Inflammatory Markers and Physical Performance Among Nonagenarians

Kristina Tiainen,¹ Mikko Hurme,²,³ Antti Hervonen,¹ Tiina Luukkaala,¹,⁴ and Marja Jylhä¹

¹Tampere School of Public Health, University of Tampere, Finland.
²Microbiology and Immunology, University of Tampere Medical School, Finland.
³The Laboratory Centre, Tampere University Hospital, Finland.
⁴Science Center, Pirkanmaa Hospital District, Tampere, Finland.

Address correspondence to Kristina Tiainen, PhD, Tampere School of Public Health, University of Tampere, FI-33014 University of Tampere, Finland. Email: kristina.tiainen@uta.fi

Background. Recent studies have suggested that inflammation may play an important role in aging and the development of disabilities, but knowledge about its importance in the development of muscle weakness and functional disabilities in very old people is limited. This study examined associations between inflammatory markers and physical performance among nonagenarians.

Methods. The population-based sample consisted of 197 women and 65 men aged 90 years. Physical performance was assessed according to the Barthel Index, the chair stand, and handgrip strength. Plasma levels of interleukin-6 (IL-6), interleukin-1 receptor antagonist (IL-1Ra), and C-reactive protein (CRP) were determined.

Results. A gender-adjusted linear regression model showed that high levels of CRP, IL-6, and IL-1Ra were significantly associated with poor handgrip strength (p = 0.041, p = 0.023, p < 0.001, respectively). After adjustment for diseases, smoking and physical exercise high levels of IL-6 and IL-1Ra were still significantly associated with poor handgrip strength (p = 0.048, p = 0.004, respectively). In the gender-adjusted model, high levels of CRP, IL-6, and IL-1Ra were significantly associated with a worse Barthel Index (p = 0.009, p = 0.04, p = 0.004, respectively). High levels of CRP and IL-6 were still significantly associated with a worse Barthel Index after adjusted for diseases, smoking and physical exercise (p = 0.034, p = 0.041, respectively). In the chair stand, no significant association with inflammatory markers was found.

Conclusions. Associations between high levels of inflammatory markers and worse handgrip strength as well as a worse Barthel Index result were evident among nonagenarians. However, the association with the chair stand was not significant.

Key Words: Inflammation—Aging—Oldest old—Disability—Muscle strength.

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FUNCTIONAL limitations and disabilities increase with aging. Poor muscle strength is a risk factor for disability, morbidity, and mortality in older people. Several studies have shown that muscle weakness is associated with an increased risk of disability, particularly among the older people (1,2). However, decreased muscle strength does not fully explain the presence of functional disabilities.

Aging is associated with a chronic low-grade inflammation and increased production of inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1 receptor antagonist (IL-1Ra), and acute-phase proteins, such as C-reactive protein (CRP) (3,4). In a normal situation among healthy individuals, IL-6 is tightly regulated and expressed at a low level. IL-6 is an important factor in acute-phase inflammatory response, and its levels increase during infection, trauma, or other stress (5). IL-6 regulates the secretion of CRP and thus an elevated CRP level is often due to increased IL-6 activity (5). CRP is a sensitive marker of inflammation and increases rapidly in many pathological conditions. IL-1Ra is part of the IL-1 gene family, which also consists of IL-1α and IL-1β proteins. The IL-1 family plays an important role in the innate immune system (6–9).

The serum/plasma level of inflammatory markers including IL-6, IL-1Ra, and CRP tend to increase with normal aging (10–12). The resulting increase may steam at least partly, from a decline in sex steroids and higher morbidity (4,13). It is also possible that increased inflammation is a secondary phenomenon, that is, due to defective antigen elimination caused by the aging-associated decline in the adaptive immunity (immunosenescence). CRP and IL-6 are cardiovascular risk markers (14,15) and predict cardiovascular mortality, morbidity, and disability (4,16–20). In addition, IL-1Ra has been shown to be a strong predictor of mortality among men and women aged 90 years (18).
The causal pathway from inflammation to functional limitation and disability is not fully understood, but it has been suggested that inflammatory markers may cause a decline in physical functioning through their catabolic effects on muscle (21). Knowledge about the association between inflammation and physical performance among nonagenarians is limited. Earlier studies, among people aged 80 years and younger, have suggested that high levels of IL-6 and CRP are associated with poor muscle strength and muscle mass, and they are also risk factors with regard to the development of functional limitations and disabilities (21–28). However, there are also longitudinal studies in which higher levels of IL-6 and CRP did not predict changes in functional performance after follow-up among 70- to 79-year-old men and women (29). High levels of IL-1Ra were also shown to be associated with poor physical performance among men and women aged 65 years and older (30).

