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ScienceDirect
Metabolism Clinical and Experimental 57 (2008) 650–657
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Increasing physical fitness does not proportionally decrease circulating C-reactive protein level in men with varying fitness

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Received 12 September 2007; accepted 13 December 2007

Abstract

Several studies have shown that low physical fitness is associated with high levels of C-reactive protein (CRP), a marker of future cardiovascular events. However, whether increasing physical fitness proportionally decreases the circulating CRP level has not been evaluated. We first evaluated the basic relationship between physical fitness, assessed by running velocity, and circulating CRP level along with cardiovascular risk factors in 1065 healthy middle-aged men. Afterward, we examined the association between annual change in fitness and changes in CRP level in 482 subjects who had the same parameters measured 1 year later without any intervention. In the cross-sectional study, physical fitness was significantly correlated with circulating CRP level ($r = 0.28$, $P < .0001$). This significance still remained after adjustment for other cardiovascular risks ($\beta = -.12$, $P = .0004$). In the follow-up study, several variables, including CRP, were significantly improved (CRP geometric mean, from 0.35 to 0.26 mg/L; $P < .001$). Improvements in fitness did not reach statistical difference ($P = .067$). Annual change in CRP was significantly correlated with creatinine kinase level 1 year later ($r = 0.16$, $P = .004$) and with annual changes in some other risks, but not with annual change in fitness. When follow-up subjects were divided into tertiles according to increase in fitness, the greatest reduction in CRP was found in subjects with mildly increased fitness and favorable risk profiles (n = 159; CRP geometric mean, from 0.35 to 0.21 mg/L; $P < .0001$), but not in those with moderately to highly increased fitness (n = 113; geometric mean, from 0.36 to 0.28 mg/L; $P = .03$). In conclusion, although physical fitness was significantly associated with circulating CRP level in a cross-sectional study, increasing fitness did not proportionally decrease circulating CRP level. Improving coincidental risks, relieving intensity of exercise-induced muscle damage, or both, in addition to increasing fitness, might be important to effectively reduce CRP level.

1. Introduction

Atherosclerosis is no longer conceived to be a pure lipid-based disorder [1]. Low-grade inflammation is involved in the initiation and progression of atherosclerosis. Thus, improving inflammatory status can be one of the strategies for the prevention of atherosclerosis and for the reduction in mortality due to cardiovascular disease.

C-reactive protein (CRP), a marker of systematic inflammation, has been considered to be a valuable maker of future cardiovascular events and type 2 diabetes mellitus [2,3]. Previous studies have revealed that reducing body weight by energy restriction alone lowered the levels of CRP [4,5]. The most plausible mechanism is that weight loss induces a decrease of visceral adipose mass, which releases several cytokines (tumor necrosis factor [TNF] α, soluble TNF-α receptor, interleukin [IL] 1 receptor antagonist, etc) including IL-6, which stimulates hepatic CRP synthesis [6]. On the other hand, circulating CRP levels are low even in really fit but not lean or overweight people, for example, runners, if their cardiorespiratory fitness is high [7-9], although the mechanism has not been established. Several cross-sectional studies have revealed that high fitness was associated with low CRP levels independent of body fat in healthy subjects as well as in patients with diabetes or coronary heart diseases [10-12]. Furthermore, physical fitness, an objective measure of recent physical activity

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doi:10.1016/j.metabol.2007.12.009

patterns, is stronger than self-reported physical activity as a predictor of several outcomes [13]. As far as we know, however, there have been few reports that have examined the association between CRP and fitness in the Japanese population, which has less fatness and lower mortality due to cardiovascular disease compared with Western populations [14]. In addition, whether increasing fitness proportionally decreases circulating CRP level has not been prospectively evaluated.

