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ORIGINAL PAPER

Association between muscular strength and inflammatory markers among elderly persons with cardiac disease: results from the KORA-Age study

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Abstract Little is known about the association between muscle strength and inflammation in diseased individuals and particularly in cardiac patients. Thus, our purpose was to examine the association of muscular strength with the inflammatory status in older adults with and without cardiac disease. The cross-sectional analysis was based on 1079 adults aged 65–94 years, who participated in the KORA-Age study. Participants underwent an interview and extensive physical examinations including anthropometric measurements, registration of diseases and drug intake, determination of health-related behaviors, collection of blood samples for measurements of interleukin-6 and hs-CRP and muscle strength measurement using hand-grip dynamometry. Cardiac patients ($n = 323$) had higher levels of IL-6 and poorer muscle strength compared with older adults without cardiac disease. Among persons with cardiac diseases, muscle strength in the lower tertile compared to the upper tertile was significantly associated with increased odds of having elevated IL-6 levels (OR 3.53, 95 % CI 1.18–10.50, $p = 0.024$) after controlling for age, gender, body fat, alcohol intake, smoking status, diseases, medications and physical activity, whereas the association between muscle strength and hs-CRP remained borderline significant (OR 2.80, 95 % CI 0.85–9.24, $p = 0.092$). The same trends, with slightly lower odds ratios, were also observed in older adults without cardiac disease. Lower levels of muscular strength are associated with higher concentrations of IL-6 and hs-CRP in elderly individuals with and without cardiac disease suggesting a significant contribution of the muscular system in reducing low-grade inflammation that accompanies cardiac disease and aging.

Keywords Cardiac disease · Muscle strength · Inflammation · Aging

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Introduction

Aging has been associated with increased levels of inflammatory cytokines such as interleukin-6 (IL-6), C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-a) and there is growing evidence that this systemic low-grade inflammation is closely connected to the muscle atrophy and weakness of older people [1, 2].

This age-related loss of muscle mass and strength (defined as sarcopenia) contributes significantly to the accelerated decline of physical function and has been linked to increased morbidity and mortality [3, 4]. This situation is further complicated in cardiac patients since they suffer from low-grade inflammation as an integral part of the development and progression of their disease's pathophysiology [5] especially if they are in an advanced age.

New scientific evidence suggests that the levels of local and systemic inflammation can be reduced by different lifestyle and pharmacological interventions including drugs, nutritional supplements, weight loss, smoking cessation or exercise [6–8]. During the last years, the significant contribution of aerobic exercise as an effective anti-inflammatory means in patients with coronary artery disease and heart failure has been well documented [9–13].

It is further known that skeletal muscle expresses and releases several cytokines and peptides (myokines) into the circulation in response to muscle contractions, acting as an endocrine organ. These myokines exert their anti-inflammatory and antiatherogenic properties either locally or systemically in several organs such as liver and adipose tissue in a hormone-like manner [14, 15].

Epidemiological studies have shown that poor muscle strength is strongly associated with high levels of inflammatory markers in middle-aged and older individuals [16–21]. However, knowledge about such an association between inflammatory indexes and muscular strength among elderly patients with cardiac diseases is missing. Given that skeletal muscle is the largest organ in the human body, it is of vital importance for these persons to preserve a sufficient level of muscle mass and strength, which is necessary not only to reduce the cardiac demands during the daily physical activities, but also to counteract the catabolic effects of chronic, subclinical inflammation affecting thereby the progression of their disease.

Thus, the purpose of our study was to examine the association of muscular strength with inflammatory status (IL-6 and hs-CRP levels) in a population-based study of elderly individuals aged 65–94 years from the general population with and without cardiac disease.

