Exercise Is Beneficial: But How and Why?

To the Editor:
The recent guidelines issued jointly by the American Diabetes Association and the American College of Sports Medicine emphasized on the importance of exercise in the management of Type 2 diabetes mellitus. These recommendations have been issued based on the evidence that regular moderate to vigorous aerobic exercise prevents the development of Type 2 diabetes mellitus, and in those with the disease, it improves it. In an extension of these recommendations, Bilińska et al showed that short-term dynamic training caused significant improvement of hemodynamic and neurohormonal responses to handgrip, cardiovascular fitness and inflammatory state in the form of handgrip-induced increases in heart rate, blood pressure, and total peripheral resistance being lower, whereas stroke volume and cardiac output were higher with a concomitant increase in nitric oxide level and a lower increase in noradrenaline, which was observed in patients who had exercised compared with controls. These results suggest that exercise is anti-inflammatory in nature, as proposed previously. Studies performed in experimental animals revealed that exercise not only improved plasma glucose and lipid profile in obese and obese/diabetic rats but also reduced interleukin (IL)-6 and tumor necrosis factor (TNF)-α content of the pancreatic β cells that could explain the improvement seen in peripheral insulin resistance. Although a direct measurement was not done in any of these studies, it is reasonable to propose that regular exercise could lead to a decreased synthesis and release of IL-6 and TNF-α from the myocardial cells and thus might improve cardiac function. Thus, exercise improves the function of not only skeletal muscle, but also of endothelial cells and myocardial cells.

Exercise enhances parasympathetic tone and decreases sympathetic tone. Acetylcholine, the principal vagal neurotransmitter, is an anti-inflammatory molecule because it (acetylcholine) significantly attenuated the release of TNF, IL-1β, IL-6 and IL-18, but not the anti-inflammatory cytokine, IL-10, in lipopolysaccharide-stimulated human macrophage cultures, whereas catecholamines of the sympathetic nervous system have pro-inflammatory properties. The inverse relationship between heart rate variability (HRV) and C-reactive protein (CRP) noted in a cross-sectional analysis suggests that cardiac parasympathetic tone increases as a compensatory mechanism to overcome the higher circulating CRP. These results emphasize the close relationship among the autonomic nervous system, pro- and anti-inflammatory cytokines, inflammation and the cardiovascular system. Furthermore, acetylcholine is a potent stimulator of endothelial nitric oxide generation.

A recent study suggested that exercise enhances the production of an anti-inflammatory lipid bioactive molecule, lipoxin A₄ (LXA₄), from arachidonic acid (AA), eicosapentaenoic (EPA) acid and docosahexaenoic acid (DHA). LXA₄ is a potent anti-inflammatory molecule that inhibits leukocyte activation, prevents platelet aggregation, and augments eNOS generation and thus can prevent, inhibit and/or reverse atherosclerosis. There is reasonable evidence to suggest that LXA₄ might prevent cardiac arrhythmias.

In this context, it is interesting to note that anti-inflammatory cytokines, IL-4 and IL-10, trigger the conversion of AA, EPA and DHA to lipoxins, resolvins, protectins and maresins, suggesting a mechanism by which they are able to suppress inflammation. In contrast, LXA₄ suppresses the production of pro-inflammatory cytokines, IL-6 and TNF-α. These results are in favor of the proposal that anti-inflammatory cytokines, IL-4 and IL-10, induce the expression and synthesis of anti-inflammatory lipid mediators, lipoxins, resolvins, protectins and maresins in addition to their ability to suppress the production of pro-inflammatory cytokines such as IL-2, IL-6, TNF-α, macrophage migration inhibitory factor and high-mobility group box 1 and leukotrienes (LTs).

Furthermore, urinary levels of LXA₄ were decreased while that of cysteinyl LTs (cysLTs, a pro-inflammatory eicosanoid) increased in volunteers aged from 26 to over 100 years, leading to a profound unbalance of the LXA₄/cysLTs ratio that might be considered an index of the endogenous anti-inflammatory potential. These results suggest that endogenous anti-inflammatory mechanisms become less efficient with age that could result in increased susceptibility to inflammatory disorders with advancing age, which might explain the increasing tendency for the development of hypertension, metabolic syndrome and coronary heart disease in the elderly. Hence, regular exercise is of benefit in the prevention of these diseases because exercise enhances LXA₄ formation.

Based on the preceding discussion, it is evident that the beneficial actions of exercise could be assessed in a more quantitative and qualitative manner by using some of these biochemical indices. Such an approach would assist patients with coronary heart disease, hypertension and metabolic syn-
drome, and normal subjects, so it is possible to evaluate to what extent the prescribed exercise benefited them. This approach could involve measuring plasma glucose, insulin, lipid profile, eNO, LXA₄, catecholamines, pro- and anti-inflammatory cytokines, in addition to clinical indices such as heart rate, blood pressure, total peripheral resistance, stroke volume, cardiac output, HRV both before and after exercise (Figure). The exercise that is being performed by an individual can be said to be adequate provided there is significant improvement in the clinical indices and a decrease in the levels of pro-inflammatory cytokines and catecholamines, and an increase in anti-inflammatory cytokines, NO and LXA₄, in addition to the lowering of plasma glucose and insulin levels and improvement in the lipid profile (such as HDL, LDL, triglycerides and cholesterol). It is possible to use peripheral leukocytes, macrophages and T cells to assess the impact of exercise in the target patient because they contain the complete intracellular machinery for the generation, release and inactivation of catecholamines, acetylcholine, eNO, LXA₄, and various cytokines. Thus, measurement of catecholamines, acetylcholine, NO, LXA₄, and various cytokines in the plasma and peripheral leukocytes could form a simple and reliable method to assess the adequacy and/or impact of exercise in a given subject. Some of these indices could also be measured in the urine, especially urinary levels of nitrite/nitrate, LXA₄ and catecholamines. Thus, it is not only interesting to study various plasma and urinary biochemical indicators as mentioned above and their clinical correlates in subjects with various diseases (such as insulin resistance, obesity, diabetes mellitus, metabolic syndrome, coronary heart disease, hypertension, hyperlipidemia, rheumatological conditions, etc) to know the adequacy of exercise being adopted by them and their beneficial effects, but it is also interesting to know which of these indices is the most suitable to assess the adequacy of exercise in a given subject/patient. Such an approach would also help to individualize exercise regimens as the response of each subject/patient to exercise might vary.

References


Undurti N Das, MD

UND Life Sciences, Shaker Heights, OH, USA; School of Biotechnology, Jawaharlal Nehru Technological University, Kakinada, India

(Released online March 9, 2011)