Organization Quality of Life (WHOQOL) Questionnaire covering energy and fatigue (WHOQOL-F2.2: "How easily do you get tired?" and WHOQOL-F2.4: "How much are you bothered by fatigue?") were scored on a scale from 1 (not at all) to 5 (extremely).[30]

Muscle Endurance

Fatigue resistance was measured using the Martin vigorimeter (Elmed Inc., Addison, IL) as described previously.[6] Briefly, the shoulder was adducted and neutrally rotated with the elbow flexed at 90°, the forearm in a neutral position, and the wrist in slight extension (0–30°). Then the subject was asked to squeeze the large bulb of the vigorimeter as hard as possible. The strongest of three attempts was noted as maximal grip strength (in KPa). Afterwards, the subject was again instructed to squeeze the bulb of the vigorimeter as hard as possible and to maintain this maximal pressure; the time (in seconds) until grip strength dropped to 50% of its maximum was recorded as fatigue resistance. This test is highly reproducible in elderly subjects, with intraclass correlation values ranging from 0.91 to 0.94 and from 0.88 to 0.91 for intra- and interobserver reliability, respectively.[6] Grip work, an estimate of the total effort produced during the fatigue resistance test, was calculated by multiplying the fatigue resistance (in seconds) by 75% of the maximal grip strength (in KPa).[8] This parameter represents the physiological work delivered by the handgrip muscles during the fatigue resistance test. All muscle endurance tests were executed with the dominant hand.

Mobility and Physical Dependence

Balance and gait were assessed using the Tinetti test (range 0–28, with higher values representing better performance).[31] Functional mobility was evaluated using the Elderly Mobility Scale (EMS; range 0 = complete immobility to 20 = minimal required mobility), an instrument allowing differentiation at the lowest range of functional mobility in frail elderly persons.[32] For descriptive purposes, nursing home residents were categorized into four groups according to physical dependency: O = independent; A = dependent for washing or dressing; B = dependent for washing, dressing, and toiletting or transfer; C = dependent for washing, dressing, toiletting, transfer, and incontinence or eating.[25]

Statistical Analysis

Statistical analysis was performed using SPSS release 15.0.1 (SPSS Inc., Chicago, IL). Average values ± standard deviations or quartile deviations (P75-P25) are given in the Results section and Table 1, depending on measure level and normality of distribution. Some data presented nonnormal distribution as evaluated using the Kolmogorov-Smirnov Goodness of Fit Test (Grip Work $P = .01$, VAS-F $P = .001$, IL-6 $P < .001$, TNF-α $P < .001$, and Hsp70 $P = .001$) or were scored on an ordinal scale (0–6 for Mob-T scale, 1–5 for WHOQOL F2.2 & F2.4, 0–28 for Tinetti test, and 0–20 for EMS). As a consequence, in the analysis of these parameters, methods including linear multiple regression analysis and analysis of variance were not suitable, and thus nonparametric tests were used when comparing and correlating these parameters.[33] Sex differences were explored using the Mann-Whitney *U*-test. The Spearman rho correlation coefficient was computed to investigate relationships between handgrip endurance and self-perceived fatigue, mobility, and inflammation. It was hypothesized that body composition[34] and gender might bias the relationships between muscle endurance and inflammatory mediators, and thus fatigue resistance and grip work were corrected by expressing the values per kg lean body mass, and correlations were computed for men and women separately. Additionally, subjects were classified according to high or low levels of serum IL-6, TNF-α, and Hsp70, considering values at the 70th percentile or greater as high and values lower than the 70th percentile as low. Differences in fatigue resistance were explored according to the combination of (1) IL-6 and Hsp70 and (2) TNF-α and Hsp70 using analysis of covariance (ANCOVA, with age and whole body muscle mass as covariates). Also, interaction with sex was assessed when computing the ANCOVA models. For grip work, values were corrected for lean body mass, and differences between combined cytokine and Hsp70 classes were analyzed using the Mann-Whitney *U*-test. Differences in circulating TNF-α between combined cytokine and Hsp70 classes were computed using the Mann-Whitney *U*-test. Significance was set a priori at two-sided $P < .05$; *P*-values ranging from .05 to .09 were considered as possible trends and highlighted as such in the results.

RESULTS

Basic information regarding the clinical condition of the participants and their scores on the outcome parameters are given in Table 2. As expected, men were significantly taller and heavier and had more total body muscle mass than women, who had weaker grip strength and scored lower on grip work. No sex differences were found for fatigue resistance or for circulating IL-6, TNF-α, or Hsp70.