Methods

Study population

Data were collected in 2009 during the KORA (Cooperative Health Research in the Region of Augsburg)-Age study, a follow-up study of the four MONICA/KORA Augsburg Surveys [22]. The KORA-Age study population consisted of a subgroup of 5991 individuals who were born in 1943 or earlier. In total, 4127 individuals participated in a standardized telephone interview (response rate 67 %). Out of this group, a randomly drawn sample of 1079 participants additionally underwent extensive physical examinations including the registration of medication, collection of blood samples, assessment of anthropometry, grip strength measurement, and an additional interview amongst others. After exclusion of 35 participants because of missing data, the final data set for the present analysis consisted of 1044 participants (519 women and 525 men) aged 65–94 years. The study was approved by the ethics committee of the Bavarian Medical Association and all participants provided a written informed consent. All investigations have been conducted according to the principles expressed in the Declaration of Helsinki.

Data collection

Trained medical staff obtained information on sociodemographic variables, physical activity level, medication, alcohol consumption, smoking habits and comorbidities during a standardized face-to-face interview. Furthermore, all study participants underwent a standardized medical examination. All measurement procedures have been described in detail elsewhere [23].

Cardiac disease assessment

Patients were considered to have a cardiac disease if they reported: (1) a history of myocardial infarction, coronary angioplasty or bypass surgery certified by a medical hospital report or (2) another cardiac disease such as angina pectoris, heart failure, atrial fibrillation, valvular heart disease or heart transplantation which was assessed during the medical examination.

Muscle strength

Grip strength was measured in kg using a hand-held dynamometer (JAMAR, Saehan Corp. UK). After adjustment for hand size, three attempts were performed with the dominant hand and all three measurements were averaged for the analysis.

Inflammatory markers

A non-fasting venous blood sample was obtained from all study participants while sitting and the serum samples were stored at −80 °C until analysis. Interleukin-6 was measured using enzyme-linked immunosorbent assay kits (R&D Systems, Abingdon, UK) and high sensitivity C-reactive protein was measured by nephelometry (BN II, Siemens, Eschborn, Germany). Interassay coefficients of variation were <13 % for IL-6 and <6 % for hs-CRP, respectively.

Covariates

Covariates included age, gender, body fat, alcohol intake, smoking habits, diabetes mellitus, arthritis/rheumatic disease, renal failure, use of statins, steroids, estrogens and antiplatelet therapy, and level of physical activity. Anthropometric measurements were taken after the participants had removed their shoes, heavy clothing and belts. Body height was measured to the nearest 0.1 cm and weight to the nearest 0.1 kg. BMI was calculated as weight (in kilograms) divided by height^2 (in square meters). Bioelectrical impedance analysis was conducted to estimate total fat-free mass and body fat using the BIA-2000-S Analyzer (Data Input, Frankfurt, Germany) [24]. Assessment of alcohol intake (in grams per day) was based on data regarding weekday and weekend consumption of beer, wine, and spirits. Participants provided information about whether they had ever smoked cigarettes regularly and they classified as current and ex-smoker or never smoker. Chronic health conditions were determined through a self-administered questionnaire and a standardized telephone interview adapted from the self-report-generated Charlson Comorbidity Index [25]. Physical activity was assessed in the personal interview based on the physical activity scale for the elderly (PASE) from which continuous physical activity scores were then calculated (PASE total, leisure and household [26]. Leisure items included questions in light, moderate, vigorous and endurance exercises, whereas household items incorporated household chores and yard work. Statins, steroids, estrogens and antiplatelet medication were recorded using the IDOM-Software [27].

Statistical analysis

Means and frequencies were used to describe demographic and other clinical characteristics of the sample populations. Differences between groups were analyzed using the *t* test for independent samples or the χ^2 test (for continuous and categorical variables, respectively). Because the inflammatory variables were not normally distributed, the parametric tests (correlation and analysis of variance) were performed using their log-transformed values. Pearson's correlation tests were used to evaluate the correlations between inflammatory markers and muscular strength. Two-Way ANOVA was applied to test for differences in IL-6 and hs-CRP levels across the incremental tertiles of muscular strength between the two groups.