The purpose of this study was to examine the association between inflammatory markers (IL-6, IL-1Ra, and CRP), and physical performance (handgrip strength, chair stand, and Barthel index) among men and women aged 90 years. Based on the earlier results with younger age groups, we hypothesized that participants with higher blood levels of inflammatory markers would have a lower level of physical performance.

**METHODS**

**Participants**

This study is part of the Vitality 90+ Study, a prospective, multidisciplinary population-based study of people aged 90 years or older in Tampere, Finland (12, 18, 31). In the present study, the population consisted of all people born from 1909 to 1910 and living in the city of Tampere in the year 2000 (n = 535). Both community-dwelling and institutionalized persons were invited to participate. Reasons for nonparticipation included death between sampling and data collection (n = 108) as well as unwillingness to participate, mostly due to poor physical or mental condition (n = 86).

During home visits, participants were interviewed, blood tests were taken, and physical performance measurements were carried out. Seven persons could not be reached. Another 45 persons refused blood tests and took part only in the interviews. Subsequently, the sample size was 289 (66% of the eligible population). Most of the participants (240, 84%) lived in the community; 45 (16%) lived in institutions. In the present study, participants who had at least one result from a physical performance measurement (handgrip strength, chair stand, or the Barthel Index) and at least one inflammatory marker measurement (IL-6, IL-1Ra, or CRP) were included. The final sample (n = 262) consisted of 65 men and 197 women. The Vitality 90+ Study design was approved by the local ethics committee, and all participants gave their written informed consent.

**Measurements**

**Physical performance measurements.**—Maximal isometric handgrip strength in kilograms was measured with a handheld dynamometer (The Martin Vigorimeter, Gebrüder Martin, Tuttlingen, Germany) with the elbow flexed at 90°. The participants were allowed to familiarize themselves with the method by doing two to three submaximal trials. Three maximal efforts with each hand were then conducted. For each participant, the best performance with the highest value was accepted as the result. In the chair stand test, the participants were asked to stand up and sit down five times as fast as possible from a normal seat, without help and with arms folded across the chest (32). Timing was started with the participant in the sitting position and ended at the final standing position at the end of the fifth stand. The elapsed time was recorded with a stopwatch in seconds. Before the test, each participant was asked to rise one time from the chair to make sure that performance of the task would be safe and possible without help. The individual’s ability to deal with activities required for daily living such as mobility demands, transfers, bathing, dressing, feeding, toilet use, and bowel and bladder care was evaluated through the use of 10-item Barthel Index (33, 34). At first, each task was scored individually (0–10) and then totally (0–100). A total score of 100 indicates maximum independence and a score of 0 reflects total dependence.

**Biochemical measurements.**—Blood samples were obtained in the morning after an overnight fast using EDTA tubes in ice. After separation of plasma by low-speed centrifugation (15 minutes at 700g), the plasma was divided into aliquots and stored at −80°C until analyzed. Concentrations of IL-6 and IL-1Ra were determined using commercially available enzyme-linked immunosorbent assay kits (Pelikine Compact human IL-6 ELISA kit; CLB, Amsterdam, The Netherlands for IL-6 and Quantikine; R&D Systems, Minneapolis, MN for IL-1Ra). The optical density of individual wells was determined with a Multiscan Biochromatic 348 (Labsystems, Helsinki, Finland) spectrophotometer. High-sensitivity CRP concentration was analyzed using a Cobas Integra 700 automatic analyzer with reagents and calibrators as recommended by the manufacturer (Hoffmann-La Roche Ltd, Basel, Switzerland; COBAS Integra C-Reactive Protein, Latex).

