Serum Interleukin-6 and Hemoglobin as Physiological Correlates in the Geriatric Syndrome of Frailty: A Pilot Study

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OBJECTIVES: To determine specific physiological correlates of the geriatric syndrome of frailty that warrant further investigation.

DESIGN: Population-based case-control study.

SETTING: General Clinical Research Center at Johns Hopkins Bayview Medical Center.

PARTICIPANTS: Community-dwelling adults aged 74 and older from Baltimore, Maryland.

MEASUREMENTS: Frailty status was determined using a recently validated screening tool that consists of weight loss, fatigue, low levels of physical activity, and measurements of grip strength and walking speed. Serum interleukin-6 (IL-6) was measured using enzyme-linked immunosorbent assay, and standard complete blood count was performed using a Coulter counter.

RESULTS: Eleven frail and 19 nonfrail subjects with mean age ± standard deviation of 84.9 ± 6.7 vs 81.3 ± 4.1 years, respectively, completed the study. The frail subjects had significantly higher serum IL-6 levels and significantly lower hemoglobin and hematocrit than the nonfrail subjects (4.4 ± 2.9 vs 2.8 ± 1.6 pg/mL, 12.1 ± 1.1 vs 13.9 ± 1.0 g/dL, and 35.8% ± 3.1% vs 40.6% ± 2.8%, respectively). No significant difference was observed in mean corpuscular volume, red blood cell distribution width, or white blood cell and platelet counts between the frail and nonfrail groups. Furthermore, there was an inverse correlation between serum IL-6 level and hemoglobin (Pearson's correlation coefficient: −0.46) and hematocrit (−0.48) in the frail group but not in the nonfrail group.

CONCLUSION: These results suggest that frail subjects have evidence of inflammation and lower hemoglobin and hematocrit levels. This subclinical anemia is normocytic and is hence unlikely due to myelosuppression or iron deficiency and is potentially related to the increased chronic inflammatory state marked by serum IL-6 elevation. Further studies are indicated to better characterize the immune and hematological changes that underlie frailty. **J Am Geriatr Soc 50:1268–1271, 2002.**

Key words: frailty; interleukin-6; hemoglobin

The geriatric syndrome of frailty has been recently defined as a wasting syndrome of older adults, characterized by weakness, fatigue, weight loss, and extreme vulnerability to stressors, that predicts increased morbidity and mortality.[1–3] Despite the profound functional, medical, and social consequences that frailty has for older adults, little is known about the underlying physiological mechanisms that influence its development. The recent development and validation of a screening tool used for the identification of these at-risk older adults has made it possible to investigate the physiological etiology of frailty.[4]

The purpose of this pilot study was to test selected physiological parameters as potential correlates of frailty, which may provide rationale for the development of more-detailed etiologic studies. It has been previously hypothesized that the decline in reserve and increase in vulnerability observed in frailty occurs across multiple physiological systems.[2,5] We further hypothesized that chronic inflammation not related to specific disease states influences the development of frailty and that serum interleukin (IL)-6 is a marker of this chronic inflammation state. Serum IL-6 was chosen because of several recent studies that demonstrated a predictive value of the elevated serum level of this proinflammatory cytokine for functional decline and mortality in older adults[6–8] as well as serum IL-6 also is known for its negative influence on skeletal muscle and hematopoiesis, which could lead to weakness and fatigue.[2,9] Hematological parameters included in complete blood count (CBC) were selected for study because of the symptoms of weakness and fatigue that are frequently associated with frailty and anemia and because of the known relationship between chronic inflammation and lower hematocrit.[10,11]

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Jeremy Walston is a Paul Beeson Physician Faculty Scholar. Support for this study came from the Beeson Award, the Brookdale Foundation, and the National Foundation for Global Cooperation.