Logistic regression was performed to estimate the association of muscular strength with the odds of having elevated inflammatory markers. For this reason, we created tertiles of handgrip strength (upper, middle and high) and split the IL-6 and hs-CRP variables (high and low) by using the value >75th percentile in the total population as a cut point (see "Results"). Several models were applied to examine the association. First, age- and gender-adjusted models were calculated (Model 1). Thereafter, analyses were additionally adjusted for body fat, alcohol intake, smoking habits, diabetes mellitus, arthritis/rheumatic disease, renal failure, and use of medications (statin, antiplatelet, steroid and estrogen use) (Model 2) and finally also for levels of physical activity (Model 3). Statistical analyses were performed using the SPSS program (version 16.0) and the level of statistical significance was set at $p < 0.05$.

Results

The characteristics of the participants with and without cardiac disease are shown in Table 1. Persons with cardiac diseases were significantly ($p < 0.05$) older, were more likely to be inactive, had a poorer health status (higher prevalence of diabetes mellitus, arthritis and renal failure), were less likely to drink alcohol, were more likely to take statins and antiplatelet medication and had higher levels of IL-6.

Among persons with cardiac diseases IL-6 and hs-CRP pointed to a significantly negative correlation with muscular strength, ($r = -0.211$ and $r = -0.225$, respectively, with $p < 0.001$ in both cases). Among those without cardiac diseases only IL-6 showed a significant correlation with muscular strength ($r = -0.135$, $p < 0.001$), whereas hs-CRP did not.

The mean values of muscular strength tertiles for cardiac patients were 15.7 ± 4.2, 25.3 ± 2.5 and 37.0 ± 5.4 kg, while the corresponding values for the persons without cardiac disease were 16.2 ± 3.9, 24.9 ± 2.5 and 37.3 ± 5.7 kg (tertiles from low, middle and high), respectively. Furthermore, we tested for differences in IL-6 and hs-CRP levels across the incremental tertiles of muscular strength between the two groups (2-way ANOVA). For both, elderly with cardiac diseases and those without cardiac diseases, no significant interaction was observed ($p < 0.05$). However, the factor ≪ strength tertiles ≫ revealed

Table 1 Characteristics of participants with and without cardiac diseases in the KORA-Age study

	Without cardiac disease ($n = 721$)	With cardiac disease ($n = 323$)	p value
Age (years)	75.4 ± 6.6	77.6 ± 6.4	<0.001
Men (%)	48.9	51.6	0.409
Weight (kg)	76.0 ± 13.6	77.8 ± 14.5	0.057
Height (cm)	163.8 ± 9.4	164.1 ± 9.5	0.573
BMI (kg/m^2)	28.3 ± 4.2	28.9 ± 4.8	0.057
Fat mass (kg)	26.2 ± 7.2	27.1 ± 8.6	0.086
Higher education (%)	30.7	32.8	0.298
PASE total score (No.)	123.2 ± 57.2	103.9 ± 51.5	<0.001
Current and ex-smokers (%)	44.1	40.0	0.209
Alcohol intake (g/day)	14.0 ± 18.7	10.3 ± 14.3	0.002
Handgrip strength (kg)	26.9 ± 9.6	25.6 ± 9.9	0.064
Cardiac diseases			
MI (%)	–	33.1	–
PTCA (%)	–	19.7	–
CABG (%)	–	16.4	–
Other cardiac diseases (%)	–	30.8	–
Chronic diseases			
Cancer (%)	3.4	5.4	0.231
Diabetes mellitus (%)	15.0	23.6	0.001
Lung diseases (%)	10.8	11.0	0.886
Arthritis/rheumatic disease (%)	16.0	22.1	0.016
Renal failure (%)	3.5	7.8	0.002
Medication			
Statins (%)	19.8	44.5	<0.001
Antiplatelet agents (%)	23.3	51.3	<0.001
Steroids (%)	6.0	8.5	0.154
Estrogen (%)	19.5	17.4	0.608
Inflammatory markers			
IL-6, median (IQR), pg/ml	1.71 (1.13–2.78)	2.16 (1.33–3.66)	<0.001
Log IL-6, median (IQR)	0.53 (0.12–1.02)	0.77 (0.27–1.29)	<0.001
hs-CRP, median (IQR), mg/L	1.65 (0.84–3.66)	1.84 (1.03–3.74)	0.158
Log hs-CRP, median (IQR)	0.50 (0.17–1.29)	0.63 (0.03–1.34)	0.101

