High-sensitivity C-reactive protein and mobility disability in older adults

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Abstract

Objective: to determine the association of high sensitivity C-reactive protein (HsCRP) levels with a risk of mobility disability and decline in older adults with and without vascular disease.
Design: prospective cohort.
Setting: community-residing population.
Subjects: six hundred and twenty-four adults age 70 and older (62% women) with gait and HsCRP assessments.
Main outcome measures: incident mobility disability (velocity <70 cm/s) and annual rates of decline on gait velocity.
Results: elevated HsCRP levels (≥3 mg/l) at baseline present in 224 of the 624 eligible subjects was associated with a faster annual decline in gait velocity of 0.91 cm/s (P = 0.02). Subjects with elevated HsCRP levels had increased risk of mobility disability (hazard ratio: 1.85, 95% CI: 1.09–3.14). Each one-unit increase in log HsCRP levels in the 406 subjects without prevalent mobility disability was associated with increased risk of mobility disability (hazard ratio: 1.33, 95% CI: 1.05–1.68). The association of baseline HsCRP levels with mobility disability and decline was stronger in the 224 individuals without vascular disease. The associations were not significant in the 400 subjects with vascular disease.
Conclusions: HsCRP levels predict mobility disability and accelerated decline in walking speed in older adults. These associations were stronger in those without vascular disease.

Keywords: cohort study, epidemiology, gait, inflammation, elderly

Introduction

Given the growing public health challenge of mobility limitations and disability in rapidly ageing populations [1], identifying seniors at a high risk for mobility decline is vital. Ageing is associated with increased inflammatory activity [2]. C-reactive protein (CRP) is an acute phase protein that is considered a general inflammatory biomarker [3]. While the exact biological actions of CRP are not established [4], it predicts risk of vascular diseases [5]. Vascular diseases are also implicated in the pathogenesis of mobility disability [6, 7]. We examined association of CRP [using a high sensitivity assay—high sensitivity C-reactive protein (HsCRP)] with incident mobility disability and gait decline in community residing seniors. Gait velocity is a good proxy for mobility, and is recommended as a functional screen in seniors [8, 9]. Since inflammation may increase risk of adverse outcomes independent of vascular mechanisms [10], we also conducted stratified analysis in individuals with and without vascular disease.

Methods

Study population

We conducted a secondary analysis in the Einstein Aging Study (EAS) [1]. The primary aim of the EAS is to identify risk factors for dementia. Study design has been reported [1, 11]. In brief, potential subjects’ ages 70 and above identified from Bronx County population lists were contacted by letter explaining the study, and then by telephone. The telephone interview included a verbal consent and a cognitive screener [12]. Exclusion criteria included severe auditory-visual loss, bed bound and institutionalisation. Potential subjects were invited for further in-person evaluations. Informed consent was obtained at enrolment.
according to protocols approved by the local institutional review board. Subjects returned annually for clinical assessments.

The study period was from February 2002 when we started measuring gait in the EAS [11] to September 2010. Of the 1,120 EAS subjects evaluated during this period, 638 had HsCRP and gait assessments. We excluded 14 subjects with prevalent dementia leaving 624 non-demented subjects with biomarker and gait data. Eligible subjects were more educated (14.0 versus 13.5 years, \( P < 0.05 \)) but similar in terms of sex and age to excluded subjects.

**Gait**

Subjects walked on an instrumented walkway (GAITRite, CIR systems, Havertown, PA, USA) in a quiet well-lit room wearing comfortable footwear. This system has excellent validity and reliability [11, 13]. The software computes velocity based on footfalls recorded on the walkway [14]. Until July 2008, subjects walked for two trials on a walkway with 15-foot recording surface. Thereafter, one trial was done on a walkway with 20-foot recording surface. Start and stop points were marked on the floor, and included three feet (four feet for longer walkway) from edge of recording surface to account for initial acceleration and terminal deceleration [13]. Correlation for gait velocity on the two walkways in 20 subjects was excellent (Pearson, \( r = 0.94 \)). Gait velocity is highly reliable in our cohort for walking trials done on the same walkway back to back (Pearson, \( r = 0.96 \)) or after few hours delay (ICC: 0.96) [15].

**Laboratory tests**

Serum levels of HsCRP were determined from frozen fasting blood samples using the CRP Ultra Wide Range Reagent Kit (Equal Diagnostics, Inc., Exton, PA, USA), a latex-enhanced turbidimetric immunoassay. The minimum detectable HsCRP level is 0.05 mg/l. Inter-assay coefficient of variations (CV) is <6%. Total cholesterol is measured in saponified serum by the cholesterol dehydrogenase method. Inter-assay CVs are <3%.

