Does Inflammation Influence Cardiovascular Risk Factor Modification?

To the Editor:

We read with interest the article by Erlinger et al. demonstrating a reduced effect of a 12-week lipid-lowering Dietary Approaches to Stop Hypertension (DASH) diet in 100 patients with elevated baseline C-reactive protein (CRP). Specifically, the authors noted less total and LDL cholesterol reductions and a greater increase in triglycerides in patients whose CRP values were above their reported median value of 2.37 mg/dL compared with subjects with CRP values below this level. In their section on study limitations, however, they raised the possibility of a Type I error and concluded, "Clearly, additional studies would be useful both to confirm the interaction and to better assess the point at which inflammation attenuates the beneficial effects of dietary change."1

Therefore, we evaluated the effects of therapeutic lifestyle change incorporating diet (low fat, Mediterranean style), exercise training, and risk factor modification in 225 consecutive patients enrolled in a cardiac rehabilitation and exercise training (CRET) program (12 weeks, 36 educational and exercise sessions) dichotomized on the basis of median values of CRP (median: 3.40 mg/dL). At baseline, there were no significant differences in age, lipids, anthropometrics, or blood pressure between subjects above and below the median CRP. Patients with lower CRP, however, had slightly higher exercise capacity (peak VO2: 17.7 versus 15.6 mL/kg · min⁻¹; P = 0.002) compared with patients with higher CRP. After CRET, there were statistically similar improvements in body weight, body fat, exercise capacity, and quality of life in both groups. In addition, the high-CRP patients had a significant improvement in HDL cholesterol (+7%; P < 0.0001) and nonsignificant changes in triglycerides (−10%; P = 0.1), total cholesterol (+1%), and LDL cholesterol (+2%), which were statistically similar to the lipid changes in the low-CRP group (+7%, −7%, +1%, and −1%, respectively). Systolic and diastolic blood pressure, however, fell 5% and 4%, respectively (each paired P < 0.05; P for interaction = 0.03) in the low-CRP group versus no change in the high-CRP group. These findings were similar regardless of whether we used our CRP median cutoff of 3.4 mg/dL or the 2.37 mg/dL cutoff from Erlinger et al.1

In conclusion, in contrast to the study by Erlinger et al.,1 we did not observe significant differences with regard to lipid changes based on initial values of CRP. However, in our larger population of cardiac patients receiving a more holistic approach to therapeutic lifestyle change, we did observe an absence of blood pressure lowering in patients with values of CRP above the median, despite similar gains in exercise capacity and weight reduction. These data may suggest an alternative mechanism by which inflammation may influence cardiovascular risk factor modification.

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Response

Milani and Lavie report a prospective analysis of 225 consecutive patients enrolled in a cardiac rehabilitation and exercise training (CRET) program. In contrast to our findings, the authors’ findings indicate that lipid changes to this comprehensive lifestyle program (“low fat, Mediterranean-style” diet and exercise) were independent of baseline C-reactive protein (CRP) levels. Further, they report that persons with lower CRP had greater reductions in blood pressure. Still, the data presented are very limited. We encourage the authors to report their findings more completely.

There are several potential explanations for the apparent differences between the studies. First, the results presented by Milani and Lavie are from a prospective analysis of a single comprehensive lifestyle intervention; hence, an intervention by baseline CRP interaction cannot be tested, much less a diet by CRP interaction. The pre-post design also leaves open the possibility of confounding, but we are not told what, if any, factors were controlled for in the analysis. More importantly, the study by Milani and Lavie involved weight loss, whereas weight was held constant in the DASH (Dietary Approaches to Stop Hypertension)–Sodium trial. Weight loss, independent of diet, is associated with an improved lipid profile. In this setting, low levels of baseline inflammation may be irrelevant or the effect of inflammation overwhelmed by changes in lipid metabolism occurring with weight loss.

The strong direct association between adiposity and CRP further complicates interpretation of their results. In a weight loss intervention, persons with higher baseline weight, and therefore higher CRP levels, might be expected to lose more weight than individuals with a lower baseline weight. This scenario could even result in an inverse association between baseline CRP and cholesterol responsiveness, ie, persons with higher CRP (and greater baseline adiposity) might lower their cholesterol to a greater extent than persons with lower CRP (and less baseline adiposity) as a result of differences in the amount of weight lost.

Their finding of a potential interaction between baseline CRP and blood pressure responsiveness is interesting. In our study, we found no significant interaction between diet and baseline CRP level on blood pressure responsiveness. However, as highlighted in the above discussion, it is difficult to compare results from different study designs and different interventions, but clearly the issues of blood pressure and lipid responsiveness to nonpharmacologic interventions deserves further investigation.

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