Inflammation and frailty measures in older people

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Abstract

Inflammation in patients defined as frail by Fried’s phenotypic definition may be related to sarcopenia. This study aimed to investigate inflammation in older patients across different frailty criteria. Frailty status was determined in 110 patients aged over 75 years (mean 83.9 years) according to function (dependent, intermediate, independent); Fried (three or more items of exhaustion, weight loss, slow walking speed, low handgrip strength, low physical activity) and Frailty Index (a measure of accumulated deficits). With increasing patient frailty as defined by function and by Fried phenotype, tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6) and C-reactive protein (CRP) increased significantly. Albumin was lowest in the frailest subjects by each definition. The greatest differences were seen between intermediate and dependent groups and between the pre-frail and frail. Adjustment for multiple covariates (age, sex, BMI category, smoking status, number of co-morbidities and number of prescribed medications) did not account for any of the observed differences in levels of inflammatory markers. The Frailty Index correlated significantly with log-transformed CRP (r = 0.221, P < 0.05), log-transformed IL-6 (r = 0.369, P < 0.01), TNF-α (r = 0.379, P < 0.01) and inversely with albumin (r = −0.545, P < 0.01). This study provides further evidence linking inflammation and frailty in older people, an association that seems consistent across different frailty measures.

Keywords: aged ≥ 80 and over • frail elderly • inflammation • tumour necrosis factor-α • C-reactive protein • interleukin-6

Introduction

Frailty is an important concept in geriatric medicine and understanding its aetiology has become a fundamental aspiration of many researchers in the aging field [1]. Chronic inflammation may play a role in the pathophysiology of frailty [2, 3]. In older people, higher circulating levels of C-reactive protein (CRP) and interleukin-6 (IL-6) are inversely correlated with poor physical performance, and muscle weakness [4] and higher circulating levels of IL-6 predict the onset of disability [5]. Plasma levels of tumour necrosis factor-α (TNF-α) are strongly associated with death in community-dwelling subjects aged 72–92 years [6] and in centenarians [7].

Older people defined as frail by operational criteria defined by Fried et al. [8] exhibit evidence of increased inflammation, with higher levels of CRP [9] and IL-6 [10]. Fried’s model has been praised for clinical reproducibility and coherency [11] and has been validated against adverse outcome in large population studies [8, 12]. However, it is based on physical parameters, whereas frailty is, arguably, a complex, multi-dimensional concept [13, 14]. Inflammation in Fried frail subjects may be related primarily to sarcopenia. In the study by Ferrucci et al. [5], most of the relationship between IL-6 and disability was accounted for by the detrimental effect on muscle strength. Furthermore, CRP, IL-6 and TNF-α receptor-2 levels are negatively correlated with rate of skeletal muscle protein synthesis [15], supporting the idea that low-grade inflammation is implicated in sarcopenia development [16].

Defining frailty is an area of ongoing debate [17] and application of different frailty criteria can give heterogeneous results in clinical practice [18]. The aim of the present study was to investigate inflammation in older patients according to varied frailty criteria.
Materials and methods

Thirty institutionalized patients were recruited from Continuing Care wards on four different hospital sites in Cardiff, South Wales. These inpatients were dependent for activities of daily living, many were cognitively impaired and all met United Kingdom National Health Service Continuing Care criteria for ongoing nursing and medical needs [19]. Forty community-dwelling patients with a history of falls referred to Day Hospital for rehabilitation and 40 independent age-matched controls recruited from poster advertisements were also studied. These patients were defined, respectively, as dependent, intermediate and independent on a functional frailty spectrum [20–22].

Frailty indicators were measured in all subjects by a single observer (REH). History of weight loss, smoking status, medical diagnoses and drug history were self-reported by independent older people or documented from medical notes for intermediate or dependent patients. Use of anti-inflammatory drugs (non-steroidal anti-inflammatory drugs, cyclooxygenase-2 selective inhibitors and steroids) was noted. Height and weight were measured without shoes and with light clothing, height to the nearest 0.5 cm and weight to the nearest 0.1 kg. Height was estimated for dependent patients who could not stand from semi-span (measured in centimetres from the ring finger root to the sternal notch) and knee height, as described by Hickson and Frost [23]. Body mass index (BMI) was calculated as weight (kg)/height (m)^2 and BMI categorized as underweight (<20), recommended weight (20.0–24.9), overweight (25.0–29.9) or obese (>30.0) [24].