Relationship Between Muscle Endurance and Fatigue

As shown in Table 3, subjects with higher scores on the fatigue resistance test tired less easily (question F2.2 of the WHOQOL $P<.05$). Similar trends were observed for fatigue during daily activities (Mob-T) and for the extent to which fatigue bothered subjects (question F2.4 of the WHOQOL). Higher grip work was associated with less self-perceived fatigue on all fatigue scales ($P<.01$, except $P<.05$ on question F2.4 of the WHOQOL).

Relationship Between Muscle Endurance and Mobility

Fatigue resistance and grip work were positively related with balance (Tinetti test) and basic mobility (EMS) (all $P<.01$; trend for relationship between fatigue resistance and EMS).

Relationship Between Muscle Endurance and Inflammatory Mediators

Because body composition can influence both muscle endurance and inflammation, fatigue resistance and grip work were expressed per kg of lean body mass. As shown in Table 4, higher levels of circulating TNF-α were related to worse fatigue resistance and grip work in the male residents ($P<.05$). Residents with both high IL-6 and Hsp70 serum levels had significantly poorer fatigue resistance (Figure 1A, ANCOVA corrected for age and lean body mass $P=.03$, no significant interaction with sex). Contrast analysis revealed significantly poorer fatigue resistance in residents with both high Hsp70 and IL-6 levels than in those with low Hsp70 and high IL-6 serum levels ($P=.007$). Grip work was also significantly worse in subjects with both high IL-6 and

Table 2. Participant Characteristics

Characteristic	Female (n = 53)	Male (n = 24)
Age, mean ± SD	81.9 ± 7.7	78.8 ± 7.0
Height, m, mean ± SD*	1.58 ± 0.06	1.71 ± 0.05
Weight, kg, mean ± SD*	59.1 ± 13.2	72.7 ± 12.9
Waist:hip ratio, mean ± SD*	0.87 ± 0.09	1.00 ± 0.06
Total body muscle mass, kg, mean ± SD*,†	20.5 ± 4.9	29.6 ± 6.5
Grip strength, kPa, mean ± SD*	32.4 ± 11.5	50.8 ± 11.1
Fatigue resistance, s, mean ± SD	49.8 ± 29.6	53.3 ± 27.7
Grip work, kPa × sec, mean ± SD*	1,255.6 ± 904.3	2,034.7 ± 1,152.1
Mobility-Tiredness scale score (range 0–6), mean ± SD‡	3.7 ± 2.1	4.0 ± 1.9
Visual Analogue Scale for Fatigue score (range 0–10), mean ± SD	3.1 ± 1.9	2.6 ± 1.3
World Health Organization Quality of Life question, score (range 0–5), mean ± SD		
F2.2	2.0 ± 1.0	2.1 ± 0.7
F2.4	1.6 ± 0.9	1.5 ± 0.7
Tinetti test, score (range 0–28), mean ± SD	22.7 ± 4.3	23.6 ± 4.5
Elderly Mobility Scale, score (range 0–20), mean ± SD	17.6 ± 3.1	18.7 ± 1.6
Interleukin-6, pg/mL, mean ± QD	10.6 ± 17.2	9.1 ± 30.3
Tumor necrosis factor alpha, pg/mL, mean ± QD	3.8 ± 4.7	5.2 ± 4.0
Heat shock protein 70, pg/mL, mean ± QD	2.7 ± 1.1	2.9 ± 1.8
Physical dependence, n		
Independent	14	6
Washing or dressing	17	10
Washing, dressing, and toiletting or transfer	13	6
Washing, dressing, toiletting, transfer, and incontinence or eating	9	2
Mini-Mental State Examination, score (range 0–30), mean ± SD	20.8 ± 6.1	22.0 ± 5.3
Comorbidity, n		
Mild dementia	31	8
Korsakoff syndrome	2	2
Psychosis or paranoia	6	2
Depression	22	14
Epilepsy	5	1
Osteoporosis	23	0
Osteoarthritis	3	3
Rheumatoid arthritis	1	0
Diabetes mellitus type 2	3	1
Chronic heart failure	22	11
Arterial hypertension	19	10
Peripheral arterial insufficiency	5	5
Glaucoma	3	0
Hyperthyroidism, stabilized	1	0
Hypothyroidism, treated	6	4
Chronic obstructive pulmonary disease	3	1
Urogenital tract disorder	3	4
Gastrointestinal disorder	7	4
Allergy	5	1
Number of different medications, mean ± SD	7.2 ± 2.9	7.6 ± 3.4

*Sex difference $P<.01$.

