Serum C-Reactive Protein Even at Very Low (<1.0 mg/l) Concentration Is Associated with Physical Performance in a Community-Based Elderly Population Aged 70 Years and Over

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Key Words

Physical performance · Inflammation · High-sensitivity C-reactive protein

Abstract

Background: Although several studies have reported that C-reactive protein (CRP) is associated with physical performance, few studies have evaluated the relationships between CRP and physical performance among subjects who had a very low range of CRP. Therefore, it is still unclear whether a lower CRP is favorably associated with physical performance even within a very low range. **Objective:** The aim of this study was to investigate the relationships between CRP and physical performance among a Japanese population with a low serum CRP concentration (CRP <1.0 mg/l). **Methods:** We designed a cross-sectional survey for 775 persons aged 70 years and older living in Japan. High-sensitivity CRP was measured using a nephelometric method. The subjects whose serum CRP concentrations were higher than 10.0 mg/l were excluded. Physical performance was assessed using a 10-meter maximum walk test, leg ex-

tension power, and a timed 'up and go' test. **Results:** The median value (interquartile range) of CRP was 0.55 (0.29–1.20) mg/l. After adjustment for potential confounding factors, an inverse relation of CRP with the 10-meter maximum walk test and leg power was observed in all subjects (*p* for trend = 0.10 and 0.04, respectively). For subjects who had a CRP <1.0 mg/l, these inverse relations were unchanged (*p* for trend = 0.03 and 0.02, respectively). **Conclusions:** Serum CRP concentration is favorably related to physical performance, even within a very low range in a community-based elderly population aged 70 years and over. The findings suggest that maintaining as low CRP levels as possible may potentially maintain better physical performance.

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Introduction

Aging is associated with decreased skeletal muscle mass, quality and function [1–4] that negatively impact quality of life and may eventually compromise independence [5, 6]. An accelerated decline in muscle mass and

strength with aging is probably one of the major causes of disability in late life [7, 8].

A chronic inflammatory state has been proposed that may be detrimental by accelerating the progression of medical conditions that result in functional decline and disability [9, 10]. Furthermore, a direct role of inflammation in the development of disability can be hypothesized based on the catabolic effects that proinflammatory cytokines may have on muscles [11]. A biological mechanism recently proposed to underlie the decline in physical function is chronic inflammation [9, 12]. Therefore, relatively high-inflammatory levels have been hypothesized to play a role in the reduction of skeletal muscle mass and physical function among the elderly.

C-reactive protein (CRP) is a classical acute-phase marker and a member of the pentraxin family of innate immune response proteins [13]. The concentration of CRP in serum is generally <2 mg/l but increases by as much as 1,000-fold in response to stimuli such as tissue injury or inflammation [14]. Following removal of the inflammatory stimulus, CRP levels decline rapidly. These features have made CRP useful as a clinical marker of an inflammatory process. Recent studies have particularly focused on CRP as measured by a high sensitivity assay (hsCRP) [15]. High-sensitivity CRP detects the same CRP molecule as older CRP tests, but its lower limit of detection is substantially lower and it can therefore detect lower levels of inflammation [15].

Several epidemiological studies assessed the relationship between CRP and physical performance in an elderly population [9, 16–19]. Although these observational studies have demonstrated that there is an inverse association of serum CRP concentrations with physical performance, the serum CRP concentration in these studies was higher than it is in the Japanese [20–25]. Our previous study showed that a higher consumption of fish may be contributing to the lower serum CRP concentrations among the older Japanese population [26]. Moreover, although the CRP concentrations of <1.0 , 1.0 – 3.0 and >3.0 mg/l have been associated with low, intermediate and high risk, respectively, for coronary heart disease (CHD) [27], serum CRP concentration may be positively associated with a preclinical inflammation status even within a very low range. However, few studies have reported the relationship between a very low range of serum CRP concentration and physical performance. Therefore, it is still unclear whether the serum CRP concentration is associated with physical performance even within a very low range.

Thus, to investigate whether lower serum CRP relates to a favorable physical performance even at concentrations <1.0 mg/l, we designed a cross-sectional study in a Japanese elderly population.

