Interrogating the Age-Old Wisdom of Exercise

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Susan Cheng, MD\textsuperscript{1,2}

\textsuperscript{1}Framingham Heart Study, Framingham, MA; \textsuperscript{2}Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women’s Hospital, Boston, MA

Address for Correspondence:
Susan Cheng, MD
Cardiovascular Division
Brigham and Women’s Hospital
75 Francis Street, PBB-119
Boston, MA 02115
Tel: 857-307-1960
Fax: 617-812-0425
E-mail: scheng3@partners.org

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We have long known that exercise is good for us. Hippocrates declared over 25 centuries ago that “if we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health.” There is now a wealth of evidence indicating that the benefits of physical activity extend across multiple organ systems and span the age spectrum.\(^1,2\) Perhaps most compelling are data highlighting the potential of exercise to prevent and attenuate chronic conditions related to insulin resistance and atherosclerosis.\(^3,4\) Despite nationwide recommendations encouraging regular exercise for all adults, fewer than 1 in 3 Americans engage in routine physical activity.\(^5\) Low adherence rates could relate in part to the fact that we still do not really understand how exercise works. For this reason, recommendations remain non-specific with respect to how frequent, how intense, how long, what type, and for whom exercise should be prescribed.\(^4\)

Investigating the biology of exercise is challenging because its effects are dynamic, multi-systemic, and dependent on a myriad of endogenous and exogenous factors. Exercise is known to modulate multiple interconnected pathways including those related to insulin and glucose metabolism, lipid metabolism, and inflammation. In the current “omic” era of research, metabolomic analyses stand as an attractive approach for systematically interrogating the effects of exercise on these pathways. Metabolite profiling of a tissue sample, such as human plasma, involves using a technology such as nuclear magnetic resonance (NMR) spectroscopy or mass spectrometry to quantify prevalent small molecules, including analyses that are precursors or products of common metabolic pathways.\(^6\) Thus, high-throughput metabolite profiling offers the opportunity to capture ‘snapshots’ of biochemical activity in an individual at multiple time points over the course of engaging in physical activity.

Anticipating that metabolite profiles will differ based on the timing of exposure to
physical activity, a combination of short-term and long-term studies may help to provide a complete picture of the biochemical response to exercise. In effect, we can use metabolite profiling to assess biochemical activity during or immediately after exercise (stress phase), following participation in an extended exercise program (conditioning phase), and in the setting of routine physical activity maintained over the longer term (conditioned phase). With respect to short-term studies, Lewis and colleagues have shown that the acute response to an exercise stress test includes increased plasma markers of glycogenolysis, lipolysis, and adenine nucleotide catabolism in addition to increased concentrations of amino acids, span 2 tricarboxylic acid cycle intermediates, and also niacinamide – a modulator of insulin release and glycemic control.

Lewis et al. also studied the metabolite changes following a prolonged exercise episode (i.e., marathon running) and noted a further increase in markers of lipolysis, an increase in products of ketogenesis, and a marked downturn in concentrations of most amino acids. With respect to the metabolite response following extended program of physical activity, Huffman and colleagues studied previously sedentary persons undergoing 6 months of aerobic exercise. In this study, inactive overweight to obese adults who underwent the exercise training had improved insulin sensitivity that was associated with increased plasma concentrations of glycine, proline, and alanine as well as increased concentrations of free fatty acids and products of fatty acid oxidation. Until recently, longer-term studies that might extend and complement the work of these shorter-term studies have been lacking.

In this issue of Circulation, Kujala and colleagues report intriguing results from the first long-term study of metabolite profiles associated with persistent physical activity. The authors used NMR spectroscopy to perform a targeted assay of metabolites that included amino acids, ketone bodies, glycolytic precursors, and lipid particles. Sixteen adult twin pairs were identified...
for their marked intra-pair discordance in daily leisure-time physical activity of up to 12 METS per day, over up to three decades of follow up, and then had metabolite profiling performed. In addition, a total of 1037 age- and sex-matched pairs of unrelated adults from 3 community-based cohorts were identified as persistently active or persistently inactive; these individuals also underwent metabolite profiling. The main findings of the study were three-fold. First, the authors noted that active compared to inactive individuals had better lipoprotein cholesterol profiles and higher levels of polyunsaturated relative to saturated fatty acids. Second, they found that the branched chain amino acid (BCAA) isoleucine was lower in active than inactive individuals, with similar findings for valine as well as tyrosine and phenylalanine. Finally, they observed that α1-acid glycoprotein, an acute phase reactant, was lower in persistently active than in persistently inactive individuals.