BMI body max index, *CABG* coronary artery bypass grafting, *IQR* interquartile range, *MI* myocardial infarction, *PTCA* percutaneous transluminal coronary angioplasty

significant main effects ($p < 0.05$). Among cardiac patients, those in the lowest tertile of muscular strength had the highest levels of inflammatory markers (for both IL-6 and hs-CRP) whereas for those without cardiac diseases the same pattern was observed only for IL-6 (Figs. 1, 2).

In the group of participants with cardiac diseases, the age- and gender-adjusted logistic regression analysis (Model 1) showed that low levels of muscle strength were significantly associated with a fourfold increased odds of having elevated IL-6 levels (OR 3.92, 95 % CI 1.57–9.77, $p < 0.01$). When the models were further adjusted for body fat, alcohol intake, smoking, diseases and medication (Model 2) as well as physical activity (Model 3), the associations still remained significant (OR 3.84, 95 % CI 1.32–11.15, $p < 0.05$ and OR 3.53, 95 % CI 1.18–10.50, $p < 0.05$, respectively).

Furthermore, elderly cardiac patients with low levels of muscle strength had a threefold increased odds of having elevated hs-CRP levels (OR 3.31, 95 % CI 1.27–8.62, $p < 0.05$) after controlling for age and gender (Model 1) as well as after adjustment for body fat, alcohol intake, smoking, diseases and medication (OR 3.61, 95 % CI 1.12–11.60, $p < 0.05$, Model 2), whereas the association remained borderline significant after the final adjustments (OR 2.80, 95 % CI 0.85–9.24, $p = 0.092$, Model 3).

The same trends regarding the associations between muscular strength and inflammatory markers were observed in older adults without cardiac disease although the

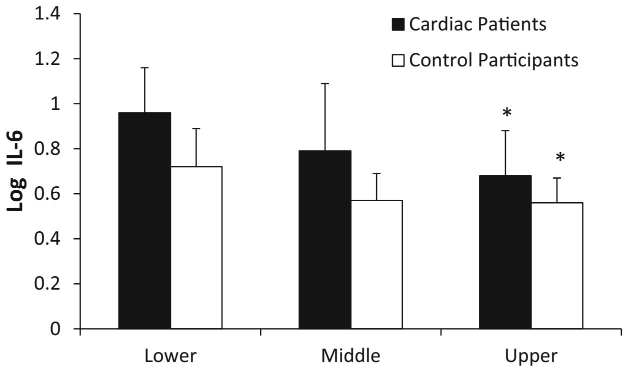

Fig. 1 Log IL-6 levels across incremental tertiles of muscle strength, $*p < 0.05$ vs lower strength, in parenthesis the mean normal values for IL-6 (cardiac patients: 3.3, 2.9, 2.5 pg/ml and control participants: 2.8, 2.3, 2.2 pg/ml for lower, middle and upper strength, respectively)

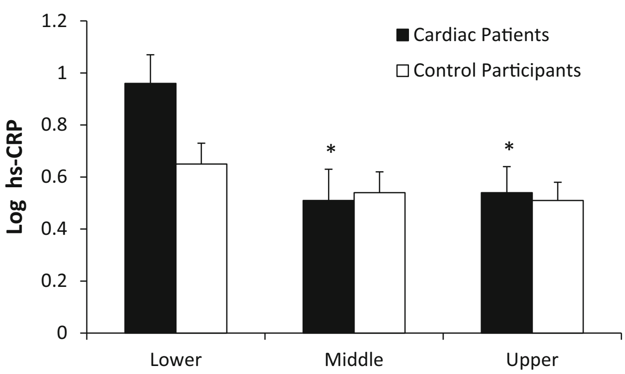

Fig. 2 Log hs-CRP levels across incremental tertiles of muscle strength, $*p < 0.05$ vs lower strength, in parenthesis the mean normal values for hs-CRP (cardiac patients: 5.9, 3.5, 3.2 mg/L and control participants: 4.0, 3.6, 3.2 mg/L for lower, middle and upper strength, respectively)

odds ratios were slightly lower than in those with cardiac diseases (Tables 2, 3).