Subjects and Methods

Study Participants

Our study population was composed of subjects aged 70 years and older who were living in the Tsurugaya area of Sendai, one of the major cities in the Tohoku area of Northern Japan. At the time of the study in 2002, there were 2,730 individuals aged 70 years and older living in Tsurugaya. All of these individuals were invited to participate in a comprehensive geriatric assessment, which included medical status, physical function, cognitive function and dental status and 1,178 of them accepted, giving their informed consent for data analysis. The protocol of this study was approved by the Institutional Review Board of the Tohoku University Graduate School of Medicine.

We excluded subjects whose hsCRP had not been measured ($n = 29$). Those subjects whose serum CRP concentrations were higher than 10.0 mg/l ($n = 35$) were also excluded, because people with acute inflammatory conditions frequently have serum CRP concentrations ≥ 10.0 mg/l [28]. In addition, subjects who did not complete the measurement on the physical performance test were excluded ($n = 89$), as were all potential subjects with notable comorbidity factors that might influence the frequency and degree of physical activity by self-reported arthritis ($n = 163$) or a history of stroke ($n = 39$), as well as 48 subjects with peripheral arterial disease (PAD; lowest leg ankle brachial index, ABI, <0.90). As a result of these exclusions, the final study population was composed of 775 subjects [age 75.9 ± 4.7 years (mean $\pm$ standard deviation, SD); men: 43.0%].

Measurement of Serum CRP

The CRP concentrations were determined using an immuno-technique on a Behring BN II analyzer (Dade Behring, Tokyo, Japan). The BN II high sensitivity assay utilizes a monoclonal antibody coated on polystyrene particles and fixed-time kinetic nephelometric measurements [29]. The detection limit of this assay is 0.02 mg/l.

Physical Performance Tests

Physical performance was measured with three tests: 10-meter maximum walk test, leg extension power and a timed up and go test. The physical performance tests were measured by a well-trained physiotherapist as follows:

- Ten-meter maximum walk test [30]: Each participant was asked to walk 10 m at maximum walking speed. A stopwatch was used for timing, and a counter was used to obtain the number of steps. To eliminate periods of acceleration and deceleration, the subjects started their laps 3 m before the beginning of the walkway and concluded them 3 m beyond its end. The test was repeated three times, and the data of the fastest walk were recorded. These data were used to determine each subject's maximum walking speed in meters per second.

- Leg extension power: The participants were placed well back on a seat, and the waist was fixed with a belt. The knee joint was angled at 90°. The isometric contractions lasted for 5 s each and were separated by 15-second rest intervals. Peak power was detected, calculated, and recorded in watts by a microcomputer. The average of the two highest measurements among 5 trials was recorded as 'isometric strength performance' (Aneropress 3500, Combi Wellness, Tokyo). To minimize differences in body mass, leg extension power was expressed as the average peak of the leg relative to body weight (W/kg).
- Timed 'up and go' test [31]: The participants were seated in a free-standing padded armchair (46 cm high) and asked to rise (with or without using the arm rests), walk to a mark 3 m away, turn around, and walk back to the chair and sit down. The time between rising from the seat and making contact with the back of the seat was measured in seconds. This test was repeated three times and the time of the fastest trial was recorded.

Assessment of Other Variables

Anthropometrics (height, body weight) were recorded using a standardized protocol. Body mass index (BMI) was calculated as weight (kg)/height (m)². Blood pressure (BP) was measured at home with an HEM747IC device (Omron Life Science Co. Ltd, Tokyo, Japan), which uses the cuff-oscillometric method to generate a digital display of systolic and diastolic pressures. The mean of 15.6 ± 10.5 (SD) BP measurements were used as the BP values. Participants who did not measure their home BP on at least 3 days were treated as having missing information on hypertension. The ABI was measured using established methods [32]. The lowest leg ABI was used in this study.

Blood samples were drawn from the antecubital vein of the seated subject with minimal tourniquet use. Specimens were collected in siliconized vacuum glass tubes containing sodium fluoride for blood glucose, and no additives for albumin, lipids and CRP analyses.