First, for the conformation of significant associations between the circulating CRP level and fitness as assessed by running velocity, we recruited apparently healthy middle-aged men, for whom the load of the treadmill test was insufficient for accurate evaluation of cardiorespiratory fitness. Because physical fitness is modified not only by regular exercise but also by cardiovascular risks such as age, obesity, smoking, diet, and genetic factors [15], taking into account the confounding effects of these factors, we followed about half of them for 1 year and evaluated the association between shift in level of fitness and changes in the circulating CRP level along with cardiovascular risks. Our main purpose was to examine whether increasing fitness proportionally decreased the circulating CRP level in subjects with varying baseline fitness. Exploration of the mechanism underlying fitness and the circulating CRP level in combination with cardiovascular risks will aid in constructing effective methods for reducing CRP level, that is, improving low-grade inflammation, which possibly induces future cardiovascular events and type 2 diabetes mellitus.

2. Methods

2.1. Subjects

For the evaluation of the basic association between cardiorespiratory fitness as assessed by running velocity and circulating CRP level, we recruited (starting in 2004) men who had worked for the Japan Self-Defense Force and who passed the regular medical checkup for the running test. Afterward, we followed about half of them without any intervention and measured the same factors 1 year later, with occasional health promotion lectures emphasizing the importance of exercise and fitness. Daily habits, such as smoking status and exercise frequency, were examined by questionnaire both at baseline and 1 year later. Habitual alcohol intake (more than 3 sessions of drinking per week) was examined only at baseline. Exclusion criteria included people with diabetes mellitus treated with medication, prevalent clinical cardiovascular diseases including angina or myocardial infarction, and use of antihypertensive medication or cholesterol-lowering drugs. Subjects with CRP level of more than 10.0 mg/L were also excluded because of possibly undetected systemic diseases at baseline and 1 year later. Furthermore, follow-up subjects with creatinine kinase (CK) level of more than 600 IU/L at 1 year later were also excluded because of moderate to severe skeletal muscle damages by acute or chronic intense exercise. In the follow-up study, we could not collect complete data in some of the original participants, mainly because of personnel changes and orthopedic damages. Overall, 1065 male subjects were recruited at baseline; and 482 participated in the follow-up study. This study was approved by the Council of the Base, and all subjects gave written informed consent to use their data for the study.

2.2. Study design

Previous studies have reported that running and walking capacity is closely associated with cardiorespiratory fitness, that is, VO_2 peak [16-18]. In this study, the physical fitness levels were assessed by the velocity of 5-km running (V5K) instead of treadmill test because most subjects studied were quite healthy with moderate to high fitness (more than 10 metabolic equivalents [METs]); thus, the treadmill load was not enough for them. Moreover, a short time such as 10 minutes and a short course such as less than 1 km of running tests did not yield appreciable differences in the measurements. Participants freely chose the day for their running test from various choices to accord to their physical condition. In the running tests, which were held under permitted weather conditions as objectively assessed by wet-bulb globe temperature (<25°C), each person ran 5 km on a flat road in each capacity and was monitored by medical staff. The running time was measured in minutes and seconds at least twice, at both baseline and 1 year later. We then calculated the V5K (meters per minute) equivalent for the best time. For the evaluation of effect of shift in fitness on change in CRP level, the 482 subjects were divided into tertiles according to the degree of changes (differences) in fitness (V5K), as follows: declined (<0 m/min, D group), mildly increased (0-10 m/min, Mi group), or moderately to highly increased (>10 m/min, MoH group).

2.3. Laboratory measurements

At least 1 week before the running test, the laboratory measurements were done. For blood sampling, the subjects avoided vigorous exercise (eg, more than 1 hour of continuous running) for a week and then fasted overnight, after which blood was obtained from the antecubital vein and plasma was then frozen at −40°C until used in assays. Plasma CRP concentrations were determined with the Dade Behring automated high-sensitivity immunoassay with a detection level of 0.11 mg/L with run-to-run coefficient of variation of 4.6%. Plasma total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), glucose (fasting plasma glucose [FPG]), ureic acid (UA), and CK concentrations were automatically measured using the HITACHI autoanalyzer. All the above variables, except CK, were measured again 1 year later. Creatinine kinase was measured only at 1 year later for the evaluation of muscle damage. Waist circumference (WC) was measured at the

height of navel level during a slight expiration. Body mass index (BMI) was calculated as weight divided by the height squared (kilograms per square meter).

