Yes, yes, IL-6: what else?

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IN THIS ISSUE of the Journal of Applied Physiology, the article “Time course of changes in inflammatory markers during a 6-mo exercise intervention in sedentary middle-aged men: a randomized-controlled trial” by Thompson and colleagues (6), independent of the specific sets of results presented in the manuscript, addresses a more general question that many laboratories, in a variety of forms, have been attempting to address in recent years: what is the role of exercise in improving inflammatory status, and what biomarkers are most suitable to gauge this effect?

I would bet that taking a random poll within scientists even loosely associated with this field of research, many would initially feel surprised that this question has not already been answered. Probably most would agree with the general concept that yes, exercise has favorable effects on inflammatory status, and IL-6 is likely to be included in a “short list” of inflammatory biomarkers whose fluctuations better parallel the onset, progression, and remission of exercise-associated inflammatory processes. These concepts, however, remain disappointingly vague; conclusive definition of the complex biochemical details of the interaction between exercise and inflammation, including the role played by IL-6 and other crucial pro- and anti-inflammatory markers, has proven extremely challenging. Part of the problem, paradoxically, may actually have been caused by the exceptionally rapid increase of available analytical techniques, the lack of standardization between different methodologies used for similar assays (a clear example are the discrepancies frequently reported between measurements of the same molecule with ELISA or with a multiplex conjugated bead assay) and the rate of discovery of new molecules involved in inflammation homeostasis (with classified cytokines now numbering in the hundreds).

In this context, in the study by Thompson et al. (6), four key observations seem to emerge: 1) the chosen inflammatory markers [IL-6 and alanine aminotransferase (ALT)] responded strongly to a 24-wk exercise intervention in generally healthy but physically inactive middle-aged men; 2) only subjects with highest initial levels of these variables responded appreciably; 3) the improvement in IL-6 (but not in ALT) was lost after just 2 wk of detraining; and 4) other indexes of inflammation [white blood cell (WBC) counts, C-reactive protein (CRP), intercellular adhesion molecule-1 (ICAM-1), heme oxygenase-1, oxidized low-density lipoproteins] were not affected. These few points effectively summarize two conceptually contrasting issues: 1) there is a remarkable, and to date largely underutilized, preventive and therapeutic potential for the effective use of exercise, requiring a thorough understanding of all biochemical mechanisms underlying its health effects; and 2) it is extremely difficult to derive homogeneous sets of the necessary preliminary results, conclusively leading the field toward solid practical applications. Let me expand on this point with a very simple question, again based on the paper by Thompson et al. (6). Can we state, based on this manuscript, and assuming that study results are solid and reproducible, that exercise reduces inflammation, and that this effect is mediated by a reduction in IL-6, but not in CRP, ICAMs, or WBC counts? The reality is that we really cannot.

For one thing, there is no such thing as “exercise” as a general entity; in each specific instance, exercise effects on inflammatory homeostasis, as well as on all other relevant adaptive mechanisms, are dictated by format, duration, intensity, repetition pattern, etc. Extrapolating these considerations to special groups of subjects, it can even be argued that in particular instances the effects of some forms of exercise may become harmful, as cleverly described in a review by Cooper et al. (2) that recently appeared in this very journal.

But even assuming that a given exercising population can indeed benefit from exercise, and after normalizing for exercise characteristics, enormous difference in exercise effects may occur based on sex, maturational status, age, ethnicity, fitness level, basal inflammatory status, and recent and past medical history. For instance, let’s consider subjects with Type 2 diabetes, a group of patients with known increased basal inflammatory status, and who are strongly encouraged to exercise as part of their condition’s management. In these subjects, let’s look at two variables from the Thompson et al. paper, one that changed with intervention, IL-6, and one that didn’t, CRP. While I do not claim to exhaustively review here the whole literature in the field, I am aware of at least two studies in which IL-6 showed conflicting trends, significantly decreasing in response to a prolonged exercise regimen in one (5), and not changing in the other (3). Similarly, the CRP was significantly affected by exercise training in only two of three studies in which it was reported (1; 3–5). What is this lack of clarity reflecting: the fact that exercise only “sometimes” is able to produce an anti-inflammatory effect, or simply our inability to capture this effect? Both possibilities are probably true.

The results of the Thompson et al. (6) paper should therefore be seen as applicable only to a narrow group of subjects (men of a restricted age range, health make-up, fitness level, and basal inflammatory status), performing a very specific exercise format for a determined amount of time, etc. A legitimate question to ask ourselves at this point should therefore be whether such a narrow range of applicability seriously limits the scientific value of this type of study. I rather believe that the contrary is true: exactly because of the extreme variability of possible results in different experimental situations, the only reasonable strategy to draw credible conclusions is to restrict the focus enough that, even if only within very well-defined limits, statements hold true. Conversely, studies reporting more “general” results, with vague confirmation of some previous
work and no definite conclusions, are likely to further confuse our understanding of the field and slow down our progression toward the generation of widely applicable guidelines.

What can we do? Designing and implementing separate studies addressing all conceivable exercise formats, and their interaction with all possible different physiological and pathological states in human subjects, is obviously impossible.

However, this may not be necessary. What is absolutely necessary is the worldwide coordination of a large number of leading exercise laboratories so that future studies (and we are probably talking about hundreds of individual studies) are carefully mapped, avoiding overlap, strategically addressing specific subject populations, standardizing data acquisition, and sharing databases. Given the number and quality of new informatics tools available to the scientific community, this is perfectly feasible, at least from the technical point of view, and I believe this is an occasion we should take full advantage of.

We find ourselves at a time in history when rising medical care costs are driven by the sophistication of newly discovered medical technologies. While these costs could be offset by healthier populations requiring less medical care, an exponential increase is instead occurring in the incidence and prevalence of preventable pathologies, such as obesity, diabetes, and cardiovascular disease, due to the unforeseen consequences of changes in social and cultural habits in Western societies. Considering the importance of inflammatory processes in the evolution of these pathologies, the effective use of exercise represents an uncharacteristically inexpensive, but possibly just as effective, alternative solution. A truly “effective” use of exercise, however, can only be based on the advanced knowledge of all aspects of its interaction with inflammatory homeostasis, which still remain nebulous. This is a call to break this vicious cycle.

REFERENCES