Participants were categorized according to Fried criteria [8] with cut-offs for positive frailty indicators set at the lowest 20% of the independent older group [25]: exhaustion (Energy and Vitality Score on Short-Form 36 of less than 40%), slow walking speed (6-min. walking distance of <=210 m) and low handgrip strength. Weight loss (>10 pounds in preceding year) and low physical activity (a score of 1 or 2 out of 6 on a validated physical activity questionnaire [26]) were also Fried frailty indicators. Individuals with three or more components were defined as frail, one or two pre-frail and those with no positive frailty indicators as non-frail.

The Frailty Index measures frailty as a continuum rather than a dichotomous state, an approach summarized as ‘the more things individuals have wrong with them, the higher the likelihood they will be frail’ [27]. For this Frailty Index, a total of 30 variables were collected, including self-reported data, symptoms, co-morbidities and performance-based tests. Deficits were combined by adding them (1 for each deficit present, 0 if absent), and the Index was the total deficits as a proportion of those counted (e.g. 6/30 = 0.20).

Total white blood cell (WBC) count was obtained using a Coulter counter in the hospital-based laboratory and serum albumin and CRP measured (Abbott AEROSET system, Abbott Laboratories, Abbott Park, IL, USA). Plasma IL-6 and TNF-α were assayed by enzyme-linked immunosorbent assay using Quantikine® Colorimetric Kits. The optical densities were measured using a Bio-Rad Laboratories Ltd. Model 3550 Plate Reader (Hemel Hempstead, Herts, UK) and the mean of duplicate samples calculated.

The study was approved by the Local Research Ethics Committee. Written-informed consent was obtained from participants or, for patients who lacked capacity to give fully informed consent, assent was obtained from next of kin.

Data were analyzed using Stata 10.1 for UNIX. For normally distributed variables data were reported as mean and standard deviation and the statistical significance of differences across degrees of frailty was examined using analysis of variance. Variables with a skewed distribution (CRP and IL-6) were expressed as median, 25th and 75th percentiles. Log-transformed CRP values were roughly normally distributed and so were tested across frailty groups using analysis of variance. A significant proportion of participants had zero detectable IL-6 level and a log transformation was not possible in those cases. Therefore, we tested the proportion of cases with non-zero IL-6 across each group using logistic regression as well as the log-transformed IL-6 values in non-zero cases. Analyses were conducted univariately and after adjustment for age, sex, BMI, smoking, number of co-morbidities and number of prescribed medications. Correlations were explored using Pearson correlation coefficients.

Results

One hundred 10 patients were recruited [28]. Forty-four patients were male (40%) and all were Caucasian. No subjects showed signs of infection or were taking antibiotic treatment. Study population characteristics are shown in Table 1.

Prevalence of Fried frailty increased from 10% in independent older people to 72.5% in the intermediate function, Day Hospital group and 100% of dependent, Continuing Care patients. Eleven Day Hospital patients (27.5%) and 14 independent older people (35%) had 1–2 frailty indicators and were ‘pre-frail’.

The Frailty Index increased significantly with increasing functional dependence: from 0.15 (standard deviation 0.08) for independent older people to 0.33 (0.08) for Day Hospital (P < 0.05) and 0.49 (0.08) for Continuing Care patients (P < 0.005).

Four patients declined venesecion. Sufficient venous specimens were obtained to measure WBC count in 106 patients (96%), albumin in 91 (83%), CRP in 89 (81%), IL-6 in 106 (96%) and TNF-α in 105 subjects (95%). One patient had an extreme CRP value of 283 mg/l and one had a high lymphocyte count secondary to known chronic lymphocytic leukaemia. These cases were excluded, respectively, from further CRP and WBC analyses.

Table 2 shows the levels of each inflammatory marker across frailty definitions, as well as the variation of each marker within each frailty group. With increasing patient frailty as defined by function (independent/intermediate/dependent) and Fried phenotype (non-frail/pre-frail/frail), TNF-α and CRP each increased significantly. Both the presence of IL-6 and the levels in those in which it was detectable were higher in the frailler participants. Albumin was lowest in the frailest subjects by each definition. Table 3 shows estimates for the differences between groups defined by increasing levels of frailty, both univariate and adjusted for multiple covariates. The greatest differences were seen between intermediate and dependent groups and between the pre-frail and frail. Adjustment for multiple covariates (age, sex, BMI category, smoking status, number of co-morbidities and number of prescribed medications) did not account for any of the observed differences in levels of inflammatory markers; many differences were more marked after adjustment.