†Estimation as described by Martin et al.[28]

‡Higher scores reflect less fatigue.

F2.2 = "How easily do you get tired?" F2.4 = "How much are you bothered by fatigue?" both scored on a 1-to-5 scale from 1 (not at all) to 5 (extremely). SD = standard deviation; QD = quartile deviation.

Table 3. Relationships Between Handgrip Endurance, Fatigue, and Mobility

Parameter	Fatigue Resistance	Grip Work
	Spearman Rho	
Mobility-Tiredness scale‡	0.22§	0.38†
Visual Analogue Scale for Fatigue	− 0.15	− 0.29†
World Health Organization Quality of Life question		
F2.2	− 0.24*	− 0.30†
F2.4	− 0.19§	− 0.27*
Tinetti test	0.31†	0.48†
Elderly Mobility Scale	0.20§	0.35†

* $P < .05$.
† $P < .01$.
‡ Higher scores reflect less fatigue.
§ $.09 > P > .05$ (trend).
F2.2 = "How easily do you get tired?" F2.4 = "How much are you bothered by fatigue?" both scored on a 1-to-5 scale from 1 (not at all) to 5 (extremely).

Hsp70 serum levels than in those with low Hsp70 and high IL-6 serum levels ($P = .045$, grip work expressed per kg of lean body mass, Figure 1B). Muscle endurance was not significantly different according to combined high or low TNF-α and Hsp70 serum levels. No significant differences in TNF-α levels were found between residents with both high IL-6 and Hsp70 serum levels and those with low Hsp70 and high IL-6 serum levels (7.39 ± 5.92 and 8.32 ± 8.12 pg/mL, respectively, $P = .92$). TNF-α was significantly lower in residents with both low IL-6 and Hsp70 serum levels (3.76 ± 2.69 pg/mL) than in those with both high IL-6 and Hsp70 (7.39 ± 5.92 pg/mL; $P = .04$) and high IL-6 and low Hsp70 (8.32 ± 8.12 pg/mL; $P = .02$).

DISCUSSION

This article reports results from an explorative study investigating the relationships between muscle endurance and self-perceived fatigue, mobility, and circulating inflammatory parameters in elderly nursing home residents. Although the test procedures were simple and easy to understand, almost 50% of the residents screened for eligibility were excluded because of cognitive or physical impairments. The participating residents had a high degree of frailty, as illustrated by important comorbidity and polypharmacy and weak grip strength. On average, strengths of 32 ± 12 kPa and 51 ± 11 kPa were registered for female and male participants, respectively, whereas 59 kPa and

Table 4. Relationships Between Muscle Endurance and Inflammatory Mediators in Serum

Parameter	Fatigue Resistance†		Grip Work†	
	Male	Female	Male	Female
	Spearman Rho			
Interleukin-6	0.02	− 0.03	0.03	− 0.09
Tumor necrosis factor alpha	− 0.45*	0.04	− 0.45*	− 0.07
Heat shock protein 70	− 0.23	− 0.12	− 0.27	− 0.05

* $P < .05$.
† Expressed per kg lean body mass.

