Association between C-reactive protein and hand grip strength in postmenopausal women

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Association between C-reactive protein and hand grip strength in postmenopausal women

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ABSTRACT

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Background: Inflammation may contribute to adverse muscle health, which is a key factor in functional declining. Menopausal period is clinically important in which muscle health changes rapidly. The purpose of this study was to clarify the relation between high sensitivity C-reactive protein (hs-CRP) and muscle strength among Korean postmenopausal women.

Methods: This study used data from the Korean National Health and Nutrition Survey (KNHANES) during the seventh term (2016-2017). A total of 1115 participants remained eligible for this study. Muscle strength was assessed using hand grip strength. Low hand grip strength was defined as the lowest 25% of study sample. After Participants were categorized into quartiles based on hs-CRP, the odds ratios (ORs) and 95% confidence intervals (CIs) for low hand grip strength according to hs-CRP quartile were calculated using multiple logistic regression analysis.

Results: The results showed that hs-CRP was negatively associated with both hand-grip strength (OR = 1.85, 95% CI = 1.05 - 3.27, OR = 2.31, 95% CI = 1.34 - 4.04 for the highest quartile of hs-CRP group relative to the 1st quartile, right and left hand respectively) when adjusted for age, body mass index, cigarette smoking, alcohol ingestion, physical activity, household income, education level, and marital status.

Conclusions: The results suggest that hs-CRP level was inversely and independently associated with low hand grip strength, suggesting it as a useful additional measure for assessing low hand grip strength, particularly in late postmenopausal women.

Key words : hand grip strength; C-reactive protein; inflammation; postmenopausal women; muscle strength

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I. INTRODUCTION

Because physical performance is a useful indicator of disability and mortality in humans, preventing declining physical functions and frailty are a very important health issue, especially for the elderly[1-4]. Recent studies have reported that inflammation plays an important role, directly or indirectly, in deterioration of physical functions and in pathophysiology of frailty[5-10].

C-reactive protein (CRP) is produced in the liver during acute or chronic inflammatory reactions[11]. CRP is a useful clinical indicator of nonspecific inflammatory conditions. CRP may increase with an acute response to injury or infection[12], but recent studies have shown that it can increase even with low-grade chronic inflammatory responses in the presence of chronic disease such as cardiovascular disease, type 2 diabetes, and metabolic syndrome[13].

Decline of physical function and frailty are closely related to loss of muscle mass and strength[14]. There are several methods for assessing muscle strength, including handgrip strength as a simple, fast, and economical indicator.

Previous studies have shown that decreased hand grip strength is closely related to increased risk of all-cause mortality, functional limitations, and disability as well as decrease in muscle mass and walking performance[15-18].

Loss of muscle mass and strength in women is accelerated during the menopausal period[19,20] and can lead to functional restrictions, disability, fractures, and premature mortality[21,22]. Therefore, decreases in muscle mass and strength in postmenopausal women are important from a public health perspective. In this regard, early identification of people at high risk for declining physical functions and frailty is important from a public health perspective, particularly in postmenopausal women who have undergone rapid physical changes. Thus, this study aimed to examine the relationship between chronic low-grade inflammation measured by high-sensitivity CRP (hs-CRP) and hand grip strength in postmenopausal women. Moreover, subgroup analysis was used to determine if there was a difference in the above relationships among the groups based on number of years after menopause.

II. MATERIALS AND METHODS

1. Survey overview and study population

This study used data from the Korean National Health and Nutrition Examination Survey (KNHANES) during the seventh term (2016-2017). The KNHANES aims to comprehensively understand the current state of health and nutrition of the Korean people and consists of independent circulation samples every three years with a yearly survey system. Each sample is a probability sample that represents the entire population of Korea. The total number of participants in the seventh term was 16,277 and included participants from the first year (2016) and second year (2017) surveys. The KNHANES is divided into three categories: health interview, nutrition survey, and health examination survey. This study only included individuals that reported undergoing natural menopause (n=2969). The following participants were excluded: individuals with an hs-CRP greater than or equal to 10 mg/L (n=7); individuals with cancer or arthritis (osteoarthritis, rheumatoid arthritis) (n = 486); individuals that were unwell in the last two weeks (acute disease or worsening of chronic diseases) (n=825); and those with data missing for handgrip strength for the right or the left hand, hs-CRP, household income, education, marital information, alcohol ingestion, smoking, physical activity, or menopause age (n=536). After these participants were excluded, a total of 1115 participants remained eligible for this study. All participants in the survey signed an informed written consent form. This study was managed by the Institutional Review Board of the Yonsei university health system (No. Y-2019-0195) and conducted according to the ethical principles of the Declaration of Helsinki.