The Frailty Index correlated significantly with log-transformed CRP (r = 0.221, P < 0.05), log-transformed IL-6 (r = 0.369, P < 0.01) and TNF-α (r = 0.379, P < 0.05).
(r = −0.545, P < 0.01) but no correlation with WBC count (r = −0.176, P = 0.072).

Discussion

In this study, we have shown significant associations between frailty and markers of inflammation. Although frailty is defined and measured in different ways, there is universal agreement that it is a state of increased vulnerability to a range of adverse outcome in later life, including death, institutionalization and worsening health [11, 13, 29–31]. We have applied three distinct measures of frailty: the ‘phenotypic frailty’ defined by Fried and colleagues, a Frailty Index and a measure of frailty defined by level of dependence. Our results were consistent, suggesting the association with inflammation does not depend on the specific definition or measure of frailty applied. Although older people in the ‘dependent’ group were disabled, and frailty is distinct from disability [32], we feel that they were also frail. There was strong face validity for choosing long-term inpatients as the ‘frailst’ group on the functional frailty spectrum. Construct validation of their frailty status is afforded by the higher prevalence of Fried frailty and significantly
higher Frailty Index score in these patients. Our results were not affected by adjusting for age, sex, BMI, smoking, the number of medications being taken or number of co-morbidities.

The study has important limitations. Number of participants was small. The variables were not operationalized exactly as proposed by Fried and colleagues [8], although similar modifications have been made by others who have replicated the work [33]. Such adaptations are less of a problem for the Frailty Index approach, which does not require the same items or the same number of items to estimate the proportions that represent the Index's values [34]. In this study, a Frailty Index was constructed from 30 variables and though 40 are recommended [27], Frailty Indices have been constructed using as few as 20 variables [35].

As with other cross-sectional studies [9, 10], the association between frailty and inflammation provides no insights into causality. Inflammation may be part of the driving force towards disability. Increased levels of IL-6 have been linked to physical decline and disability [36, 37], and the development of age-related conditions such as dementia, Parkinson's disease, atherosclerosis and type 2 diabetes is associated with elevated levels of inflammatory mediators [38]. Furthermore, the association of inflammation with obesity, smoking and physical inactivity may constitute a link between life-style factors and frailty development [39].

Alternatively, inflammation may be a compensatory response. Some genotypes are associated with increased production of certain cytokines [40]. A direct link between such genotypes and frailty development or mortality would support a direct pathogenetic role of inflammatory mediators. To date, no such link has been established and the evidence regarding polymorphisms and longevity is conflicting [39]. One of the main functions of IL-6 is self-limiting inflammation [41]. Thus, elevated levels of IL-6 in frailty may be aimed at resolving an inflammatory response [42] initially triggered by viral antigens such as cytomegalovirus [43] or other sub-clinical disease such as asymptomatic bacteriuria [44].

Thirdly, inflammation may be an epi-phenomenon, merely a marker of the key causal mechanism. Excessive and unopposed oxidative stress may be the core mechanism leading to age-associated frailty [42]. Oxidative damage accumulates with age.

| Function | Fried | Non-frail | Pre-frail | Frail | Independent | Intermediate | Dependent |
|----------|-------|-----------|-----------|-------|-------------|--------------|-----------|
|          |       | n = 22    | n = 25    | n = 63 | n = 40      | n = 40       | n = 30    |
| White blood cell count \( \times 10^{9}/l \) mean (standard deviation) |       | 6.7 (1.3) | 7.1 (1.7) | 7.7 (2.4) | 7.1 (2.1) | 7.3 (2.0) | 7.8 (2.3) |
| Albumin g/l mean (standard deviation) |       | 43.4 (5.3) | 44.2 (3.5) | 39.5 (5.6) | 44.0 (4.5) | 43.0 (3.4) | 34.7 (4.7) |
| C-reactive protein mg/l median (25th and 75th percentile) |       | 3.0 (2.0–5.0) | 4.0 (2.0–6.0) | 5.0 (3.0–13.0) | 3.5 (2.0–5.5) | 4.0 (2.0–11.0) | 5.5 (2–21.5) |
| IL-6 pg/ml median (25th and 75th percentile) |       | 0 (0–1.51) | 0 (0–3.99) | 3.59 (0.26–10.44) | 0 (0–2.81) | 1.48 (0–5.94) | 6.97 (2.56–38.34) |
| % With detectable IL-6 |       | 41% | 44% | 80% | 45% | 67% | 81% |
| TNF-\( \alpha \) pg/ml mean (standard deviation) |       | 1.50 (0.89) | 1.86 (1.23) | 3.19 (2.68) | 1.68 (1.12) | 2.01 (1.16) | 4.58 (3.30) |