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0002-8614/02/$15.00

METHODS

Human Subjects

Community-dwelling adults aged 74 and older from Baltimore, Maryland, were recruited from outpatient medical clinics, senior centers, and residential retirement communities and screened by a trained clinical coordinator between 1999 and 2000. The screening criteria, recently validated in a large cohort of older adults and published, included unintentional weight loss of more than 10 pounds in the past year, low grip strength by gender and body mass index, slow walking speed measured during a 15-foot timed walk, subjective exhaustion, and low levels of physical activity.[4] Those meeting three or more of five criteria were categorized as frail and those who had zero as nonfrail. Those meeting one or two of the criteria were deemed intermediate and were not included in the clinical study. Exclusion criteria included previously diagnosed Parkinson's disease, cerebrovascular accident with residual hemiparesis, symptomatic rheumatoid arthritis or any inflammatory condition requiring therapy with corticosteroids or immune-modulating agents, severe congestive heart failure, malignancy, or Folstein Mini-Mental State Examination score below 18/30. Subjects with these conditions were excluded to minimize the effect of one single, severe disease or disability driving the presence of frailty. Those who qualified came to the General Clinical Research Center at Johns Hopkins Bayview Medical Center for a detailed history and physical examination by a physician investigator to ensure that they met the inclusion criteria and did not have an acute viral illness.

Laboratory Studies

Serum IL-6 was measured in duplicate by enzyme-linked immunosorbent assay from frozen specimens, using a commercial kit (High Sensitivity Quantikine kit, R&D Systems, Minneapolis, MN); the average of the two measures was used in the analysis. The detectable limit for IL-6 was 0.015 pg/mL. Standard CBC was performed using a Coulter counter at Quest Laboratory.

Data Analyses

The findings are presented as mean ± standard deviation. Student *t* test was employed to determine the statistical significance of a difference between two means (*P*-value). Pearson correlation coefficient (*r*) was used for assessing the association between serum IL-6 and hemoglobin or hematocrit levels.

RESULTS

Characteristics of the Study Subjects

More than 200 community-dwelling older adults aged 74 and older were screened. Approximately 8% of those met the entry criteria, and 11 frail and 19 nonfrail subjects completed the study. The mean age was 84.9 ± 6.7 for the frail group (range 77–98) and 81.3 ± 4.1 for the nonfrail group (range 74–89). The mean age, race, and gender ratio are shown in Table 1.

Disease and Medication Status

The frail group, as expected, had an higher number of medical diagnoses than the nonfrail group (4.3 ± 1.9 vs 2.6 ± 1.1, $P = .006$). There was no difference between the two groups in the number of medications taken (4.6 ± 2.9 vs 4.1 ± 2.0). There was no difference between the frail and nonfrail groups in aspirin or nonsteroidal anti-inflammatory drug use (46% vs 47%). No subject in either group had any active inflammatory disease or history of inflammatory disease. The nonfrail group had a higher percentage of hypertension (58% vs 45%), previously diagnosed and reportedly cured cancer (10% vs 0%), and hyperlipidemia (21% vs 18%). The frail group had a higher percentage of hypothyroidism on treatment (45% vs 5%), diabetes mellitus (18% vs 0%), history of cerebrovascular accident without residual deficit (27% vs 5%), and osteoarthritis (36% vs 21%). Two frail subjects (18%) had previous diagnoses that are associated with potential gastrointestinal blood loss (peptic ulcer disease and diverticulosis), as did three nonfrail subjects (15%) (two with colonic polyps and one

Table 1. Characteristics of the Study Subjects, Serum IL-6 Level, and Selected Complete Blood Count Data

Characteristic	Frail (n = 11)	Nonfrail (n = 19)
Age, mean ± SD	84.9 ± 6.7	81.3 ± 4.1
Gender, male:female	2:9	5:14
Race	White	White
Total number of diagnoses per subject, mean ± SD*	4.3 ± 1.9	2.6 ± 1.1
Total number of medications per subject, mean ± SD	4.6 ± 2.9	4.1 ± 2.0
Serum interleukin-6, pg/ml, mean ± SD*	4.4 ± 2.9	2.8 ± 1.6
Hemoglobin, g/dL, mean ± SD†	12.1 ± 1.1	13.9 ± 1.0
Hematocrit, %, mean ± SD†	35.8 ± 3.1	40.6 ± 2.8
Mean corpuscular volume, fL, mean ± SD	91.5 ± 6.5	93.5 ± 5.3
Red blood cell distribution width, %, mean ± SD	13.3 ± 1.3	12.9 ± 0.7
White blood cell count, 10^3/cm, mean ± SD	6.8 ± 2.2	6.0 ± 1.3
Platelets, 10^3/cm, mean ± SD	252.5 ± 65.0	244.1 ± 67.2