2.4. Statistical analysis

Data are presented as means (SD). The distribution of CRP levels was highly skewed. Therefore, $\log_{10}$-transformed (CRP in milligrams per liter) values of CRP (logCRP) were used in all analyses, with results expressed as geometric means (interquartiles). In addition, smoking status and exercise frequency as well as other variables were taken into account for analysis by being labeled with number, as follows: current smoking: no = 0; if yes, the number of cigarettes smoked per day; and exercise frequency (more than 30 minutes of aerobic running that ranged from approximately 5-8 km/30-80 minutes): never/rarely = 0, <1 time a week = 1, 1 to 3 times a week = 2, 4 to 6 times a week = 3, or daily = 4. The logCRP and other variables were tested using 1-way analysis of covariance under a general linear model. Annual changes in variables were also tested using repeated-measures analysis of variance (ANOVA), with tertile as one factor. Differences between tertiles were examined by the Bonferroni method. The correlations between variables studied were assessed by Pearson correlation test. For multivariate linear regression, we first used a stepwise model, including all variables significantly associated with logCRP. Variables selected by stepwise procedure were then included in a new model. Statistical analysis was performed with SPSS (version 11.0; SPSS, Chicago, IL) and StatView (version 5.0; SAS, Cary, NC). A P value of less than .05 was considered as statistically significant.

3. Results

3.1. An assessment of association between V5K and CRP level in a cross-sectional study

The characteristics of subjects are summarized in Table 1. Most of the subjects were nonobese with moderate-to-high fitness, that is, an average of 196 m/min, equivalent to approximately 12.7 METs, which is generally vigorous intense fitness compared with other population studies [19]. All subjects could run 5 km safely, with favorable cardiovascular profiles including low levels of circulating CRP (0.37 mg/L).

As shown in Fig. 1, the circulating CRP level was decreased across the quintile of fitness as assessed by V5K (P for trend < .0001). Although data are not shown, the logCRP level was more significantly correlated to V5K level than self-reported exercise frequency ($r = -0.28$, $P < .0001$ and $r = -0.07$, $P = .03$, respectively). Multiple regression analysis revealed that this significance remained ($\beta = -.12$, $P = .0004$) after adjustment for age, BMI, WC, TC, TG, HDL-C, UA, FPG, blood pressures, smoking, and exercise frequency (Table 2).

3.2. Annual follow-up study

Table 3 shows the metabolic characteristics of subjects who participated in the follow-up study at baseline and 1 year later according to tertile. In the full group of subjects, they exercised for a mean of 4 to 6 times per week. C-reactive protein, TC, diastolic blood pressure, and UA were improved. Increases in fitness did not reach statistical difference ($P = .067$). At baseline, there were no significant trends in variables across the tertiles, except for HDL-C and V5K. When the annual difference in logCRP level was examined in combination with tertile of increase in fitness, a confounding reaction between CRP reduction and change in fitness was recognized (Fig. 2; $P = .012$, 2-way repeated-measures ANOVA); CRP reduction was dependent on the degree of improvement of fitness. Thus, we evaluated significance of difference in logCRP levels between baseline and 1 year later by 1-way repeated-measures ANOVA at every tertile (Table 3). Unexpectedly, the most significant reduction in CRP level was found in the Mi group ($P < .0001$), but not in MoH group ($P = .03$), which was irrespective of significant weight loss ($P < .05$). Moreover, the significant difference in logCRP reduction was recognized only between the D and Mi groups (Fig. 3, $P = .003$), suggesting a disproportional association between increase in fitness and CRP reduction. Table 4 shows correlation coefficients between annual changes in logCRP

Table 1
Physical characteristics of subjects at baseline (N = 1065)