2. Data collection

Experienced medical staff measured patient height and weight to the nearest 0.1 cm and 0.1 kg, respectively, according to the standardized procedure of the mobile examination center. BMI was calculated as weight divided by height squared (kg/m^2), and waist circumference was measured at the midpoint between the inferior margin of the last rib and the iliac crest in the horizontal plane, based on World Health Organization guidelines. Blood pressure was measured manually using mercury sphygmomanometers (Baumanometer Wall unit 33; W.A. Baum, Copiague, NY) by the standardized measurement method with the patient in the sitting position, and all subjects were measured three times at five minute intervals. Final blood pressure values were calculated as an average of the second and third blood pressure readings. Data on smoking status, alcohol consumption, physical activity, education level, household income, and marital status were collected from self-report questionnaires. With regard to smoking habits, a smoker was defined as an individual that smoked more than 5 packs (100 cigarettes) in their lifetime and those that currently smoke. Alcohol consumption was defined as at least one drink per month in recent years. Physically active participants were defined as those who had performed exercise for at least 2 hours 30 minutes of moderate or 1 hour 15 minutes of high intensity physical activity per week. One minute of high intensity physical activity was calculated as 2 minutes of moderate intensity. Here, moderate intensity refers to activity that caused an increase in breathing or increase in heart rate, and high intensity refers to a vigorous physical activity that causes loss of breath or rapid increase in heart rate. Level of education was divided into elementary school, middle school, high school, and college. Household income was divided into quartiles according to income, and marital status was classified into single, married, or other such as separated or divorced. Systolic blood pressure and diastolic blood pressure were assessed three times in the right upper arm using a standard mercury sphygmomanometer (Baumanometer; Baum, Copiague, NY, USA), and the mean of the second and third blood pressure readings was used for analysis. Blood samples were obtained from the antecubital vein after each participant had fasted overnight for a minimum of 12 hours and were analyzed within 24 hours after isolation. Fasting plasma glucose, triglycerides, and high-density lipoprotein (HDL) cholesterol levels were measured using the Hitachi 7600-110 automated chemistry analyzer (Hitachi Co., Tokyo, Japan). Hs-CRP level was measured using Cobas immunoturbidimetry (Roche Co., Berlin, Germany). Handgrip strength was measured three times in each hand, using a digital grip strength dynamometer (TKK 5401; Takei Scientific Instruments Co., Ltd., Tokyo, Japan). Experienced medical technicians instructed seated participants to grip the dynamometer handle as tightly as possible. After standing, patient handgrip strength was measured during expiration. Each participant was measured three times for each hand and allowed one minute of rest to recover between measurements. Hand-grip strength was reported as the average of the three measurements. Relative handgrip strength was defined as grip strength per unit of body mass index (BMI). In this study, we adopted the first quartile of relative HGS as the defined cut-off point for “low hand grip strength.”

3. Statistical analyses

Participants were categorized into quartiles based on hs-CRP (Q1, ≤ 0.39 mg/L; Q2, 0.40-0.58 mg/L; Q3, 0.59-1.08 mg/L; Q4, >1.08 mg/L). The results were expressed as means and standard errors (SEs) or percentages and SEs for quantitative variables. Participant characteristics were analyzed according to hs-CRP quartiles using analysis of variance for continuous variables and chi-square tests for categorical variables. The odds ratios (ORs) and 95% CIs for low hand-grip strength according to hs-CRP quartile were calculated using binary logistic regression analysis. For subgroup analysis, the subjects were divided into three groups based on time since menopause, based on STRAW classification[23] (Early; ≤ 6 years since menopause, Borderline; 7-9 years since menopause, Late; ≥10 years since menopause). Logistic regression analysis was used in each of the three groups to calculate the odds ratio (ORs) and 95% CIs for low hand grip strength according to hs-CRP quartile. All analyses were conducted using SPSS statistical software, version 22 (SPSS Institute Inc.), and a P-value of <0.05 was considered statistically significant.