* \( P \) = significance of differences in log-transformed values.
### Table 3

Differences in inflammatory markers between frailty groups, with 95% confidence intervals.

| Function                  | Intermediate versus independent | Dependent versus intermediate |
|---------------------------|---------------------------------|------------------------------|
|                           | Effect  | 95% CI            | P-value | Effect  | 95% CI            | P-value |
| Univariate                |         |                   |         |         |                   |         |
| White blood cell count    | 0.19    | (−0.74, 1.13)     | 0.683   | 0.47    | (−0.56, 1.50)     | 0.378   |
| Albumin                   | −1.00   | (−2.94, 0.94)     | 0.315   | −8.31   | (−10.53, −6.08)   | P < 0.005 |
| Log-transformed C-reactive protein | 0.30    | (−0.23, 0.83)     | 0.276   | 0.57    | (−0.03, 1.16)     | 0.068   |
| Log-transformed IL-6      | 0.25    | (−0.58, 1.08)     | 0.563   | 1.78    | (1.00, 2.57)      | P < 0.005 |
| Detectable IL-6†          | 2.44    | (0.98, 6.09)      | 0.055   | 2.20    | (0.68, 7.14)      | 0.189   |
| TNF-α                     | 0.32    | (−0.52, 1.17)     | 0.454   | 2.57    | (1.62, 3.52)      | P < 0.005 |
| Adjusted                  |         |                   |         |         |                   |         |
| White blood cell count    | −0.37   | (−1.39, 0.66)     | 0.485   | 1.85    | (0.50, 3.20)      | 0.009   |
| Albumin                   | −1.23   | (−3.41, 0.96)     | 0.276   | −7.60   | (−10.88, −4.33)   | P < 0.005 |
| Log-transformed C-reactive protein | 0.42    | (−0.14, 0.98)     | 0.143   | 1.07    | (0.24, 1.90)      | 0.014   |
| Log-transformed IL-6      | 0.17    | (−0.85, 1.19)     | 0.746   | 2.70    | (1.53, 3.86)      | P < 0.005 |
| Detectable IL-6†          | 1.76    | (0.58, 0.54)      | 0.317   | 13.60   | (1.35, 136.93)    | 0.027   |
| TNF-α                     | 0.43    | (−0.39, 1.25)     | 0.310   | 3.50    | (2.38, 4.62)      | P < 0.005 |
| Fried                     |         |                   |         |         |                   |         |
| Pre-frail versus non-frail|         |                   |         |         |                   |         |
| White blood cell count    | 0.47    | (−0.73, 1.67)     | 0.443   | 0.61    | (−0.37, 1.59)     | 0.225   |
| Albumin                   | 0.82    | (−2.39, 4.02)     | 0.618   | −4.71   | (−7.33, −2.09)    | P < 0.005 |
| Log-transformed C-reactive protein | 0.04    | (−0.67, 0.74)     | 0.918   | 0.70    | (0.13, 1.27)      | 0.019   |
| Log-transformed IL-6      | 0.83    | (−0.57, 2.23)     | 0.249   | 0.50    | (−0.54, 1.55)     | 0.349   |
| Detectable IL-6†          | 1.13    | (0.36, 3.62)      | 0.831   | 4.50    | (1.65, 12.26)     | P < 0.005 |
| TNF-α                     | 0.37    | (−0.85, 1.59)     | 0.556   | 1.33    | (0.33, 2.32)      | 0.011   |
| Frail versus pre-frail    |         |                   |         |         |                   |         |
| White blood cell count    | 0.14    | (−1.26, 1.54)     | 0.844   | 0.79    | (−0.28, 1.85)     | 0.145   |
| Albumin                   | 0.36    | (−3.14, 3.86)     | 0.841   | −3.18   | (−5.75, −0.60)    | 0.018   |
| Log-transformed C-reactive protein | 0.26    | (−0.53, 1.04)     | 0.523   | 0.83    | (0.24, 1.41)      | 0.007   |
| Log-transformed IL-6      | 1.14    | (−0.48, 2.77)     | 0.173   | 0.47    | (−0.81, 1.75)     | 0.473   |
| Detectable IL-6†          | 1.00    | (0.22, 4.53)      | 0.999   | 8.28    | (2.29, 29.92)     | P < 0.005 |
| TNF-α                     | 0.85    | (−0.44, 2.14)     | 0.200   | 1.39    | (0.41, 2.36)      | 0.007   |