Variables	
Age (y)	44.1 ± 6.2
Weight (kg)	69.3 ± 10.1
BMI (kg/m^2)	24.0 ± 3.1
WC (cm)	82.7 ± 8.4
SBP (mm Hg)	126.8 ± 15.3
DBP (mm Hg)	75.8 ± 12.6
TC (mg/dL)	214.0 ± 36.2
HDL-C (mg/dL)	51.5 ± 13.5
TG (mg/dL)	107 (74-159)
UA (mg/dL)	6.2 ± 1.3
FPG (mg/dL)	102.8 ± 14.4
CRP (mg/L)	0.37 (0.18-0.71)
Fitness, V5K (m/min)	196.7 ± 28.8
Smoking status (%)	
Never	48.1
Current	43.2
Past	8.7
Alcohol (% yes)	57.3
Hypertension (% yes)	11.6
Diabetes (% yes)	5.1
Exercise activity (%)	
Daily	11.5
4-6 times/wk	27.2
1-3 times/wk	23.8
<1 time/wk	27.6
Never/rarely	9.9

Values are mean ± SD. C-reactive protein is expressed as geometric means (interquartiles). SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

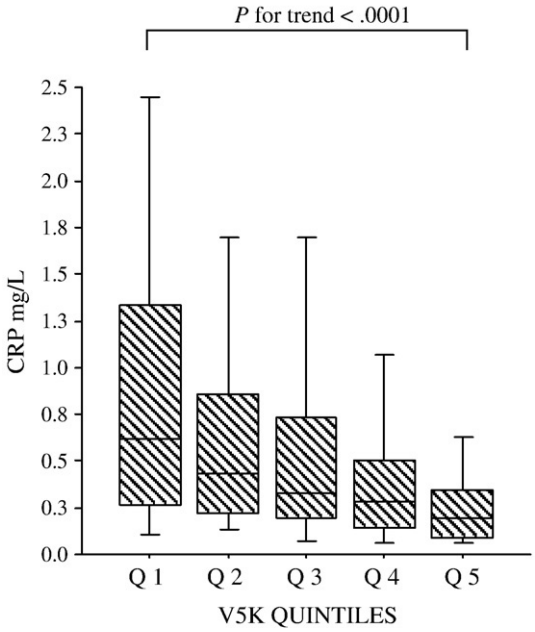

Fig. 1. Circulating CRP concentrations according to quintiles of V5K. The CRP level was significantly decreased across the quintiles of V5K, as follows: Q1, ≤150 m/min (98); Q2, 151 to 180 m/min (294); Q3, 181 to 210 m/min (297); Q4, 211 to 230 m/min (256); and Q5, ≥231 m/min (120). Numbers are represented in parentheses.

and changes in variables, including both V5K and logCRP at baseline, and CK level at 1 year later. The change in logCRP was significantly correlated with changes in other coincidental risks, TC, HDL-C, UA, and FPG, but not with change in V5K (P = .87). Furthermore, there was a significant correlation between change in logCRP and CK level at 1 year later (r = 0.16, P = .004), indicating a potential association between CRP levels and muscle damage in this study.

4. Discussion

In this cross-sectional study, we confirmed a significant association at baseline between cardiorespiratory fitness, as assessed by running velocity, and the circulating CRP level in middle-aged men with varying fitness, despite the low geometric mean level of CRP (0.37 mg/L) compared with other studies [8,9,12]. Consistent with previous reports [10-12], V5K was significantly and negatively correlated with CRP level independent of other risks, especially body fatness (BMI and WC). Moreover, the logCRP level was more strongly correlated with V5K than with self-reported exercise frequency. Thus, we believe that running capacity, especially in apparently healthy middle-aged adults, who do not always have favorable cardiovascular risk profiles, is suited for the evaluation of fitness if caution is carefully paid for emergency in the running test. As for the reproductivity of the 5-km running test, unfortunately, we could not evaluate this appropriately. However, unlike a general population, the participants studied were well accustomed to running tests, which were held frequently at regular intervals quite apart from the current study, and were also well acquainted with their own fitness and physical condition. Therefore, the subjects yielded reasonably stable best results that accorded to their fitness. Nevertheless, further studies are needed to show more precisely the validity of running capacity as an assessment for cardiorespiratory fitness.