**Covariates**

The presence or absence of vascular diseases (any of the following: diabetes, heart failure, hypertension, angina, myocardial infarction or strokes) and other chronic illnesses (depression, Parkinson’s disease, chronic bronchitis or arthritis) was used to calculate a summary illness index (range 0–10). Medication use was recorded. The Blessed-Information-Memory-Concentration test (range from 0 to 33, higher worse) assesses orientation, recent and remote memory, and concentration to identify cognitive impairment and estimate its severity [16]. The Blessed test has been validated against other mental status tests and correlates highly with dementia pathology [17, 18].

**Data analysis**

HsCRP distribution was skewed, and was log-transformed for analyses. Mobility disability was defined using a recommended gait velocity cutscore of \( \leq 70 \text{ cm/s} \) [8]. Hazard ratios (HRs) with 95% confidence intervals (CIs) for developing mobility disability based on baseline HsCRP levels were computed using Cox proportional hazards models [19]. HsCRP was examined continuously (per one-log unit increase) and categorically (elevated versus rest). Elevated HsCRP levels were defined as \( \geq 3 \text{ mg/l} \), a recommended cardiovascular risk cutscore [3, 10]. All analyses were adjusted for age, sex, education, illness index, Blessed scores, total cholesterol, low physical activity, previous fall and medications that might influence inflammation (statins, prednisone, non-steroidal anti-inflammatory drugs or oestrogens) [6]. Time to event was from baseline to incident mobility disability or final contact, whichever came first. This analysis was repeated in individuals with and without vascular disease. Proportional hazards assumptions of models were examined and adequately met [19].

To determine association of log HsCRP with gait decline (cm/s/year), linear mixed effects models [20] controlled for confounders were applied to 624 eligible subjects as well as in individuals with and without vascular disease. All analyses were performed using SAS 9.2 (SAS Institute, Inc, Cary, NC, USA).

**Results**

Table 1 shows baseline characteristics of the cohort and comparisons by HsCRP status (elevated versus rest). The median follow-up was 2.0 years (1,227 person years). The mean annual follow-up visits were 2.1. The median baseline HsCRP level was 3.7 mg/l. There were 224 subjects with ‘elevated’ HsCRP levels (median 5.5 mg/l, IQR 4.1–9.4) and 400 with ‘low’ levels (median 1.1 mg/l, IQR 0.6–1.9). Participants with elevated HsCRP levels walked slower, used more medications, had higher illnesses burden, worse Blessed test scores and higher cholesterol levels than remaining subjects (Table 1).

**Mobility disability**

There were 95 prevalent mobility disability cases and 123 without follow-up leaving 406 eligible subjects with follow-up. Each one-log unit increase in HsCRP levels increased risk of mobility disability (HR: 1.33, 95% CI: 1.05–1.68). Elevated HsCRP levels were also associated with mobility disability (HR versus rest 1.85, 95% CI: 1.09–3.14).

Table 2 shows that HsCRP was a significant predictor of incident mobility disability in 119 individuals without vascular disease (HR: 2.02, 95% CI: 1.08–3.80), but not in 287 with vascular disease (HR: 1.20, 95% CI: 0.91–1.57). A similar pattern was seen for elevated HsCRP levels in the ‘no vascular disease’ (HR: 5.56, 95% CI: 1.51–20.47) and ‘vascular disease’ subgroups (HR: 1.38, 95% CI: 0.76–2.52).
The annual rate of gait velocity decline was 2.76 cm/s/year. Baseline HsCRP predicted gait decline when examined as a categorical (elevated versus rest estimate — 0.89 cm/s/year, 95% CI: −1.69 to −0.10, P = 0.03) but not as a continuous variable (per one-log unit increase −0.26 cm/s/year, 95% CI: −0.59 to −0.07, P = 0.12). HsCRP predicted gait decline in the 224 subjects without vascular disease both as a continuous variable (−0.55 cm/s/year, 95% CI: −1.16 to 0.07, P = 0.08) and categorically (−2.46 cm/s/year, 95% CI: −4.10 to −0.82, P = 0.004). The association of HsCRP with gait decline was not significant in 400 subjects with vascular disease. See Supplementary data available in Age and Ageing online, Appendix 1.