Table 1. Clinical characteristics of study population by high sensitivity C-reactive protein quartiles

	High sensitivity C-reactive protein quartiles				
	Q1, ≤ 0.39 mg/L	Q2, 0.40-0.58 mg/L	Q3, 0.59-1.08 mg/L	Q4, >1.08 mg/L	P-value
Age	59.3 (0.5)	61.4 (0.6)	61.4 (0.6	61.7 (0.7)	0.004
Body mass index (kg/m^2)	22.5 (0.2)	23.2 (0.2)	24.6 (0.2)	24.9 (0.2)	<0.001
Waist circumference (cm)	76.5 (0.5)	79.3 (0.5)	82.5 (0.6)	84.0 (0.6)	<0.001
Systolic blood pressure (mmHg)	120.0 (1.2)	121.9 (1.2)	124.5 (1.3)	125.2 (1.2)	0.003
Diastolic blood pressure (mmHg)	74.8 (0.7)	74.9 (0.6)	76.2 (0.7)	76.4 (0.6)	0.185
Education (%)					0.510
≤ Elementary school	19.9 (3.0)	29.4 (3.3)	35.4 (3.1)	34.2 (3.1)	
Middle school	18.3 (2.9)	18.5 (2.8)	17.2 (2.6)	15.6 (2.4)	
High School	40.1 (3.3)	31.0 (3.3)	30.0 (3.2)	33.9 (3.2)	
≥ College	21.8 (2.9)	21.1 (3.2)	17.4 (2.9)	16.3 (2.5)	
Household income (%)					0.396
Quartile 1 (lowest)	16.7 (2.7)	21.2 (2.9)	20.3 (2.6)	26.1 (3.1)	
Quartile 2	23.7 (2.9)	27.9 (3.0)	29.9 (3.2)	26.1 (2.9)	
Quartile 3	27.8 (3.2)	22.3 (2.9)	21.4 (2.9)	22.7 (2.8)	
Quartile 4 (highest)	31.8 (3.7)	28.7 (3.2)	28.4 (3.2)	25.1 (3.1)	
Marital status					0.735
Single	1.3 (0.7)	1.6 (0.7)	0.7 (0.5)	1.2 (0.6)	
Married	75.4 (3.1)	72.8 (2.7)	76.1 (2.7)	70.0 (3.1)	
Separation or divorced	23.3 (3.0)	25.6 (3.1)	23.1 (2.7)	28.7 (3.1)	
Current smoking (%)	2.2 (0.9)	4.4 (1.5)	3.1 (1.5)	5.0 (1.8)	0.493
Alcohol ingestion (%)	36.1 (3.3)	35.4 (3.2)	28.8 (3.3)	27.3 (2.9)	0.112
Fasting plasma glucose (mg/dL)	97.6 (1.5)	102.5 (1.6)	102.5 (1.4)	107.2 (1.7)	<0.001
Total cholesterol (mg/dL)	202.35 (2.4)	200.6 (2.4)	206.0 (2.8)	207.5 (3.2)	0.254
HDL-cholesterol (mg/dL)	58.0 (1.0)	54.6 (0.9)	52.4 (0.8)	49.2 (0.8)	<0.001
Triglyceride (mg/dL)	105.9 (3.9)	118.6 (3.9)	140.7 (5.1)	149.3 (9.5)	<0.001
Creatinine (mg/dL)	0.72 (0.01)	0.72 (0.01)	0.73 (0.01)	0.76 (0.02)	0.146
Physical activity (%)	53.9 (3.3)	40.3 (3.5)	39.1 (3.2)	36.4 (3.2)	0.001
Hypertension (%)	20.5 (2.6)	30.6 (3.1)	33.4 (2.9)	35.8 (3.5)	0.004
Dyslipidemia (%)	25.1 (2.6)	32.5 (3.3)	29.1 (2.9)	26.8 (3.2)	0.332
Diabetes mellitus (%)	6.5 (1.5)	16.1 (2.6)	13.8 (2.5)	15.3 (2.6)	0.011
Stroke (%)	0.8 (0.5)	0.6 (0.4)	3.9 (1.3)	1.2 (0.6)	0.005
Coronary heart disease (%)	2.3 (0.8)	1.4 (0.7)	1.9 (0.9)	3.6 (1.4)	0.365
Hand grip strength					
Absolute right (kg)	22.1 (0.3)	21.1 (0.3)	21.5 (0.3)	20.6 (0.4)	0.008
Absolute left (kg)	21.2 (0.2)	20.1 (0.3)	20.5 (0.3)	19.4 (0.4)	<0.001
Relative right (kg/kg/m^2)	1.00 (0.01)	0.92 (0.01)	0.88 (0.01)	0.84 (0.02)	<0.001
Relative left (kg/kg/m^2)	0.96 (0.01)	0.87 (0.01)	0.84 (0.01)	0.79 (0.02)	<0.001