Tomaszewski et al [9] reported that CRP concentrations are markedly lower in ultramarathon runners who had high cardiorespiratory fitness compared with sedentary controls of similar BMI. They speculated that factors other than less body fat might account for the lower CRP concentration in such marathon runners. Although the mechanism of high physical fitness in relation with low levels of CRP has not been fully understood, in the beginning, we had speculated that a similar degree of increasing fitness proportionally reduces CRP level in a dose-response relationship, even in men with varying fitness. In the group of follow-up subjects, CRP decreased without weight loss and was accompanied with a tendency toward increased fitness with significant improvement of several risks. As for these improvements, some subjects might simultaneously perform diet therapy themselves, for example, refraining from a meat diet, probably because of the initial health promotion lectures. Taking into account the degree of increase in fitness, the CRP reduction was not proportionally associated with improvement of fitness. Furthermore, the greatest CRP reduction was not found in the MoH group, irrespective of a significant reduction in BMI.

One possible explanation for the disproportional association is related to the intensity of exercise, although significant differences in exercise frequency were not found between baseline and 1 year later for each tertile. Because the fitness level in the D and Mi groups had already been high at baseline, the intensity of exercise that they continued was not vigorous for them. However, the intensity of exercise the MoH group carried out could be somewhat vigorous for them because, at baseline, the fitness in the MoH group was the lowest of the tertiles. Consistent with our results, several studies have shown that exercise training accompanied with modest improvements in fitness is not associated with improved levels of CRP [20,21]. Moreover, Okita et al [22] reported that the CRP reduction after exercise and diet, which was consequently linked to increased fitness,

Table 2
Multivariate regression analysis for logCRP

Variables	B	SE	β	P value
BMI	0.057	0.006	.35	<.0001
V5K	−0.002	0.001	−.12	.0004
Smoking	0.007	0.002	.11	.0007
FPG	0.003	0.001	.09	.007
UA	0.024	0.012	.07	.04

Adjusted total R^2 = 0.23.