### Discussion

In this well characterised community-dwelling elderly cohort, elevated HsCRP levels predicted risk of mobility disability and mobility decline. Each one-unit increase in baseline log HsCRP (1.7 times increase in untransformed HsCRP levels) was associated with a 33% increased risk of developing mobility disability even after accounting for several confounders. Subjects with elevated HsCRP levels (≥3 mg/l) had an 85% increased risk of developing mobility disability as well as a 0.89 cm/s per year faster decline in gait velocity compared with the remaining subjects. Our findings are supported by some but not all studies. Elevated CRP predicted self-reported mobility loss in the Health ABC cohort [21]. CRP levels were associated with walking speed at cross-section but not longitudinal decline in another cohort [22]. However, the prospective analysis included only those participants who completed 7-year follow-up. High CRP levels were not associated at cross-section with a composite measure that included walking

Table 2. Association between baseline HsCRP levels and risk of incident mobility disability (gait velocity <70 cm/s) in subjects without prevalent mobility disability at study entry

<table>
<thead>
<tr>
<th>Sample</th>
<th>n</th>
<th>Incident cases</th>
<th>HsCRP level</th>
<th>Elevated versus low HsCRP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adjusted HR (CI), P-value</td>
<td>Adjusted HR (CI), P-value</td>
</tr>
<tr>
<td>Overall</td>
<td>406</td>
<td>62</td>
<td>1.32 (1.05–1.67), 0.02</td>
<td>1.86 (1.10–3.14), 0.02</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>287</td>
<td>47</td>
<td>1.18 (0.90–1.54), 0.31</td>
<td></td>
</tr>
<tr>
<td>No vascular disease</td>
<td>119</td>
<td>15</td>
<td>2.06 (1.10–3.88), 0.007</td>
<td></td>
</tr>
</tbody>
</table>

Hazard ratios with P-values obtained by Cox survival analysis adjusted for age, sex, education, Blessed test score, medical illness, serum cholesterol levels, low physical activity, falls and medications (see section ‘Methods’).

Elevated HsCRP defined as values of 3 mg/l or higher. Low HsCRP includes remaining subjects.

*Per one-unit (mg/l) increase in baseline log HsCRP levels.
High sensitivity C-reactive protein levels predict mobility loss in seniors without vascular disease supports involvement of non-vascular pathways. Consistent relationships of CRP with walking speed were reported in individuals with chronic bronchitis, cardiac failure or disability [24]. Elevated CRP levels have been associated with incident mobility limitations in subjects with and without diabetes [25] and even when prevalent or incident cardiovascular diseases were excluded [21]. Elevated CRP levels may also be a non-specific acute phase reactant [4] or act as a marker of biological ageing [3, 26, 27]. The latter hypothesis is supported by the association of HsCRP with gait velocity, another marker of biological ageing [8, 28].

Limitations
Medical illnesses, including vascular diseases, were based on self-report. The HsCRP levels are specific to our cohort but ranges provided should facilitate comparisons. The results were not materially different (data not shown) when the analyses were repeated using the highest HsCRP tertile (≥3.37 mg/l) to define elevated levels [5, 10].

In conclusion, HsCRP levels predict risk of mobility disability and gait decline in community-residing older adults especially those without vascular disease. If our findings are corroborated, HsCRP levels could help improve current mobility and disability risk assessments in clinical practice.

Key points
- High sensitivity C-reactive protein levels predict mobility disability and decline in walking speed in community-residing older adults.
- High sensitivity C-reactive protein levels predict mobility disability stronger in older adults without vascular disease.
- High sensitivity C-reactive protein may be a marker of biological ageing.

Conflicts of interest
No conflict of interests to declare for Drs Verghese, Holtzer and Wang. Dr Lipton has provided consultancy services to many pharmaceutical companies such as Bristol Meyers Squibb, GlaxoSmithKline and Novartis. However, none of these services was related to the current investigation.

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Supplementary data
Supplementary data mentioned in the text is available to subscribers in Age and Ageing online.

References
Dyspnoea and mortality in older people in the community: a 10-year follow-up

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Abstract

Background: examine baseline dyspnoea and subsequent 10-year mortality adjusting for age and gender and determine whether dyspnoea is related to early or late mortality or both. Examine the relationship between dyspnoea and mortality adjusting for confounding effects of underlying diseases.

Methods: we sent modified Medical Research Council (MRC) dyspnoea questionnaire to identify breathlessness in 1,404 randomly selected subjects from general practitioner lists of 5,002 subjects aged 70 years and over living in the community. A further random sample of 500 subjects underwent clinical assessment including pulmonary function tests, electrocardiography and echocardiography. Subjects were followed up for 10 years and all deaths were recorded, using general practitioner records and the local death registry.

Results: prevalence of dyspnoea was 32.3%. Breathlessness was associated with early or late mortality. At 2 years 10.1% breathless subjects died compared with 3.4% non-breathless (P = 0.02). At 10 years 63.3% breathless had died compared with 40.5% non-breathless (P = 0.0001). Increasing grade of MRC dyspnoea was associated with 10 mortality. Advancing age (OR: 2.27), male gender (OR: 1.95), breathlessness (OR: 2.53), left ventricular dysfunction (OR: 5.01) and chronic airways disease (OR: 3.04) were all significantly associated with 10-year mortality. After adjustment of age, gender and underlying diseases breathlessness was associated with 10-year mortality (P = 0.02).