Total cholesterol (T-C), high-density lipoprotein cholesterol (HDL-C) concentrations and blood glucose concentrations were measured by enzymatic methods (T-C, Denka Seiken, Tokyo, Japan; HDL-C, Daiichi Pure Chemicals, Tokyo, Japan; blood glucose, Shino-Test, Tokyo, Japan). Information on smoking status, drinking status, use of medication and histories of prior CHD, cancer and stroke were obtained from the questionnaire survey. The drug information was confirmed by a well-trained pharmacist. All individuals were told to bring their own drug to the scene of the conduct, and were checked and recorded by pharmacist. The 30-item Geriatric Depression Scale (GDS) [33] was used to assess depressive symptoms. Cognitive functioning was measured with the Mini-Mental State Examination (MMSE) [34]. The mean daily intake of nutrients including energy and n-3 polyunsaturated fatty acids (n-3 PUFA), was obtained from a brief self-administered diet-history questionnaire [35]. Detailed information is provided in our previous reports [26].

Definitions of Variables

We categorized the study participants on the basis of the recently proposed cutoff points for CRP as having low concentrations (<1.0 mg/l) or high concentrations (at least 1.0 mg/l) [35, 36].

Hypertension was defined as a home systolic BP (SBP) of 135 mm Hg or over and/or a home diastolic BP (DBP) of 85 mm Hg or over or use of antihypertensive agents [37]. Diabetes was defined as a casual blood glucose concentration of 200 mg/dl or over or current use of an antidiabetic medication. Hypercholesterolemia was defined as a concentration of T-C of 220 mg/dl or over, or current use of nonstatin lipid-lowering agents. We treated statin agents as independent confounding factors because they have been reported to lower CRP concentrations [38].

Physical activity (PA) was assessed first by a self-reported single-item question on whether the participant obtained any PA in the past year. If yes, questions were asked about the frequency and duration of walking, brisk walking, and sports. PA was then classified into 3 categories based on the frequency and duration in the participant: (1) High, at least 3–4 times per week for at least 30 min each time; (2) Low, reporting some activity in the past year, but not enough to meet high levels, and (3) None, no PA. PA was then further classified into six levels based on the above three categories and each physical activity such as walking, brisk walking, and sports: (1) Level 1, no walking, no brisk walking, no sports; (2) Level 2, low walking, no brisk walking, no sports; (3) Level 3, high walking, no brisk walking, no sports; (4) Level 4, any walking, low brisk walking, no sports; (5) Level 5, any walking, high brisk walking, no sports; (6) Level 6, any walking, any brisk walking, low or high sports. Detailed information is provided in previous reports [39]. Finally, the subjects were divided into two categories: level 3 or lower or higher than level 3. A GDS score of ≥11 was used to indicate depressive symptoms [40]. An MMSE score of <26 was used to indicate cognitive impairment [41].

Statistical Analysis

Descriptive data are presented as means (95% confidence interval, 95% CI) or percentages. The values of the physical performance measurement were used as the dependent variable and the serum CRP concentration level as the independent variable. The CRP levels were categorized as follows: CRP ≥1.0 mg/l and the tertiles of CRP <1.0 mg/l. The differences in variables among the CRP groups were examined by analysis of covariance (ANCOVA) for continuous variables or by multiple logistic regression analysis for variables of proportion after adjustment for age and sex. ANCOVA was used to examine the relation of CRP with physical performance after adjustment for age, sex, BMI, serum albumin concentration, hypercholesterolemia (nonstatin drugs), low HDL cholesterol (≤40 mg/dl), history of CHD, hypertension, diabetes, history of cancer, depressive symptoms, impaired cognitive function, smoking habits/history, PA, use of nonsteroidal anti-inflammatory drugs (NSAIDs), statin drugs, aspirin, angiotensin-converting enzyme inhibitors and n-3 PUFA intake levels (the consumption of n-3 PUFA per 2,000 kcal of energy intake categorized in tertiles) in all subjects or in subjects who had a very low serum CRP concentration (<1.0 mg/l). All p values for linear trend across the tertile of CRP and CRP >1.0 mg/l group were calculated by using the median of each CRP group. Tukey post-hoc analysis also was conducted. The interactions were assessed by testing the interaction term added to the adjusted model as a covariate. Furthermore, multiple linear regression analysis was used to establish the relationship between log-transformed CRP levels, treated as a continuous variable and physical performance after adjustment for the same covari-