Data presented as mean (SE) or percentages, unless otherwise indicated. P-values were calculated by weighted ANOVA test for continuous variables and weighted chi-square for categorical variables.

III. RESULTS

Table 1 shows the demographic and biochemical characteristics of the participants by hs-CRP quartile. In the fourth hs-CRP quartile, the mean values of age, BMI, waist circumference, systolic blood pressure, fasting plasma glucose, and triglycerides were highest, whereas HDL-cholesterol level was lowest. In addition, the proportion of hypertension was largest in the highest quartile, whereas individuals with regular physical activity were most prevalent in the highest quartile of hs-CRP.

Table 2. Odds ratios and 95% confidence intervals for low hand grip strength according to high sensitivity C-reactive protein quartiles in postmenopausal women

		High sensitivity C-reactive protein quartiles			
		Q1, ≤ 0.39 mg/L	Q2, 0.40-0.58 mg/L	Q3, 0.59-1.08 mg/L	Q4, >1.08 mg/L
Unadjusted	Right	1.00	2.15 (1.23-3.74)	2.19 (1.28-3.76)	3.66 (2.21-6.07)
	Left	1.00	2.46 (1.45-4.18)	2.51 (1.50-4.22)	4.58 (2.85-7.37)
Model 1	Right	1.00	1.61 (0.88-2.97)	1.19 (0.65-2.15)	2.00 (1.15-3.48)
	Left	1.00	1.88 (1.03-3.44)	1.33 (0.74-2.39)	2.54 (1.48-4.36)
Model 2	Right	1.00	1.58 (0.86-2.89)	1.10 (0.60-2.02)	1.85 (1.05-3.27)
	Left	1.00	1.90 (1.05-3.46)	1.20 (0.67-2.17)	2.31 (1.34-4.04)

Model 1: Adjusted for age and body mass index. Model 2: Adjusted for age, body mass index, education, household income, marital status, physical activity, smoking, and alcohol ingestion.

Table 2 shows the results of multiple logistic regression analysis to assess the odds for predicting low hand-grip strength in terms of hs-CRP quartile. Compared with the lowest quartile, the ORs (95% CIs) for low hand-grip strength of the highest quartile were approximately two or four fold higher after adjusting for age, BMI, cigarette smoking, alcohol ingestion, physical activity, household income, education level, and marital status.

In subgroup analysis, the OR for low hand-grip strength was significantly higher in the highest quartile of hs-CRP among late postmenopausal women but not in early or borderline postmenopausal women (Table 3).