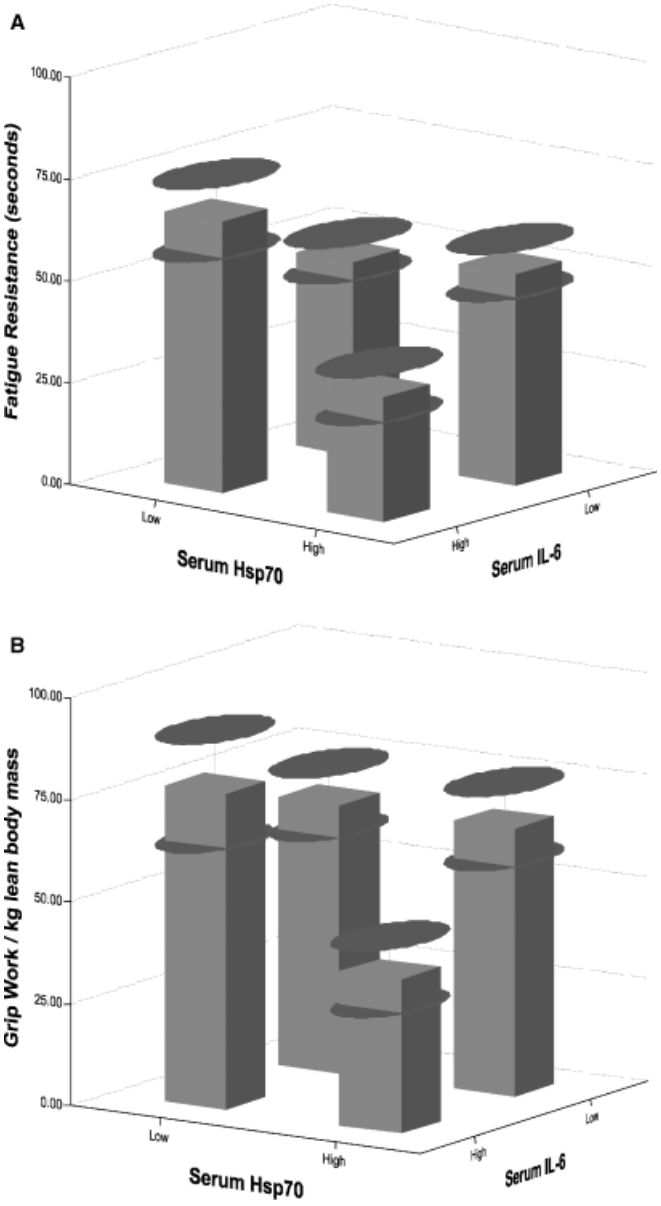

Figure 1. Fatigue resistance in relation to extracellular heat shock protein (Hsp)70 and interleukin (IL)-6 in nursing home residents. Bars represent means ± standard errors. Serum Hsp70 and IL-6 values at the 70th percentile and higher were considered as high levels. (A) Fatigue resistance represents the time during which grip strength decreased to 50% of its maximum value. The interaction between serum Hsp70 and IL-6 levels significantly affected fatigue resistance (analysis of covariance $P = .03$, corrected for age and whole body muscle mass). Subjects with high Hsp70 and high IL-6 serum levels presented significantly worse fatigue resistance than those with low Hsp70 and high IL-6 serum levels ($P = .007$). No interaction with sex was found. (B) Grip work expressed per kg of lean body mass. Subjects with high Hsp70 and high IL-6 serum levels had poorer grip work than those with low Hsp70 and high IL-6 serum levels ($P = .045$).

75 kPa are normative values at the age of 80 to 84.[35] Moreover, 74% of the participants had some degree of physical dependency, as assessed according to Katz et al.[25] Therefore, the population in this study can be considered representative of frail elderly nursing home residents without severe cognitive dysfunction or acute medical problems.

Muscle endurance was measured as fatigue resistance and work output delivered during the fatigue resistance test, offering a refinement of the classical evaluation of muscle performance in frail elderly people. In addition, fatigue was approached from different angles. The subjective sensation of basic fatigue as such (VAS), the effect of fatigue on quality of life (WHOQOL F2.2 and F2.4), and the extent to which activities of daily living caused fatigue (Mob-T scale) were evaluated. Better grip work was significantly related to less sensation of basic fatigue and less fatigue related to daily activities. Also, participants with higher grip work were less easily fatigued and less bothered by fatigue. Similar relationships were observed for muscle fatigue resistance, but the relationships were less pronounced, a finding that can be explained by the fact that the outcome on the fatigue resistance test is a measure relative to each individual's maximal strength. Grip work integrates maximal strength and how long it can be maintained, reflecting capacity to apply muscle strength in movements or daily activities.[8] The results of this study are in agreement with previous findings in community-dwelling elderly people without inflammation[8] and represent additional evidence for the validity of fatigue resistance and grip work as parameters for muscle endurance. Most importantly, these results demonstrate that physicians and nursing staff need to take complaints about fatigue or tiredness during activities of daily living in elderly nursing home residents seriously, because these complaints are significantly related to reduced muscle endurance.

Two tests (Tinetti test and EMS) capable of differentiating subjects at the lower range of functional mobility were used to assess mobility. Both tests showed significant positive relationships with fatigue resistance and grip work (except trend for the correlation between fatigue resistance and EMS). A previous study[36] described significant relationships between grip strength and the capacity to walk as a measure of mobility. The results of the current study show that not only maximal strength but also resistance to fatigue and work output during sustained contractions are related to mobility. It is possible that maximal strength is critical for the ability to initiate a certain activity, and sufficient muscle endurance is mandatory for continuing and completing the task. Therefore, the evaluation of muscle endurance may also (with maximal strength) be an important means of evaluating functional capacity in elderly subjects.