Table 1. Age- and sex-adjusted baseline characteristics according to serum CRP levels (n = 775)

	CRP tertiles, mg/l			CRP 1.01–9.92 mg/l	p for trend ^a
	0.05–0.28	0.28–0.51	0.51–1.00		
Participants	181	182	182	230	–
Age, years ^b	75.51 (74.82–76.2)	76.19 (75.51–76.88)	75.96 (75.28–76.65)	75.68 (75.06–76.29)	0.36
Males, %	38.1	44.0	45.1	44.4	0.44
BMI ^b	22.05 (21.60–22.50)	23.33 (22.88–23.77)	24.37 (23.93–24.82)	24.86 (24.46–25.26)	<0.0001
Albumin, g/dl ^b	4.33 (4.29–4.37)	4.36 (4.32–4.39)	4.36 (4.32–4.39)	4.32 (4.29–4.36)	0.31
Hypercholesterolemia, %	28.2	33.0	37.4	43.5	<0.001
Low HDL cholesterol (≤ 40 mg/dl), %	7.7	7.7	13.2	14.8	0.02
History of CHD, %	6.6	10.4	11.0	10.4	0.44
Hypertension, %	54.7	68.1	72.0	75.2	<0.001
Diabetes, %	3.9	8.2	11.0	12.2	0.01
History of cancer, %	6.6	7.7	2.8	7.4	0.68
Depressive symptoms (GDS ≥ 11), %	35.9	25.3	30.2	28.7	0.58
Cognitively impaired (MMSE < 26), %	18.2	13.2	18.7	15.2	0.77
Smoker					
Current smoker, %	12.2	9.9	11.5	17.4	0.03
Ex-smoker, %	20.4	33.0	33.5	32.6	0.17
Nonsmoker, %	67.4	57.1	55.0	50.0	<0.001
Drinking					
Current drinker, %	44.3	45.6	42.3	41.4	0.26
Ex-drinker, %	8.6	13.0	12.0	14.1	0.21
Nondrinker, %	47.1	41.4	45.7	44.5	0.70
Use of NSAIDs, %	9.9	13.2	13.7	11.7	0.90
Use of statin drugs, %	13.8	12.6	17.0	14.8	0.69
Use of aspirin drugs, %	4.4	9.9	6.6	11.3	0.04
Use of ACE inhibitors, %	5.0	6.0	7.7	8.3	0.22
n-3 PUFA intake, g/day $\times 2,000$ kcal	3.42 (3.27–3.58)	3.38 (3.23–3.53)	3.52 (3.36–3.67)	3.26 (3.13–3.40)	0.41

ACE = Angiotensin-converting enzyme.

^a Analysis of covariance (age, albumin and BMI) or multiple logistic regression adjusted for age and sex where appropriate.^b Adjusted least squares mean (95% CI).

ates. When we calculated log-transformed CRP, 1.0 was added [CRP value (mg/l) + 1] before transformation. A significant difference was defined as $p < 0.05$. All statistical analyses were performed using Statistical Analysis System 9.1 edition for Windows (SAS Institute Inc., Cary, N.C., USA).

Results

In this study, the subjects whose serum CRP concentrations were higher than 10.0 mg/l were excluded. The median value (interquartile range) of CRP was 0.55 (0.29–1.20) mg/l.

Age- and sex-adjusted baseline characteristics according to the tertiles of a serum CRP concentration < 1.0 mg/l or > 1.0 mg/l are presented in table 1. Mean BMI was significantly higher across CRP levels (p for trend < 0.0001). The prevalence of hypercholesterolemia, low

HDL cholesterol, hypertension, diabetes and the use of aspirin drugs were significantly larger in the higher CRP levels (p for trend ≤ 0.04). The proportion of nonsmokers was significantly lower in the higher CRP levels (p for trend < 0.001). In contrast, the proportion of current smokers was significantly higher in the higher CRP levels (p for trend = 0.03). Otherwise, no significant difference was observed among CRP levels (p for trend ≥ 0.17).