Table 3. Odds ratios and 95% confidence intervals for low hand grip strength according to high sensitivity C-reactive protein quartiles in early, borderline and late postmenopausal women

Early postmenopausal women		High sensitivity C-reactive protein quartiles			
		Q1, ≤ 0.38 mg/L	Q2, 0.39-0.53 mg/L	Q3, 0.54-1.00 mg/L	Q4, >1.00 mg/L
Unadjusted	Right	1.00	1.14 (0.57-2.23)	1.21 (0.59-2.48)	2.13 (1.07-4.23)
	Left	1.00	1.45 (0.67-3.15)	1.76 (0.82-3.76)	3.10 (1.46-6.61)
Model 1	Right	1.00	1.06 (0.51-2.22)	0.50 (0.23-1.10)	0.92 (0.44-1.94)
	Left	1.00	1.40 (0.62-3.17)	0.93 (0.42-2.09)	1.67 (0.74-3.77)
Model 2	Right	1.00	1.00 (0.47-2.14)	0.46 (0.20-1.06)	0.89 (0.40-1.97)
	Left	1.00	1.31 (0.57-3.02)	0.84 (0.37-1.93)	1.54 (0.65-3.63)
Borderline postmenopausal women		High sensitivity C-reactive protein quartiles			
		Q1, ≤ 0.36 mg/L	Q2, 0.37-0.53 mg/L	Q3, 0.54-1.20 mg/L	Q4, >1.20 mg/L
Unadjusted	Right	1.00	7.44 (1.17-47.40)	5.31 (0.81-34.93)	5.12 (0.82-31.89)
	Left	1.00	4.23 (0.76-23.57)	4.33 (0.78-24.07)	5.16 (0.99-26.78)
Model 1	Right	1.00	8.30 (1.72-39.92)	2.79 (0.55-14.21)	2.34 (0.46-11.97)
	Left	1.00	4.18 (0.94-18.69)	2.29 (0.48-11.02)	2.36 (0.55-10.22)
Model 2	Right	1.00	9.98 (1.78-55.90)	1.10 (0.18-6.94)	2.75 (0.38-20.18)
	Left	1.00	4.29 (0.94-19.67)	1.21 (0.20-7.17)	1.94 (0.35-10.62)
Late postmenopausal women		High sensitivity C-reactive protein quartiles			
		Q1, ≤ 0.40 mg/L	Q2, 0.41-0.60 mg/L	Q3, 0.61-1.10 mg/L	Q4, >1.10 mg/L
Unadjusted	Right	1.00	1.24 (0.67-2.31)	2.05 (1.11-3.78)	3.58 (2.10-6.13)
	Left	1.00	1.54 (0.78-3.05)	2.45 (1.28-4.68)	4.08 (2.37-7.04)
Model 1	Right	1.00	0.98 (0.51-1.90)	1.34 (0.65-2.74)	2.59 (1.41-4.74)
	Left	1.00	1.17 (0.56-2.46)	1.41 (0.65-3.08)	2.88 (1.53-5.41)
Model 2	Right	1.00	0.96 (0.48-1.94)	1.34 (0.63-2.89)	2.41 (1.25-4.63)
	Left	1.00	1.23 (0.60-2.54)	1.52 (0.68-3.42)	2.88 (1.49-5.57)

Model 1: Adjusted for age and body mass index. Model 2: Adjusted for age, body mass index, education, household income, marital status, physical activity, smoking, and alcohol ingestion.

IV. DISCUSSION

In this nationally representative cross-sectional study, hs-CRP level was inversely and independently associated with relative HGS in postmenopausal women, particularly among late postmenopausal women. Our results are consistent with previous studies showing an inverse association between CRP and muscle strength. Several cross-sectional population-based studies have demonstrated that a high level of CRP was associated with low physical performance[7,10,24]. These findings suggest that chronic low-grade inflammation could contribute to decreases in physical performance, including muscle mass and strength. A more recent meta-analysis also showed that sarcopenia is associated with elevated CRP level[25].

However, most of the previous reports did not consider relative hand grip strength, which reflects not only the maximal hand grip strength of each hand, but also minimizes the confounding effect of body size. Thus, relative hand grip strength is superior to absolute hand grip strength as a marker of frailty and functional decline and is a more sensitive index that can explain low physical performance[26]. In this regard, we used relative hand grip strength and confirmed the inverse relationship between hs-CRP and handgrip strength in postmenopausal women.