*$P < .05$, †$P < .001$.
SD = standard deviation.

with gastritis). The two groups had similar percentages of osteoporosis (9% vs 11%).

Serum IL-6 and Complete Blood Counts

Frail subjects had significantly higher serum IL-6 than nonfrail subjects (4.4 ± 2.9 vs 2.8 ± 1.6 pg/mL, $P = .03$) (Table 1). They also had significantly lower hemoglobin and hematocrit than the nonfrail subjects (12.1 ± 1.1 vs 13.9 ± 1.0 g/dL, $P < .001$ and 35.8% ± 3.1 vs 40.6% ± 2.8, $P < .001$, respectively). No significant difference was detected in mean corpuscular volume, red blood cell distribution width between the two groups (91.5% ± 6.5% vs 90.0% ± 14.8%, $P = .384$ and 13.3% ± 1.3% vs 12.8% ± 1.0%, $P = .146$, respectively). Total white blood cell and platelet counts were slightly higher in the frail group than in the nonfrail group, although not statistically significantly (6.8 ± 2.2 vs 6.0 ± 1.3 10^3/mL, $P = .112$ and 252.5 ± 65.0 vs 224.4 ± 80.5 10^3/mL, $P = .167$, respectively).

Correlation Between Serum IL-6 Level and Hemoglobin or Hematocrit

To explore contributing factor(s) to the frailty-related lower hemoglobin concentrations, further analyses were performed on the relationship between serum IL-6 level and hemoglobin or hematocrit. Figure 1 demonstrates the inverse correlation observed between serum IL-6 level and hemoglobin ($r = -0.46$) in the frail group (solid line), but not in the nonfrail group (broken line) (Figure 1).

An inverse association was also observed between serum IL-6 and hematocrit in the frail group ($r = -0.48$) but not in the nonfrail group (data not shown).

DISCUSSION

In this pilot study, we identified elevated serum IL-6 and lower levels of hemoglobin and hematocrit as physiological correlates of frailty that warrant further exploration. Although several previous studies have established the predictive value of serum IL-6 for functional decline and mortality, none has demonstrated an association between elevated serum IL-6 and frailty. The serum IL-6 levels from this study are comparable with that reported by other studies.[6–8] The cutoff level of serum IL-6 for increased risk of disability and mortality in one study was 3.51 pg/mL, consistent with our findings of 4.4 pg/mL in the frail group.[8] The mean serum IL-6 level of nonfrail subjects was 2.8 pg/mL, slightly higher than that of subjects with low morbidity-disability previously reported (2.51 pg/mL or less).[8] Serum IL-6 levels are usually undetectable in younger subjects and increase with age.[9,12] Although the age difference between the frail and nonfrail subjects did not reach statistical significance, the older age of the frail participants may have influenced our findings.

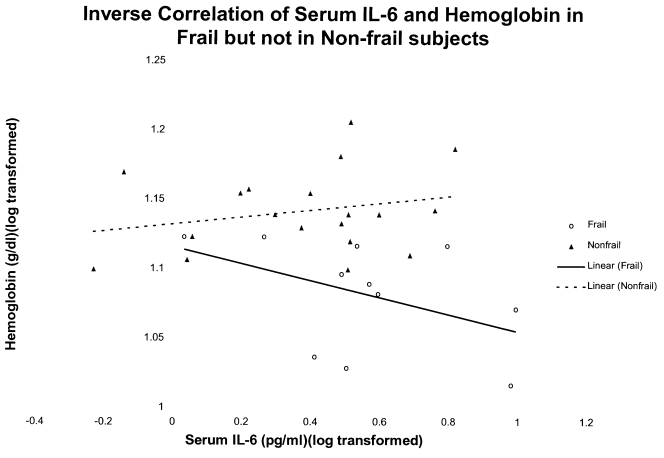

Figure 1. Correlation between serum interleukin (IL)-6 and hemoglobin in frail (n = 11) and nonfrail (n = 19) subjects using log transformed values. Pearson's correlation analysis demonstrated an inverse correlation between hemoglobin and serum IL-6 in frail ($r = -0.46$) but not in nonfrail ($r = 0.24$) subjects.