Discussion

To our knowledge, this is the first population-based study in which the association between muscular strength and inflammatory markers among elderly persons with cardiac disease has been investigated. Our results reveal that low muscular strength is significantly associated with an increased odd of having elevated circulating inflammatory markers (IL-6 and hs-CRP), even after controlling for potential confounders including physical activity.

Our results are in agreement with earlier studies among elderly subjects in whom lower muscle strength was associated with higher levels of IL-6 and CRP [16–21]. Visser et al. [16] were among the first who reported that lower muscle mass and lower muscle strength were associated with higher cytokine levels in well-functioning older men and women, and this association has also been confirmed in very old people aged 90 years [21]. In these studies, almost the same covariates for adjustment were used (age, gender, BMI or fat mass, race, smoking habits, diseases and use of medications) and some authors have further accounted for physical activity [16, 20, 21], a well-known determinant of muscular fitness. The fact that the association between muscle strength and inflammation was independent of physical activity levels, as also observed in our study, shows that there are autonomous effects of muscular strength in relation to inflammation. Given that we measured both the leisure time and the household physical activity for our adjustments, strengthens our findings even more.

However, the mechanisms for this association between muscular strength and inflammation reported in the literature are still not completely understood. From animal studies, it is known that the administration of IL-6 or TNF-α causes skeletal muscle catabolism simultaneously impairing the rate of protein synthesis [28]. This has been confirmed in a prospective study in older men and women, aged 74.6 years on average, where higher levels of IL-6 and CRP were associated with a two to threefold greater risk of losing more than 40 % of grip muscular strength over a period of 3-year follow-up [18]. Based on these studies, inflammation seems to explain a significant part of the development of sarcopenia during aging and our data showed that elderly persons with cardiac diseases, who have a low muscular strength, are at an increased risk of having an abnormal inflammatory status.

On the other hand, resistance exercise can accelerate the rate of protein synthesis in the contracting muscles and increase muscle mass counteracting by this way the catabolic effects of inflammation. Thus, performing resistance training is of significant importance for elderly cardiac patients (especially those with chronic heart failure who suffer from progressive muscle wasting) and may act as a preventive factor to reduce chronic inflammation and thus atherosclerotic complications. Indeed, we recently reported normal pro-inflammatory (IL-6, CRP and TNF-a) and positive anti-inflammatory alterations (IL-10 and TGF-β1) during acute resistance exercise at a usual (50 % of 1 RM) and at a higher intensity (75 % of 1 RM) in patients with coronary artery disease [29]. All the above are of clinical interest since the abnormal inflammatory status is an independent risk factor that predicts cardiovascular outcomes and mortality [30, 31].

In our study, we observed that cardiac patients had slightly greater odds of having elevated inflammatory markers with lower levels of muscular strength compared to older adults without cardiac disease and to our knowledge, this is the first study nowadays presented on this

Table 2 Odds ratios for increased IL-6 levels (75th percentile) by tertiles of grip strength in older adults with and without cardiac disease

	Odds ratio (95 % CI)					
	Model 1		Model 2		Model 3	
With cardiac disease ($n = 323$)						
Upper	Reference	*p*	Reference	*p*	Reference	*p*
Middle	1.70 (0.85–3.42)	0.136	1.53 (0.69–3.41)	0.293	1.57 (0.70–3.55)	0.275
Lower	3.92 (1.57–9.78)	0.003	3.84 (1.32–11.15)	0.014	3.53 (1.18–10.50)	0.024
Without cardiac disease ($n = 721$)						
Upper	Reference	*p*	Reference	*p*	Reference	*p*
Middle	1.88 (1.10–3.23)	0.021	1.79 (1.02–3.14)	0.041	1.83 (1.04–3.23)	0.036
Lower	2.92 (1.42–5.99)	0.004	3.07 (1.45–6.47)	0.003	2.96 (1.38–6.32)	0.005