Low-grade inflammation was evaluated by determining circulating levels of inflammatory mediators (IL-6 and TNF-α) known to be possible correlates for muscle function and frailty at older age.[2,37] Body composition has been shown to be related to inflammation and sarcopenia in elderly persons,[37,38] and thus fatigue resistance and grip work were corrected for lean body mass to avoid bias in the correlations. Worse scores on both fatigue resistance and grip work were significantly ($P < .05$) related to higher serum levels of TNF-α in male residents. To the authors' knowledge, this is the first report demonstrating the relationship between TNF-α in serum and muscle endurance in frail nursing home residents. The fact that TNF-α might depress muscle contractility by increasing cellular production of reactive oxygen species and nitric oxide (see[39] for review) and thus reduce muscle endurance can explain this relationship. A previous, study[40] showed that "detectable serum levels of TNF-α" (>40 pg/mL) seemed to be a predictor of early mortality in elderly nursing home residents. These subjects might also have had a higher risk for progression of frailty, and it cannot be excluded that they were also weaker and more easily fatigued, although the study did not assess muscle strength, endurance, or fatigue. In the current study, the detection limit for TNF-α in serum was 1.7 pg/mL, allowing a more refined statistical analysis. Another study[41] found that higher serum levels of soluble TNF-α receptors might impair strength gain after resistance exercise in elderly nursing home residents, although they did not measure muscle endurance, and the lack of a significant correlation in their study between baseline muscle strength and circulating TNF-α might be the result of a small sample size ($N = 21$, of whom 19 were women). The current study did not find a negative relationship between muscle endurance and serum TNF-α in women. A possible explanation might be the slightly, although not significantly, higher concentration of circulating TNF-α in men than in women (5.2 ± 4.0 vs 3.8 ± 4.7 pg/mL). It is possible that a threshold value exists for low-grade inflammation above which an irreversible state is attained, as suggested previously,[16] resulting in an effect on muscle performance. Higher values of circulating TNF-α in men than in women have been reported previously in subjects aged 80 and older.[42] Moreover, TNF-α was found to be a significant predictive factor for mortality in men but not in women.[42] Muscle performance was not measured in that study, and the sex differences of circulating TNF-α levels and its effect on survival remained unexplained.

Contrary to previous studies,[5,7,8] no significant relationship was found between muscle endurance and circulating IL-6. In studies with hospitalized geriatric patients with acute infection,[5,7] fatigue resistance correlated negatively with IL-6; whereas in community-dwelling elderly subjects without acute illness or infection, fatigue resistance and grip work were positively related to IL-6.[8] The fact that IL-6 can exert pro- and antiinflammatory signaling can explain this apparent discrepancy.[14] In addition, contracting muscles release IL-6 into the circulation, acting as a myokine to signal the need for endogenous glucose production.[43,44] Because chaperone expression of the Hsp70 family and IL-6 release in the blood circulation are closely related,[18,45] extracellular levels of Hsp70 in the serum have also been determined to be a potential interfering mediator. Muscle endurance was significantly different according to the combination of high or low serum levels of IL-6 and Hsp70; subjects with high serum levels of both IL-6 and Hsp70 showed significantly worse muscle endurance (as measured by fatigue resistance and muscle work) than those with high IL-6 and low Hsp70. It has been reported that, in the absence of serious inflammatory conditions, low levels of serum Hsp70 are associated with successful biological aging[24] and might reflect strong antiinflammatory properties of the individuals' immune system.[46] In the current study, residents with acute conditions were excluded. In this

situation, the signaling function of IL-6 is probably less inflammation-related, although high levels of serum Hsp70 can be seen as reflecting higher and less-controlled low-grade inflammatory activity,[18] with detrimental effects on muscle cells. No such interacting relationship between TNF-α and Hsp70 and muscle endurance was found, and TNF-α levels were not significantly different in subjects with both high IL-6 and Hsp70 levels and those with high IL-6 and low Hsp70 levels. The results indicate that circulating IL-6 and TNF-α, although related, appear to play different roles, which concords with previous studies reporting that IL-6 and TNF-α are independent predictors for survival in octogenarians.[42] Frail nursing home residents present typically complex clinical situations with high risk for rapid progression of frailty. The data collected in the current study indicate that (dis)balances between inflammation-related processes might characterize patients with the lowest muscle endurance among frail nursing home residents.

From the results of this study it can be concluded that the sensation of fatigue in elderly nursing home residents is related to lower muscle endurance, which is related to reduced mobility. Residents with both high IL-6 and Hsp70 serum levels show worse muscle endurance, as do male residents with higher circulating TNF-α.

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