The frail group had more chronic diseases than the nonfrail group, which may have also influenced our findings of high serum IL-6 level. Several diseases common to older adults, including osteoporosis, Alzheimer's disease, and some malignant tumors, have been linked to increased levels of serum IL-6,[9] but the diagnosis of osteoporosis was equally distributed between the two study groups, and our extensive exclusion criteria helped to exclude apparent malignancies and advanced Alzheimer's disease, making it less likely that these conditions contributed to the elevated IL-6 observed in the frail subset. Alternatively, even though we carefully excluded all potential participants with known inflammatory conditions and viral or bacterial illness by using record review, history, and physical examinations, some subjects with immune-altering conditions may have inadvertently been enrolled into the study. It is also plausible that subclinical diseases not evident based on history and physical examination may trigger chronic inflammation and elevated IL-6. In fact, a recently published study demonstrated an association between subclinical cardiovascular disease and frailty as determined by the same screening criteria used in this study.[13]

We have also demonstrated lower levels of hemoglobin and hematocrit in the frail subjects than in the nonfrail subjects. The subclinical anemia identified in the frail group was normocytic with normal white blood cell and platelet counts, which makes it less likely to be due to iron, vitamin B_{12}, or folate deficiency or myelosuppression. Only two or three of the subjects in each group had diagnoses in their past medical history that might have contributed to anemia, including two with colonic polyps, one with diverticulosis, one with peptic ulcer disease and one with gastritis. Overall, the frail group had more medical diagnoses, which would give them the clinical diagnosis of anemia of chronic disease, the most common form of anemia in older adults.[10,14] There are many disease states that influence anemia through chronic inflammation. For example, increased production of proinflammatory cytokines clearly influences the development of cancer-related anemia.[15] Inflammation characterized by elevated IL-6, tumor necrosis factor-α, and IL-1β has been implicated in the pathogenesis of anemia in rheumatoid arthritis patients.[11]

The inverse correlation between serum IL-6 level and hemoglobin/hematocrit in the frail group but not in the nonfrail group (Figure 1) is intriguing and provides supportive evidence for the influence of chronic, low-grade inflammation as a contributing factor to decreased hemoglo-

bin in the frail group. The inhibitory effects on hematopoiesis from IL-6 and other proinflammatory cytokines have been well documented in in vivo and in vitro studies.[16–18] We have no clear explanation as to why a substantial subset of nonfrail participants has elevated serum IL-6 and normal hemoglobin. We could speculate that IL-6 elevation in the nonfrail group is from an acute rather than chronic elevation and that this proinflammatory cytokine has not yet influenced hematopoiesis. This finding, along with evidence linking serum IL-6 to functional decline and mortality, highlights the need for further studies of the patterns of IL-6 production and its regulation in older adults with and without specific acute or chronic disease. In addition, mechanisms of how chronic elevation of IL-6 modifies disease state and normal physiology in older adults remains to be investigated.

Consistent with our hypothesis, we have identified an association between frailty and elevated serum IL-6 and frailty and lower hemoglobin/hematocrit in this pilot study. We have also identified an inverse correlation between IL-6 and hemoglobin/hematocrit in the frail but not in the nonfrail group. We recognize that firm conclusions cannot be drawn from these data given the small number of participants and that large numbers of well-characterized subjects and more complex analyses involving modeling will be required to replicate and extend these findings. Nevertheless, these preliminary results provide rationale for further studies of chronic inflammation and hematopoiesis in the geriatric syndrome of frailty.

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