The findings overall are noteworthy for several reasons. Importantly, the main results were remarkably consistent and in the expected direction across all 4 study cohorts despite differences between the cohorts in mean age, the instruments used to assess physical activity, and the durations of follow up. The results are also informative. Compared to mass spectrometry, NMR spectroscopy has a lower sensitivity for detecting less abundant metabolites. Nonetheless, NMR was used to effectively identify metabolites associated with exercise from across multiple functional domains, including lipid metabolism, amino acid metabolism, and inflammation. The relation of more optimal lipid profiles with long-term physical activity is not surprising and could be considered an experimental control. On the other hand, the observed relation of lower isoleucine with physical fitness is novel. Recently published clinical and experimental data indicate that elevated circulating levels of BCAAs are associated cross-sectionally with insulin resistance and cardiometabolic risk factors as well as longitudinally with incidence of diabetes
and cardiovascular events.\textsuperscript{10-13} Therefore, these data extend from prior studies and suggest that exercise has the potential to favorably alter BCAA metabolism over the longer term and not just the shorter term. Similarly, α1-acid glycoprotein could represent a marker of inflammatory and oxidative stress that is attenuated by long-term physical fitness.

While expanding the body of evidence linking BCAAs to cardiometabolic health, the data provided by Kujala and colleagues offer clues regarding the extent to which BCAAs may be pathobiological markers or mediators or both. In addition to the main analyses, they collected muscle and adipose tissue samples from 10 of the studied twin pairs and identified gene sets that were up-regulated in active compared to inactive twins. In a network analysis, the gene expression sets that appeared the most closely linked to physical activity were those for ubiquinone and oxidative phosphorylation, suggesting a prominent role of mitochondrial function. There is a burgeoning literature on the relationship between cardiometabolic fitness and mitochondrial function. In animal models, aerobic exercise augments mitochondrial size and oxidative activity as well as overall number.\textsuperscript{14} In turn, skeletal muscle electron transport chain activity increases, and this increase has been associated with improved insulin sensitivity and glucose handling in obese adults.\textsuperscript{15} Interestingly, experimental studies indicate that circulating amino acids can induce mitochondrial biogenesis to promote amino acid catabolism – where BCAA oxidation enzymes residing in adipose as well as muscle respond to increased BCAA concentrations resulting from exercise-stimulated protein breakdown.\textsuperscript{16} Accordingly, nodes representing gene expression for BCAA degradation are part of the network proposed by Kujala and colleagues, and variations in BCAA as well as other amino acids are linked most closely to measures of adiposity.

Clearly much more work is needed to unravel the mechanisms by which exercise confers
health benefits. That said, this large clinical study of physical activity as a long-term exposure offers additional strong evidence in support of the view that exercise is a chronic intervention with pleiotropic effects. Future research – including functional investigations and outcomes studies – are needed to elucidate exactly how exercise-related alterations in lipids, amino acids, and inflammatory markers as well as mitochondrial function may serve to optimize cardiometabolic risk. For instance, the extent to which exercise is associated with BCAA levels independent from its relation to insulin sensitization or weight loss remains uncertain.17 Research is also needed to further examine how genetic variants, dietary intake patterns, and the gut microbiome may impact the association of exercise with metabolites.18-20 All such investigations will continue to be challenging because an individual’s metabolic profile is intrinsically dynamic and in constant flux. However, it is precisely this aspect of the human metabolome that makes it an ideal subject of research focused on the attributes of exercise. By integrating the influences of active endogenous and exogenous factors at a given point in time, a whole body metabolite profile could eventually offer up-to-date, individual-specific data that are useful not only for characterizing risk for disease and determining potential for risk reduction but also for tailoring a prescription for intervention.

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