Although the exact mechanism for the underlying association between hs-CRP and low hand grip strength is uncertain, there are currently some potential hypotheses. Chronic low-grade inflammation is a potentially important pathophysiological factor that leads to functional decline through direct or intermediary mechanisms that are involved in muscle health deterioration. Chronic low-grade inflammation increases the imbalance of muscle proteins by causing changes in mitochondrial dynamics through activation of the ubiquitin proteasome pathway[27]. Moreover, chronic low-grade inflammation may lead to cell death and apoptosis[28], and inflammatory cytokines could disrupt satellite cells, which play an important role in muscle regeneration and repair[29].

Oxidative stress, which is closely related to chronic inflammation, might increase NF-κB activity, which is involved in chronic inflammation-induced skeletal muscle degeneration[30].

Loss of muscle strength is a very important factor in muscle wasting and sarcopenia and adversely affects physical function and mobility in postmenopausal women[21,22]. Therefore, it is very important to identify measures that can be used to improve and maintain quality of life by preventing physical performance deterioration, which is a key component of frailty. Our study suggests that hs-CRP is a simple and useful indicator that can help predict functional decline by recognizing the associated risk of losing muscle strength in postmenopausal women.

There were several limitations to this study. First, our study had a cross-sectional design and was not able to clarify the causal relationship between hs-CRP and hand-grip strength. The results might be due to a bidirectional relationship and reflect reverse causality in the association between these variables. Thus, further prospective studies with a long follow-up period are required to identify whether there is a cause-and-effect relationship between hs-CRP and hand-grip strength. Second, because we used secondary data from KNHANES, we could not evaluate other inflammatory markers such as IL-6 and TNF-α. Assessing the relationship between other inflammatory cytokines and muscle strength will help increase the reliability of the results. Finally, some potential residual confounding variables such as a history of medications (aspirin or NSAIDs) affecting hs-CRP level were not taken into account in the multiple logistic regression analysis model due to the nature of the secondary KNHANES dataset.

V. CONCLUSIONS

In conclusion, hs-CRP level was inversely and independently associated with low hand grip strength, suggesting it as a useful additional measure for assessing low hand grip strength, particularly in late-postmenopausal women.

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ABSTRACT (IN KOREAN)

폐경 후 여성에서 C-반응단백과 악력의 연관성

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정영효

배경 : 신체기능의 저하(Functional declining)와 신체수행능력(Physical performance)의 저하는 장애나 사망과 매우 관련성이 높다. 염증은 근육량(Muscle mass)과 근력(Muscle strength)의 감소에 영향을 끼침으로써 신체수행능력의 저하를 가져올 수 있다. 여성에게 폐경기는 근력 등 신체변화가 급격히 일어나는 임상적으로 중요한 시기이다. 본 연구의 목적은 폐경 이후 한국 여성에서 염증과 근력의 관계를 알아 보는 것이다.

방법 : 2016-2017년 한국 국민건강 영양조사자료를 이용하여, 해당연도에서 1115명의 대상자를 선정하여 연구를 진행하였다. 근력은 악력을 이용하여 평가하였으며, 낮은 악력은 대상자 중 하위 25% 로 정의하였다. 대상자를 고감도 C-반응단백(High sensitivity C-Reactive protein, hs-CRP) 수치에 따라 4군으로 나누어 악력 저하의 위험도를 알아보고자 다중 로지스틱 회귀분석(Multiple logistic regression analysis)을 이용하여 교차곱비 Odds Ratios(ORs)를 구하였다.

결과 : 나이, 체질량지수, 교육수준, 가계수입, 결혼, 신체활동, 흡연, 음주를 보정한 후에 가장 낮은 고감도 C-반응 단백 그룹과 비교하여 가장 높은 고감도 C-반응 단백 그룹의 악력 저하에 대한 ORs 값은 오른손 1.85 (95% Confidence Intervals : 1.05 – 3.27) 왼손 2.31 (95% Confidence Intervals 1.34 - 4.04) 이었다.

결론 : 폐경 이후의 한국 여성에서 고감도 C-반응 단백이 높을수록 악력 저하의 위험도가 높았다.

핵심되는 말 : 악력; C-반응단백; 염증; 폐경 후 여성; 근력