*Both univariate differences and differences adjusted for age, sex, BMI, smoking, number of co-morbidities and number of prescribed medications are presented. Frailty is defined both by function (top) and by Fried frailty criteria (bottom).
†Reported effect size is the odds ratio of the presence of detectable levels of IL-6 between groups.
causing DNA, muscle and lipid damage sufficient to impair cellular and organ function [45]. Recent evidence supports a direct causal role for reactive oxygen species (ROS) in skeletal muscle damage. Protein carbonylation, an indirect measure of ROS muscle damage, was associated with low grip strength in the Women’s Health and Ageing Study 1 [46].

This study provides further evidence linking inflammation and frailty in older people, an association that seems consistent across different frailty measures. Further studies are needed to establish the nature of this association – whether inflammation is primarily causal, compensatory or an epi-phenomenon. Intervention studies modulating the production or effect of inflammatory mediators are therefore a more distant prospect.

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References
1. Ferrucci L, Mahallati A, Simonsick EM. Frailty and the foolishness of Eos. J Gerontol A Biol Sci Med Sci. 2006; 61: 260–1.
2. Hamerman D. Toward an understanding of frailty. Ann Intern Med. 1999;130: 945–50.
3. Morley JE, Baumgartner RN. Cytokine-related aging process. J Gerontol A Biol Sci Med Sci. 2004; 59: 924–9.
4. 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: 242–8.
5. 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: 639–46.
6. Roubenoff R, Parise H, Payette HA, et al. Cytokines, insulin-like growth factor 1, sarcopenia, and mortality in very old community-dwelling men and women: the Framingham Heart Study. Am J Med. 2003; 115: 429–35.
7. Bruunsgaard H, Ladelund S, Pedersen LR, et al. Elevated levels of tumor necrosis factor alpha and mortality in centenarians. Am J Med. 2003; 115: 278–83.
8. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001; 56: M146–56.
9. Walston J, McBurnie MA, Newman A, et al. Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study. Arch Intern Med. 2002; 162: 2333–41.
10. Leng SX, Xue Q-L, Tian J, et al. Inflammation and frailty in older women. J Am Geriatr Soc. 2007; 55: 864–871.
11. Bergman H, Ferrucci L, Guralnik J, et al. Frailty: an emerging research and clinical paradigm–issues and controversies. J Gerontol A Biol Sci Med Sci. 2007; 62: 731–7.
12. Bandeen-Roche K, Xue QL, Ferrucci L, et al. Phenotype of frailty: characterization in the women’s health and aging studies. J Gerontol A Biol Sci Med Sci 2006; 61: 262–6.
13. Hogan DB, Macknight C, Bergman H. Steering Committee, Canadian Initiative on Frailty and Aging. Models, definitions, and criteria of frailty. Aging Clin Exp Res. 2003; 15: 1–29.
14. Markle-Reid M, Browne G. Conceptualisations of frailty in relation to older adults. J Adv Nurs 2003; 44: 58–68.
15. Toth MJ, Matthews DE, Tracy RP, et al. Age-related differences in skeletal muscle protein synthesis: relation to markers of immune activation. Am J Physiol Endocrinol Metab. 2005; 288: E883–91.
16. Mayot G, Vidal K, Combaret L, et al. Presence of low-grade inflammation in old rats does not worsen skeletal muscle loss under an endotoxicemia and dietetic stress. Exp Gerontol. 2007; 42: 1167–75.
17. Fisher AL. Just what defines frailty? J Am Geriaritr Soc. 2005; 53: 2229–30.
18. van Iersel MB, Olde Rikkert MG. Frailty criteria give heterogeneous results when applied in clinical practice. J Am Geriatr Soc. 2006; 54: 728–9.
19. Welsh Assembly Government. Further advice to the NHS and Local Authorities on constructing a common meaning, definition and conceptual framework. Int J Rehabil Res. 1995; 18: 93–102.