Model 1: adjusted for age and gender. Model 2: in addition to model 1 further adjusted for body fat, alcohol intake, smoking status, diabetes mellitus, arthritis/rheumatic disease, renal failure and use of medications (statins, antiplatelets, steroids and estrogens). Model 3: in addition to model 2 further adjusted for physical activity

Table 3 Odds ratios for increased hs-CRP levels (75th percentile) by tertiles of grip strength in older adults with and without cardiac disease

	Odds ratio (95 % CI)					
	Model 1		Model 2		Model 3	
With cardiac disease ($n = 323$)						
Upper	Reference	*p*	Reference	*p*	Reference	*p*
Middle	0.87 (0.40–1.88)	0.724	1.06 (0.42–2.67)	0.893	0.95 (0.37–2.46)	0.925
Lower	3.31 (1.27–8.62)	0.014	3.61 (1.12–11.60)	0.031	2.80 (0.85–9.24)	0.092
Without cardiac disease ($n = 721$)						
Upper	Reference	*p*	Reference	*p*	Reference	*p*
Middle	1.70 (1.03–2.80)	0.037	1.78 (1.05–3.04)	0.033	1.78 (1.04–3.07)	0.037
Lower	2.28 (1.18–4.40)	0.014	2.87 (1.43–5.77)	0.003	2.64 (1.29–5.38)	0.008

Model 1: adjusted for age and gender. Model 2: in addition to model 1 further adjusted for body fat, alcohol intake, smoking status, diabetes mellitus, arthritis/rheumatic disease, renal failure and use of medications (statins, antiplatelets, steroids and estrogens). Model 3: in addition to model 2 further adjusted for physical activity

topic. This can be explained by the different health status as well as by the fact that they were somewhat older and had higher indices of inflammation and lower levels of muscular strength.

Our results have several clinical applications. Because higher muscle strength is associated with lower inflammation, physicians and other health care professionals should encourage cardiac patients to enhance their level of muscular strength by performing regular resistance training. Such programs are likely to improve body strength which may counteract the catabolic effects of chronic, subclinical inflammation affecting thereby the progression of the atherosclerotic disease. Increased muscle strength may have an even greater clinical implication for the aging cardiac patient due to the well-known association that exists between systemic low-grade inflammation and muscle atrophy/weakness of older people. Resistance exercise has been effectively applied in cardiac rehabilitation settings during the last 2–3 decades with many physiological benefits. It remains to be cleared if this type of training provides an anti-inflammatory protection in these patients. However, more interventional studies are needed (and especially randomized controlled studies and large multicenter trials) to further confirm our findings and to provide definite evidence whether or not resistance exercise reduces inflammation and if this accompanies with an improvement of the individuals' clinical outcomes.

Limitations

Because of the cross-sectional character of the study, we only report on associations and cannot conclude on underlying mechanisms and pathophysiology between inflammatory markers and muscle strength. Although we adjusted for several confounders, it may well by that other, unmeasured factors might have affected the observed association between muscular strength and inflammatory markers. Furthermore, our results could not be generalized to all cardiac patients and especially to those who are at a younger age or to those who suffer from congenital heart diseases or other heart diseases affecting young people (for example non-ischemic cardiomyopathy). Another limitation is that physical activity, although assessed using a validated questionnaire, did not accurate measures the individuals' level of physical fitness. Finally, grip strength might not necessarily represent muscle strength in the lower extremities or total body strength; thus, more studies using strength measures of overall muscle strength are needed to confirm our findings.

Conclusion

Our findings suggest that lower levels of muscle strength may be a marker of chronic inflammation in older persons with cardiac diseases, independent of potential confounders including physical activity. Thus, the implementation of resistance exercise training for these individuals, as currently recommended by numerous health organizations, seems to be essential to reduce the direct adverse effects of chronic inflammation and aging on muscle catabolism.

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Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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