**Covariants.**—Regression analyses were adjusted for (i) sex, (ii) then also for diseases, and (iii) then also for smoking and physical exercise. Diseases were indicated by medical diagnoses collected from records maintained by public health care physicians and included diagnoses made in hospitals. Diseases were categorized as follows: infectious diseases, cancer, diabetes, and heart conditions. Smoking status was dichotomized into groups of (i) current or former and (ii) never-smokers. Physical exercise was categorized as (i) every day and (ii) less than every day. Information about smoking and physical exercise was collected by interview.
Differences between men and women were analyzed using the Mann–Whitney’s U test or the independent samples t test. Spearman’s correlation tests were used to evaluate the correlations between inflammatory markers and physical performance. Linear regression analysis was performed separately for each measurement of physical performance in order to evaluate their associations with inflammatory markers. First, gender-adjusted linear regression models were calculated (Model 1). Then, analyses were adjusted also for diseases (Model 2) and, finally, also for smoking and physical exercise (Model 3). Because the variables were not normally distributed, the linear regression analyses were performed on their transformed values. Transformations were performed as follows: handgrip strength = −1 (handgrip strength), chair stand = LG10 (chair stand), Barthel Index = LG10 (100 – Barthel Index), CRP, IL-6, and IL-1Ra = 1/(1 + variable).

Statistical analyses were performed by the SPSS program, version 15. The level of statistical significance was set at $p < .05$.

**Statistical Methods**

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Statistical analyses were performed by the SPSS program, version 15. The level of statistical significance was set at $p < .05$.

**Results**

The characteristics of the participants are shown in Table 1. Among women, CRP, IL-6, and IL-1Ra correlated significantly with handgrip strength ($r = −.203$, $r = −.175$, $r = −.280$, respectively) and also with the Barthel Index ($r = −.188$, $r = −.207$, $r = −.183$, respectively). Among men, a statistically significant correlation was seen only between the Barthel Index and CRP ($r = −.327$). The correlations between chair stand time and inflammatory markers were very low and nonsignificant for both genders (Table 2).

**Handgrip Strength**

The gender-adjusted linear regression analysis (Table 3, Model 1) showed that high levels of CRP, IL-6, and IL-1Ra were significantly associated with poor handgrip strength ($p = .041$, $p = .023$, $p < .001$, respectively). When the linear regression models were also adjusted for diseases (Model 2), high levels of IL-6 and IL-1Ra were still associated significantly with poor handgrip strength ($p = .025$, $p = .002$, respectively) and the associations were maintained in the final model (Model 3), where all smoking and physical exercise were included ($p = .048$, $p = .004$, respectively). The association between CRP and handgrip strength was no longer significant after adjusted for diseases (Model 2) and smoking and physical exercise (Model 3).

**Barthel Index**

Adjusted for gender, high levels of CRP, IL-6, and IL-1Ra were significantly associated with a worse Barthel
Index ($p = .009$, $p = .004$, $p = .004$, respectively; Table 3, Model 1). The associations were still significant when adjusted for diseases (Model 2). In the model where smoking and physical exercise were also included (Table 3, Model 3), high levels of CRP and IL-6 were still associated with a worse Barthel Index. In men, no significant association with inflammatory markers was found. In gender-specific regression models, heart conditions and lower physical exercise and smoking in men and heart conditions and lower physical exercise in women were significantly associated with a worse handgrip strength. Lower physical exercise was significantly associated with a worse Barthel Index in men and women. Lower physical exercise was also associated with poor chair stand test in women (data were not shown).

**Discussion**

In the present study, we investigated the association between inflammatory markers and physical performance among 90-year-old men and women. Although the recent studies have suggested that inflammation may play an important role in the process of aging and in the development of disabilities, the knowledge about the role of inflammation in the development of muscle weakness and functional disabilities among nonagenarians is limited. Our results showed that high levels of CRP, IL-6, and IL-1Ra were significantly associated with a worse handgrip strength and with a worse Barthel Index, respectively. The associations were still significant between high level of IL-6 and a worse Barthel Index when adjusted for diseases (Model 2). In the model where smoking and physical exercise were also included (Model 3), high levels of CRP and IL-6 were associated with a worse Barthel Index. In women, high levels of CRP, IL-6, and IL-1Ra were significantly associated with a worse handgrip strength and with a worse Barthel Index, respectively. The associations were still significant between high level of IL-6 and a worse Barthel Index when adjusted for diseases (Model 2). In the model where smoking and physical exercise were also included (Model 3), high levels of CRP and IL-6 were associated with a worse Barthel Index.