Table 3
Annual change in variables at the 1-year follow-up

	Whole subjects (n = 482)		*P* baseline vs 1 y later	D group (n = 210)		Mi group (n = 159)		MoH group (n = 113)		*P* for trend	
	Baseline	1 y later		Baseline	1 y later	Baseline	1 y later	Baseline	1 y later	Baseline	1 y later
Age (y)	42.5 ± 5.5	–	–	42.8 ± 5.5	–	42.4 ± 5.7	–	41.9 ± 5.2	–	NS	–
Weight (kg)	69.2 ± 10.2	69.2 ± 10.4	NS	69.8 ± 10.3	70.0 ± 10.2 *	68.5 ± 10.3	68.4 ± 10.2	69.4 ± 10.7	68.9 ± 10.2 *	NS	NS
BMI (kg/m^2)	23.9 ± 3.0	23.9 ± 2.9	NS	23.9 ± 3.0	24.0 ± 3.0 *	23.7 ± 2.8	23.7 ± 2.8	24.1 ± 3.2	23.9 ± 3.1 *	NS	NS
WC (cm)	82.7 ± 8.0	82.5 ± 8.1	NS	83.3 ± 8.2	83.3 ± 8.3	81.6 ± 8.0	81.9 ± 8.0	82.3 ± 7.7	82.7 ± 7.8	NS	NS
SBP (mm Hg)	127.0 ± 14.7	126.7 ± 14.8	NS	128.1 ± 14.5	127.1 ± 14.4	126.7 ± 16.3	126.5 ± 15.2	125.5 ± 12.6	126.1 ± 15.2	NS	NS
DBP (mm Hg)	75.7 ± 12.1	74.4 ± 12.0	.01	76.9 ± 12.6	76.0 ± 11.8	75.2 ± 12.5	73.7 ± 12.3	74.4 ± 11.7	72.4 ± 11.9	NS	.02
TC (mg/dL)	212.0 ± 34.7	195.3 ± 30.1	<.0001	211.0 ± 36.5	194.5 ± 31.2 ‡	214.2 ± 34.1	195.7 ± 28.1 ‡	210.5 ± 32.0	196.3 ± 31.0 ‡	NS	NS
HDL-C (mg/dL)	52.3 ± 14.3	52.8 ± 15.4	NS	50.5 ± 14.4	50.5 ± 12.9	54.3 ± 14.8	55.2 ± 15.8	52.9 ± 15.8	53.7 ± 16.1	.04	.01
TG (mg/dL)	128.1 ± 99.6	121.0 ± 80.1	NS	134.7 ± 109.7	124.5 ± 75.4	115.9 ± 88.5	116.0 ± 85.9	132.7 ± 93.2	121.2 ± 80.4 *	NS	NS
UA (mg/dL)	6.2 ± 1.3	5.9 ± 1.2	<.0001	6.1 ± 1.2	5.9 ± 1.1 ‡	6.2 ± 1.2	5.9 ± 1.2 ‡	6.3 ± 1.3	6.1 ± 1.2 †	NS	NS
FPG (mg/dL)	101.9 ± 14.2	102.5 ± 14.7	NS	103.5 ± 18.1	104.1 ± 17.8	100.4 ± 9.8	100.5 ± 10.0	101.2 ± 10.6	102.4 ± 13.6	NS	NS
CRP (mg/L)	0.35 (0.17-0.70)	0.26 (0.05-0.78)	<.0001 [a]	0.34 (0.17-0.68)	0.30 [a] (0.08-0.87)	0.35 (0.18-0.68)	0.21 ‡, [a] (0.05-0.55)	0.36 (0.17-0.81)	0.28 *, [a] (0.05-0.88)	NS [a]	NS [a]
V5K (m/min)	199.0 ± 27.6	200.4 ± 28.8	NS	205.4 ± 26.4	193.7 ± 27.6 ‡	197.3 ± 25.6	201.3 26.0 ‡	189.2 ± 29.3	211.7 ± 31.1 ‡	<.0001	<.0001
CK (mg/dL)	–	154.2 ± 133.7	–	–	153.7 ± 149.2	–	140.0 ± 84.7	–	175.0 ± 156.1	–	NS
Exercise	3.16 ± 1.14	3.16 ± 1.14	NS	3.16 ± 1.11	3.13 ± 1.15	3.17 ± 1.17	3.17 ± 1.10	3.09 ± 1.16	3.21 ± 1.20	NS	NS
Smoking	6.2 ± 7.1	6.2 ± 7.1	NS [a]	6.3 ± 6.9	6.4 ± 6.9 [a]	6.0 ± 7.3	6.0 ± 7.3 [a]	6.3 ± 7.2	6.2 ± 7.2 [a]	NS [a]	NS [a]

[a] Statistical significance was analyzed after data were log transformed.
*<.05.
†<.001.
‡<.0001.

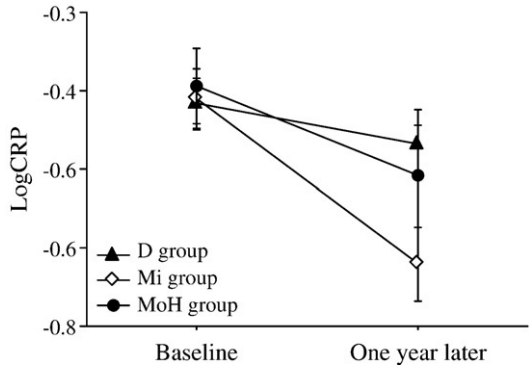

Fig. 2. Annual change in logCRP level according to tertile. A confounding interaction between change in CRP and change in fitness was recognized (P = .012, 2-way repeated-measures ANOVA).

did not correlate proportionally with the change in body weight in obese Japanese women. Nevertheless, epidemiologic studies have shown a greater reduction in risk of cardiovascular disease with vigorous (typically ≥6 METs) than with moderate-intensity physical activity [19]. Taken together, there might be subtle differences between CRP or inflammation markers and other risks in response to exercise training that significantly increases fitness.