Table 2 shows the adjusted association between CRP level and physical performance. After adjustment for potential confounding factors, the significant inverse relation of the CRP level with leg power was observed in all subjects. Similarly, although not statistically significant, increasing CRP levels tended to relate inversely to 10-meter walk at maximum speed (p for trend = 0.10). For subjects who had CRP < 1.0 mg/l, the CRP levels showed a significant inverse relationship with 10-meter walk at maximum speed (p for trend = 0.03) and leg power (p for

Table 2. Adjusted C-reactive protein levels in relation to physical activity

	CRP tertiles, mg/l			CRP 1.01–9.92 mg/l	p for trend	p for trend ^b
	0.05–0.28	0.28–0.51	0.51–1.00			
Participants	181	182	182	230	–	–
Ten-meter walk at max. speed, m/s						
Age-, sex-adjusted	1.80 (1.76–1.85)	1.75 (1.71–1.79)	1.73 (1.68–1.77)	1.69 (1.65–1.72)	<0.01	<0.01
Multiple adjusted ^a	1.44 (1.23–1.66)	1.40 (1.19–1.61)	1.39 (1.18–1.60)	1.36 (1.15–1.57)	0.10	0.03
Leg power, W/kg						
Age-, sex-adjusted	11.49 (11.03–11.95)	11.07 (10.61–11.52)	10.35 (9.90–10.81)	10.32 (9.91–10.73)	<0.001	<0.001
Multiple adjusted ^a	9.23 (6.92–11.53)	9.05 (6.76–11.34)	8.57 (6.32–10.81)	8.64 (6.37–10.91)	0.04	0.02
Timed up and go, s						
Age-, sex-adjusted	9.29 (8.98–9.59)	9.22 (8.92–9.52)	9.10 (8.8–9.41)	9.56 (9.29–9.83)	0.41	0.42
Multiple adjusted ^a	11.92 (10.37–13.47)	11.80 (10.26–13.35)	11.57 (10.05–13.08)	11.99 (10.46–13.52)	0.11	0.16

Variables are presented as least squares means (95% CI).

^a Adjusted for age, sex, body mass index, serum albumin concentration, hypercholesterolemia (nonstatin drugs), low high-density lipoprotein-cholesterol (≤ 40 mg/dl), history of coronary heart diseases, history of cancer, hypertension, diabetes, depressive symptoms, impaired cognitive

function, smoking habits/history, PA, use of nonsteroidal anti-inflammatory drugs, statin drugs, aspirin, angiotensin-converting enzyme inhibitors and tertile of n-3 polyunsaturated fatty acids intake.

^b Only for subjects who had a C-reactive protein <1.0 mg/l.

trend = 0.02). No relation was found between the tertiles of serum CRP concentration <1.0 mg/l, >1.0 mg/l and timed up and go test in all models (p for trend ≥ 0.11). Furthermore, because the test for interaction between CRP levels and sex was statistically significant (p for interaction for 10-meter walk at maximum speed: 0.02; p for interaction for leg power: 0.04), we conducted stratified analysis for sex. Although not statistically significant, increasing CRP levels had a stronger relationship with 10-meter walk at maximum speed (p for trend = 0.23) and leg power (p for trend = 0.16) in men as compared to women (p for trend = 0.60 and 0.35, respectively).

The multiple regression model analysis also showed an inverse and significant relationship between log-transformed CRP and leg power (standard regression coefficient = -0.07 , $p = 0.03$) after adjustment for covariates in table 2 in subjects who had CRP <1.0 mg/l. Although not statistically significant, log-transformed CRP was inversely related to 10-meter walk at maximum speed (standard regression coefficient = -0.06 , $p = 0.09$). In contrast, no relation was found between log-transformed CRP and TUGT (standard regression coefficient = -0.05 , $p = 0.19$).

Discussion

In this cross-sectional study, we examined the relationship between serum CRP concentrations and physical performance in an elderly Japanese population. We

also examined the relationship between CRP and physical performance in subjects with a serum CRP concentration <1.0 mg/l. These results suggested that a lower serum CRP concentration is favorably associated with physical performance even within a very low range.