20. Woodhouse KW, Wynne H, Baillie S, et al. Who are the frail elderly? Q J Med. 1988; 68: 505–6.
21. Hickson M, Frost G. A comparison of three methods for estimating height in the acutely ill elderly population. J Hum Nutr Dietet 2003; 16: 13–20.
22. Lang IA, Llewellyn DJ, Alexander K, et al. Obesity, physical function, and mortality in older adults. J Am Geriatr Soc. 2008; 56: 1474–8.
23. Hubbard RE, O’Mahony MS, Woodhouse KW. Characterising frailty in the clinical setting – a comparison of different approaches. Age Ageing. 2008 Nov 13. [Epub ahead of print] PMID: 19008304.
24. Pedersen AN, Ovesen L, Schroll M, et al. Body composition of 80-years old men and women and its relation to muscle strength, physical ability and functional ability. J Nutr Health Ageing. 2002; 6: 413–20.
25. Rockwood K, Milntiska A. Frailty in relation to the accumulation of deficits. J Gerontol Med Sci. 2007; 62: 722–7.
26. Hubbard RE, O’Mahony MS, Calver BL, et al. Nutrition, inflammation, and leptin levels in aging and frailty. J Am Geriatr Soc. 2008; 56: 279–84.
27. Ahmed N, Mandel R, Fain MJ. Frailty: an emerging geriatric syndrome. Am J Med. 2007; 120: 748–53.
28. Abellan van Kan G, Rolland Y, Bergman H, et al. The I.A.N.A Task Force on frailty assessment of older people in clinical practice. J Nutr Health Aging. 2008; 12: 29–37.
29. Whitson HE, Purser JL, Cohen HJ. Frailty: thy name is … Phrailty?. J Gerontol A Biol Sci Med Sci. 2007; 62: 728–30.
30. Puts MT, Lips P, Deeg DJ. Sex differences in the risk of frailty for mortality independent
of disability and chronic diseases.  
33. Gill TM, Gahbauer EA, Allore HG, et al. Transitions between frailty states among community-living older persons. Arch Int Med. 2006; 166: 418–23.
34. Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. J Gerontol A Biol Sci Med. 2007; 62: 738–43.
35. Mitnitski A, Bao L, Rockwood K. Going from bad to worse: a stochastic model of transitions in deficit accumulation, in relation to mortality. Mech Ageing Dev. 2006; 127: 490–3.
36. Cohen HJ, Harris T, Pieper CF. Coagulation and activation of inflammatory pathways in the development of functional decline and mortality in the elderly. Am J Med. 2003; 114: 180–7.
37. Cappola AR, Xue QL, Ferrucci L, et al. Insulin-like growth factor I and interleukin-6 contribute synergistically to disability and mortality in older women. J Clin Endocrinol Metab. 2003; 88: 2019–25.
38. De Martinis M, Franceschi C, Monti D, et al. Inflammation markers predicting frailty and mortality in the elderly. Exp Mol Pathol. 2006; 80: 219–27.
39. Krabbe KS, Pedersen M, Bruunsgaard H. Inflammatory mediators in the elderly. Exp Gerontol. 2004; 39: 687–99.
40. Wang XY, Hurme M, Jylha M, et al. Lack of association between human longevity and polymorphisms of IL-1 cluster, IL-6, IL-10 and TNF-alpha genes in Finnish nonagenarians. Mech Ageing Dev. 2001; 123: 29–38.
41. Gabay C, Kushner I. Acute phase proteins and other systemic responses to inflammation. N Engl J Med 1999; 340: 448–53.
42. Maggio M, Guralnik JM, Longo DL, et al. Interleukin-6 in aging and chronic disease: a magnificent pathway. J Gerontol Med Sci. 2006; 61: 575–84.
43. Schmaltz HN, Fried LP, Xue QL, et al. Chronic cytomegalovirus infection and inflammation are associated with prevalent frailty in community-dwelling older women. J Am Geriatr Soc. 2005; 53: 747–54.
44. Kuller LH. Serum IL-6 and development of disability in older persons. J Am Geriatr Soc. 1999; 47: 755–6.
45. Ershler WB. A gripping reality: oxidative stress, inflammation, and the pathway to frailty. J Appl Physiol. 2007; 103: 3–5.
46. Howard C, Ferrucci L, Sun K, et al. Oxidative protein damage is associated with poor grip strength among older women living in the community. J Appl Physiol. 2007; 103: 17–20.

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