In relation to these findings, logCRP was significantly associated with CK level at 1 year later. Prolonged daily training and intense exercise produce chronically elevated serum enzyme levels such as CK and lactate dehydrogenase [23,24]. Creatinine kinase increases more with exercise in untrained than well-trained people [24]. Although we excluded those subjects with apparent inflammation as assessed by CRP value and clinical symptoms and those with muscle damages as evaluated by elevated CK, low-grade inflammation was probably still present. Thus, similar to CK, CRP might also increase more with exercise, especially intense exercise, in untrained people, who are equivalent to the subjects in the MoH group at baseline. Concerning the change of CRP, 2 studies have reported that circulating CRP levels only increased significantly at 12 to 24 hours post a single bout of moderate to intense training compared with those before training [25,26]. Thus, any acute effects of exercise on CRP levels would be excluded because participants were advised not to undertake hard exercise before blood sampling. Meanwhile, chronic intense exercise would be associated not only with inducing muscle damage but also with provoking the release of insulin counter-regulatory hormones such as glucagon and catecholamines [27], possibly deteriorating the inflammatory status.

Another possible explanation for the disproportionate association is the presence of coincidental cardiovascular risk factors, which probably independently affect circulating CRP level. Although significant differences were not recognized in most variables among the tertiles, subjects in the Mi group had a more favorable cardiovascular profile at both baseline and 1 year later. Surely, annual changes in some of these variables were significantly associated with the annual change in logCRP. As regards the possible contribution of smoking and alcohol to CRP level, several studies have indicated that moderate alcohol consumption is associated with lower CRP level and that cigarette smoking is associated with CRP elevation [28,29]. Indeed, the numbers of cigarettes smoked per day were higher in the MoH than the Mi group regardless of the slight difference, suggesting that smoking might impede lowering CRP level, especially in the MoH group. Meanwhile, in the stepwise regression analysis at baseline, alcohol was not selected as a significant predictive factor for variation of CRP (Table 2).

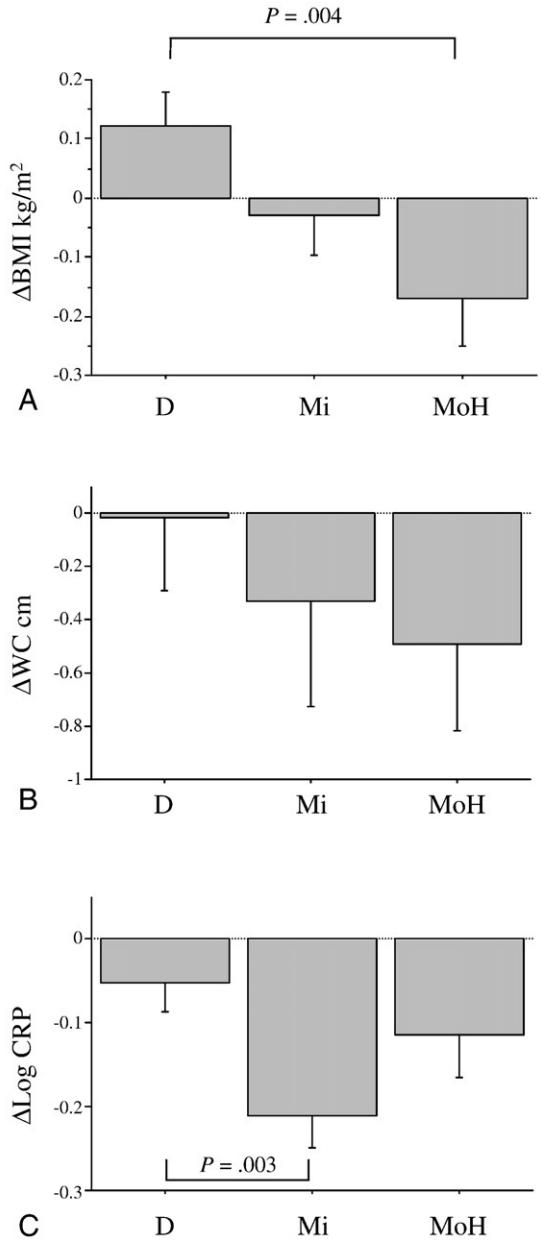

Fig. 3. Annual differences (Δ) in BMI (A), WC (B), and logCRP (C) according to tertile. A significant difference was seen in ΔBMI between the D and MoH groups (A) and in ΔlogCRP between the D and Mi groups (C).

