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Letters to the Editor

Biological markers, lifestyle factors, and metabolic syndrome

To the Editor:

One-year randomized controlled trial with special reference to diet and/or physical activity on serum C-reactive protein (high-sensitivity C-reactive protein [hs-CRP]) was presented by Camhi et al [1]. The analysis was stratified by the existence of metabolic syndrome (MetS), and precise intervention protocol was adopted. A randomized controlled trial is the most valid procedure to elucidate cause-effect relationship, and they concluded that low-fat diet was the strongest predictor to reduce CRP as a biological marker in women.

You et al [2] reported the association between the MetS and circulating adipokines; and Naharci [3] recently made a recommendation to add some information such as comorbidities, lipid profile, and medication for hypertension for better understanding of the relationship. Kressel et al [4] also reported that systemic and vascular markers of inflammation showed significant association with insulin resistance and the MetS. Among them, resistin is significantly related to insulin resistance and MetS via plasminogen activator inhibitor–1 (PAI-1) [5]. Plasminogen activator inhibitor–1 is related to blood coagulation and suppresses smooth blood circulation [6-8].

We have continuously conducted health survey to know the relationship between biological markers and MetS for female inhabitants who continue their habitual exercise. For the present time, female population with habitual exercise showed poor association between vascular inflammatory and coagulation markers and MetS. Our research was summarized as follows.

To investigate the characteristics of serum PAI-1 activity and hs-CRP levels in a group having regular exercise, female subjects who have history of exercise for more than 5 years with frequency being more than once per week were registered. We also assessed the visceral adiposity evaluated by waist circumference (WC), percentage body fat, and body mass index. Metabolic syndrome was judged by the International Diabetes Federation criteria.

Mean age and standard deviation were 66.2 and 6.1 years, respectively. Geometric means (95% confidence interval) of PAI-1 and hs-CRP were 16.5 (4.7-57.7) ng/mL and 0.43 (0.08–2.42) mg/L, respectively. Plasminogen activator inhibitor–1 was positively associated with hs-CRP ($n = 68$, $r = 0.52$, $P < .001$; adjusted for age). After adjustment for age, systolic and diastolic blood pressure, WC, high-density lipoprotein cholesterol, triglyceride, and fasting plasma glucose, the relationship remained significant ($n = 62$, $r = 0.28$, $P < .05$). The stepwise multiple regression analysis was conducted to predict PAI-1 or hs-CRP using age, body mass index, percentage body fat, WC, high-density lipoprotein cholesterol, triglyceride, fasting plasma glucose, systolic blood pressure, and diastolic blood pressure as independent variables. Each dependent variable was also used as an independent variable. As a result (Table 1), logarithm of PAI-1 was significantly associated with percentage body fat ($P < .01$) and logarithm of hs-CRP ($P < .05$). Furthermore, logarithm of hs-CRP was also significantly associated with WC ($P < .001$). Namely, PAI-1 as a marker of blood coagulation was related to hs-CRP as an inflammatory marker and total amount of body fat. In addition, hs-CRP was associated with central obesity. Plasminogen activator inhibitor–1 and hs-CRP were interrelated, and obesity index was associated with them.

Multiple logistic regression analysis was conducted to predict MetS by using age, PAI-1, and hs-CRP. However, each odds ratio did not reach significant level to predict MetS. Obesity is a component of MetS, and it is significantly related to inflammatory and coagulation factors by multiple regression

Table 1
Stepwise multiple linear regression analysis for identifying determinants of the log-transformed values of PAI-1 and hs-CRP using components of MetS including age

Independent variable	*B*	Standard error	*β*-Coefficient	Significance
PAI-1				
% Body fat	0.021	0.006	0.417	<.001
Logarithm of hs-CRP	0.206	0.090	0.262	<.05
hs-CRP				
WC	0.018	0.005	0.435	<.001
Logarithm of PAI-1	0.328	0.142	0.259	<.05

Adjusted square values of multiple regression coefficient for PAI-1 and hs-CRP were 0.338 and 0.353, respectively.

analysis. There is a possibility that dietary factor would relate to PAI-1 or hs-CRP via obesity, which can be speculated by the stratification of MetS presented by Camhi et al [1].

In parallel to clarify the significance of inflammation and coagulation factors to insulin resistance and MetS, dietary factor is indispensable to know the effect of lifestyle factors on systemic vascular marker and the component of MetS.

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Potential mechanisms linking low-fat diet to inflammation and metabolic syndrome

To the Editor:

We thank Dr Kawada for his interest and comments regarding our recent publication on low-fat diet and C-reactive protein (CRP) [1] and welcome the opportunity to respond.

In our study, results showed that change in CRP was significantly greater in the low-fat diet group compared with the exercise group, but only in women classified with metabolic syndrome [1]. The positive effects of a low-fat diet on inflammation were not found in men overall, women overall, men with or without the metabolic syndrome, or women without the metabolic syndrome [1].

We agree with Dr Kawada that dietary intake may be important for reducing inflammation, although the exact physiologic mechanism relating low-fat diet to CRP is poorly understood. Increased intake of dietary fat can induce a proinflammatory profile, increasing circulating levels of cytokines such as interleukin-6 and tumor necrosis factor−α [2]. Consumption of n-3 polyunsaturated fatty acids, a type of fat common in low-fat foods, can inhibit cytokine release directly from the endothelium in a vascular model of atherosclerosis [3]. The lower levels of cytokines may result in lower circulating CRP levels. Low-fat foods also may simultaneously change macronutrient intake and quality [4]. Individuals who consume low-fat diets also tend to increase intake of fruits, vegetables, and whole grains [4]. Increased fruit and vegetable consumption can induce anti-inflammatory effects, which may also lower CRP levels [5]. Meals that cause a rise in insulin and epinephrine output are associated with higher levels of CRP [6]. Interleukin-6 release is also hypothesized to be stimulated by the amount of insulin and catecholamine in the bloodstream [7]. Thus, meals that limit the increase in postprandial glucose may also reduce levels of cytokines and CRP in the bloodstream [8]. In fact, consumption of meals that limit the rise in insulin and glucose, such as low-glycemic diets, reduces CRP levels [9]. Our study does not allow us to comment if any of these potential mechanisms played a role in our results. Future studies are needed to elucidate the mechanism linking low-fat diet to inflammation.

Dr Kawada suggests that the possible explanatory physiologic mechanism linking low-fat diet and CRP may be through obesity. If the low-fat diet from our research did promote a change in CRP through obesity, then changes in obesity (or body composition, namely, adipose tissue) would be expected to predict the change in CRP. Our analysis included the covariate for percentage body fat change. Results showed that the change in body fat was not a significant predictor for change in CRP in men, in women, or in men and women with or without metabolic syndrome. Interestingly, women without metabolic syndrome did lose a significant amount of body fat in the low-fat diet group (−1.7%), but without any significant changes in CRP. In contrast, women with metabolic syndrome in the low-fat diet group had significant changes in CRP, but without significant reductions in body fat (−0.6%). Thus, results from a randomized controlled trial suggest that the link between low-fat diet and inflammation is not mediated through obesity per se.