The comparisons of the various inflammatory markers, including soluble adhesion molecules (e.g. E-selectin, P-selectin, intracellular adhesion molecule-1, vascular cell adhesion molecule-1), cytokines (e.g. interleukin-1 β , -6, -8, and -10 and tumor necrosis factor- α), acute phase reactants (e.g. fibrinogen, serum amyloid A protein and hs-CRP) and WBC count, favor CRP from the clinical chemistry perspective [27]. Although the detection of elevated levels of CRP in the serum is not specific for any particular disease, it is a useful indicator of inflammatory processes [42]. High-sensitivity CRP is the term applied to a test that detects serum CRP concentration at lower levels than previous generations of laboratory tests. The lower limit of detection is substantially lower and can therefore detect lower levels of inflammation. In Western countries, the concentrations of CRP are proposed to be <1.0 mg/l as low risk, 1.0 – 3.0 mg/l as intermediate risk, and >3.0 mg/l as high risk for CHD [27]. Nonetheless, the current results suggested that high CRP also is independently related to poorer physical performance in elderly populations who have a serum CRP concentration <1.0 mg/l.

Several epidemiological studies assessed the relationship between CRP and physical performance [9, 16–19].

Most of these studies reported an inverse relation between CRP and physical performance or disability. However, the level of serum CRP was remarkably higher in these studies compared to the present study. In three of these studies, hsCRP was not used [9, 16, 17]. Only two studies used hsCRP to assess the relationship between CRP and physical performance [18, 19]. McDermott et al. [18] reported that higher CRP levels were associated with lower physical performance among subjects with PAD but not among those without non-PAD. Another cross-sectional study used hsCRP to assess that the relationship between CRP and physical performance in a community-based elderly population aged ≥ 60 years, but in their study, several confounding factors such as use of NSAIDs [43], statin drugs [38], and PAD [18, 35] associated with CRP were not considered [19]. Moreover, although multiple linear regression was conducted to assess the natural-log-transformed CRP and physical performance in their study, it was not shown whether the CRP also is associated with physical performance even within a very low range (CRP <1.0 mg/l). Compared with these studies, hsCRP was used in this study, and the median CRP value of 0.55 mg/l of our participants was lower. This population with low CRP and hsCRP measure gave us an opportunity to examine the relationship between a very low range of CRP and physical performance. In the current study, we found that the serum CRP concentration is inversely associated with physical performance, even within a very low range (CRP <1.0 mg/l). Therefore, maintaining lower CRP levels may be important in clinical or subclinical practice. However, whether reducing inflammatory status by use of a drug will lead to a reduced risk of dependency in old age remains to be an important research question.

Since the concentrations of CRP are proposed to be <1.0 mg/l as low risk, 1.0–3.0 mg/l as intermediate risk, and >3.0 mg/l as high risk for CHD [27], the current results have also shown that levels associated with risk of coronary artery disease may be less sensitive than muscular performance for those participants with CRP <1.0 mg/l.

Although the association of CRP and disability or mortality has been proven by a large number of studies [9, 16–19], a direct mechanistic impact of CRP on mortality or disability has to be regarded as still doubtful. The underlying processes may have certainly more impact on risk factors and functionality than CRP. For example, the BMI is known to relate to the length of life with disability before death or severity of disability [44]. Because the BMI has been strongly associated with the serum CRP

levels [45], the present study suggests that one possible pathway by which the control of BMI may reduce these risks is through decreasing serum CRP levels. Further study is required to explore the mechanisms that are involved in the associations.

We did not find significant associations between CRP and TUGT. Since TUGT [31] was not a test concerning peak physical performance as compared to 10-meter maximum walk test and leg extension power, CRP may be sensitively associated with peak physical performance within a very low range.

This study had several limitations. First, since all assessment was carried out in a public facility, participants were sufficiently active and healthy. Therefore, our results may not represent an elderly general population. Second, since this study was a cross-sectional study, we were not able to infer causality from our results. Still, several prospective studies suggested that CRP was associated with a decline in physical performance [9, 16, 17]. Therefore, the current results may be reliable. Further, although compared to those without fractures, individuals with a hip, arm, or clinical spinal fracture have shown similar global declines in physical performance [46], the results were not adjusted for fracture status because of a lack of information.

In summary, a lower serum CRP concentration is favorably related to physical performance, even within a very low range. The findings suggest that maintaining CRP levels as low as possible may potentially maintain better physical performance.

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