Because the correlations between inflammatory markers and physical performance were different for men and women, the linear regression models were also calculated separately for each gender. In women, high levels of CRP, IL-6, and IL-1Ra were significantly associated with a worse handgrip strength and with a worse Barthel Index, respectively. The associations were still significant between high level of IL-6 and a worse Barthel Index when adjusted for diseases (Model 2). In the model where smoking and physical exercise were also included (Model 3), high levels of CRP and IL-6 were associated with a worse Barthel Index. In men, no significant association with inflammatory markers was found. In gender-specific regression models, heart conditions and lower physical exercise and smoking in men and heart conditions and lower physical exercise in women were significantly associated with a worse handgrip strength.

**Chair Stand**

In the chair stand test, no significant association with inflammatory markers were found (Table 3).

Gender showed a significant association with handgrip strength in all three models but not with chair stand test. In part of the analysis of the Barthel Index, gender had significant effect. The effect of diseases was statistically nonsignificant. Smoking had a significant association only with handgrip strength. Low physical exercise was significantly associated with all physical performance variables.

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**Table 2. Spearman’s Correlations Between Inflammatory Markers and Physical Performance Among 90-Year-Old Men and Women**

<table>
<thead>
<tr>
<th>Inflammatory Markers</th>
<th>CRP</th>
<th>IL-6</th>
<th>IL-1Ra</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Handgrip strength</td>
<td>.019</td>
<td>-.203</td>
<td>.003</td>
</tr>
<tr>
<td></td>
<td>-.091</td>
<td>.081</td>
<td>.045</td>
</tr>
<tr>
<td></td>
<td>-.327</td>
<td>-.188</td>
<td>.024</td>
</tr>
<tr>
<td>Chair stand</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barthel Index</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: CRP = C-reactive protein; IL-6 = interleukin-6; IL-1Ra = interleukin-1 receptor antagonist.

$p < .05$, $\dagger p < .01$.

**Table 3. Associations Between Inflammatory Markers and Physical Performance**

<table>
<thead>
<tr>
<th></th>
<th>Model 1 (adjusted for gender)</th>
<th>Model 2 (adjusted for gender and diseases)</th>
<th>Model 3 (adjusted for gender, diseases, smoking and physical exercise)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$</td>
<td>$p$</td>
<td>$\beta$</td>
</tr>
<tr>
<td>Handgrip</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>−.113</td>
<td>.041</td>
<td>−.113</td>
</tr>
<tr>
<td>IL-6</td>
<td>−.125</td>
<td>.023</td>
<td>−.131</td>
</tr>
<tr>
<td>IL-1Ra</td>
<td>−.195</td>
<td>&lt;.001</td>
<td>−.182</td>
</tr>
<tr>
<td>Barthel Index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>−.214</td>
<td>.009</td>
<td>−.172</td>
</tr>
<tr>
<td>IL-6</td>
<td>−.230</td>
<td>.004</td>
<td>−.228</td>
</tr>
<tr>
<td>IL-1Ra</td>
<td>−.234</td>
<td>.004</td>
<td>−.193</td>
</tr>
<tr>
<td>Chair stand</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>−.022</td>
<td>.769</td>
<td>.028</td>
</tr>
<tr>
<td>IL-6</td>
<td>−.027</td>
<td>.714</td>
<td>−.062</td>
</tr>
<tr>
<td>IL-1Ra</td>
<td>.045</td>
<td>.546</td>
<td>.034</td>
</tr>
</tbody>
</table>

Notes: Results of the linear regression analyses are shown by standardized betas with $p$ values. Models were performed separately for each measure of physical performance (handgrip strength, Barthel Index, and chair stand). CRP = C-reactive protein; IL-6 = interleukin-6; IL-1Ra = interleukin-1 receptor antagonist.
significant when the model was adjusted also for diseases and smoking and physical exercise. In the Barthel Index, the association between IL-1Ra was no longer significant when adjusted for also smoking and physical exercise.