Table 4
Correlation coefficients between annual changes in variables at the 1-year follow-up

	ΔlogCRP	ΔV5K
ΔlogCRP	–	−0.04
ΔV5K	−0.04	–
ΔBMI	0.01	−0.17†
ΔWC	0.04	−0.07
ΔSBP	−0.06	0.06
ΔDBP	−0.03	−0.05
ΔTC	−0.10*	0.02
ΔHDL-C	−0.11*	0.01
ΔTG	−0.07	−0.02
ΔUA	0.09*	0.01
ΔFPG	0.11*	−0.04
ΔExercise	−0.04	0.06
ΔSmoking	0.03	0.05
CK at 1 y	0.16†	0.02
V5K at baseline	−0.02	−0.25‡
logCRP at baseline	−0.17†	0.01

*$P < .05$.
†$P < .001$.
‡$P < .0001$.

Thus, we excluded alcohol as a factor in the analysis that followed. Although the data were not shown, the percentages of those with habitual alcohol intake at baseline were 57.6%, 64.3%, and 57.1% for the D, Mi, and MoH groups, respectively (no significant difference between groups, χ^2 test). Again, despite the slight difference, moderate alcohol consumption might effectively contribute to lowering CRP in the Mi group. Taken together, further improving coincidental risks such as smoking and alcohol intake, in addition to increasing fitness, may be important to effectively reduce circulating CRP levels.

Alternatively, although the circulating CRP level was not effectively reduced in the MoH group, there is a possibility that atherogenicity may be consequently decreased because exercise also produces an increase in various anti-inflammatory mediators. Drenth et al [30] reported that a 5-km run elicits both the production of acute-phase mediators (leukocytosis and elevation of CRP) along with anti-inflammatory counter-regulation, as judged by an increase in circulating concentrations of IL-1 receptor antagonist and soluble TNFs and a down-regulation of TNF-α production. Moreover, it has been suggested that posttraining muscle-derived IL-6 contributes to mediate beneficial metabolic effects of exercise and may inhibit TNF-α production and insulin resistance not only within skeletal muscle but also at distant sites [31]. Thus, there are parallel protective anti-inflammatory counter-regulatory mechanisms that are part of the response to exercise. In this context, measuring only CRP may be insufficient to assess the degree of low-grade inflammation.

Finally, intake of some specific nutrition and supplements such as antioxidant vitamins could affect the association between fitness and CRP level [32] because individuals with healthy intention and regular exercise are likely to pay attention to diet and nutrition at the same time. Unfortunately, we did not examine such special or anti-inflammatory factors.

Further studies, including measurement of anti-inflammatory factors and lifestyle-related confounders, as well as several inflammatory factors, are needed to elucidate this complicated mechanism in more detail.

4.1. Conclusion

We have demonstrated in healthy middle-aged men with varying physical fitness that fitness, as assessed by running capacity, is significantly and independently associated with the circulating CRP level. In our follow-up study 1 year later, increasing fitness did not proportionally decrease the CRP level. Improving coincidental risks and/or relieving the intensity of exercise-induced muscle damage, in addition to increasing fitness, might be important to reduce CRP level effectively.

4.2. Caution from the study

We think that the running tolerance test, not necessarily 5 km, is better for the evaluation of cardiorespiratory fitness in middle-aged subjects with moderate to high fitness. In addition to regular medical checkup, caution must be exercised with beginners and elders, especially those with cardiovascular risk factors. Moreover, acute or endurance exercise, especially for untrained persons, may induce acute orthopedic damages instead of the expected benefits.

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