Our results are in line with the earlier studies among younger age group (23,25,30). In the study by Cesari and colleagues (30) among men and women aged from 65 to 102 years, lower handgrip strength was associated with higher levels of CRP and IL-6. However, they did not find association with handgrip strength and IL-1Ra. Also Brinkley and colleagues (23) showed that higher levels of CRP and IL-6 were associated with lower handgrip strength and poorer physical function among men and women older than 55 years. In the study by Visser and colleagues (25), higher level of IL-6 was associated with lower muscle strength in well-functioning men and women aged 70–79 years. We used the Barthel Index to measure how well he or she could deal with mobility demands, transfers, bathing, dressing, feeding, toilet use, and bowel and bladder care (33,34). Earlier studies (23,30) with younger–older people have also shown the association between high levels of CRP and poor physical function.

In our study, we did not find any association between inflammatory markers and chair stand results. This is in line with the study carried out by Taaffe and colleagues (29) who found that, among 70- to 79-year-old men and women, the levels of IL-6 and CRP were not associated with their ability to rise from a chair. However, recent studies have also shown that elevated CRP levels are associated with requiring a longer time to complete five chair raises among 65-year-and-older old men and women (23,35). A comparison of the results is difficult because of the differences in the age. At least in very old age, the ability to rise from a chair and the time it takes is likely depend on several other factors than only muscle strength, such as balance, function of the joints, and also the cognitive status.

An earlier study of the present sample showed that IL-1Ra is a significant predictor of mortality (18). IL-1Ra and the balance between IL-1 and IL-1Ra play an important role in the complex inflammatory processes (9). At this stage, we do not know the exact mechanisms that cause the associations of IL-1Ra with strength and mortality in the oldest old. CRP and IL-6 are cardiovascular risk markers (14,15), and predict cardiovascular mortality, morbidity, and disability (4,16–20). Higher levels of IL-6 and CRP are associated with lower muscle strength but they also increased risk of further muscle strength loss (27) and in that way may increase risk of functional limitations and disability.

Explanations for the associations of the inflammation and functional limitation are still unclear. Several studies have shown that elevated levels that exist between inflammatory markers are associated with many different diseases (5,15,36). It is unclear whether the elevated levels of inflammatory markers are results of chronic diseases or markers of chronic diseases that have an effect on functional performance or if inflammatory markers have their own effect upon the aging process. It is possible that elevated inflammation levels might not be a necessary consequence of aging but could be due to the increased number and accumulated effects of diseases (3). Chronic diseases have long-term effects on one’s ability to manage the everyday life and thus causing functional disabilities. Inflammatory biomarkers have catabolic effects on muscle, and via that pathway, they may cause a decline in physical functioning (21), which can again decrease muscle strength. It could also be that inflammatory markers are not only risk factors for the age-related diseases but also the link between lifestyle factors, infectious diseases, and physiological changes during the aging process (4).

Our study is one of only a few studies to investigate the relation of inflammation to physical functioning among very old people. The advantage of our study is that it is a population-based sample including both home-dwelling and institutionalized people whose functional ability varied from well functioning to a high disability and dependence. The limitation of the study, however, is that because of its cross-sectional character, we have not been able to determine the causal directions of the observed association between inflammatory markers and physical function.

In summary, we found significant associations between IL-6, IL-1Ra, and CRP and poor handgrip strength and between IL-6, IL-1Ra, and CRP and worse Barthel Index scores among the nonagenarians included in our study. The association between inflammatory markers and the chair stand results was not significant. Our findings suggest that in nonagenarians, the association of inflammatory biomarkers with physical performance is evident. However, the association may not be as strong as in younger age groups. To better understand the effects of bioinflammatory markers on physical performance in the oldest old and to prevent functional disability, more studies, especially longitudinal studies, will be needed.

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