Interrogating the Age-Old Wisdom of Exercise

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We have long known that exercise is good for us. Hippocrates declared more than 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 guidelines 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 nonspecific 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, multisystemic, 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 spectroscopy or mass spectrometry to quantify prevalent small molecules, including analytes 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.

If we anticipate 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),7 after participation in an extended exercise program (conditioning phase),8 and in the setting of routine physical activity maintained over the longer term (conditioned phase). With respect to short-term studies, Lewis and colleagues7 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 niacinamide, a modulator of insulin release and glycemic control. Lewis et al7 also studied the metabolite changes that follow a prolonged exercise episode (ie, 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 after an extended program of physical activity, Huffman and colleagues8 studied previously sedentary persons undergoing 6 months of aerobic exercise. In that 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 colleagues9 report intriguing results from the first long-term study of metabolite profiles associated with persistent physical activity. The authors used nuclear magnetic resonance 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 intrapair discordance in daily leisure-time physical activity of up to 12 metabolic equivalents per day, over up to 3 decades of followup, 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 3-fold. First, the authors noted that active compared with 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 followup. The results are also informative. Compared with mass spectrometry, nuclear magnetic resonance spectroscopy has a lower sensitivity for detecting less abundant metabolites. Nonetheless, nuclear magnetic resonance 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 mellitus and cardiovascular events. 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, c1-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, mediators, or both. In addition to the main analyses, they collected adipose and muscle tissue samples from 10 of the studied twin pairs and identified gene sets that were upregulated in active compared with 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, which suggests 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. 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. Interestingly, experimental studies indicate that circulating amino acids can induce mitochondrial biogenesis to promote amino acid catabolism, in which BCAA oxidation enzymes residing in adipose and muscle tissue respond to increased BCAA concentrations that result from exercise-stimulated protein breakdown. Accordingly, nodes that represent 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, is needed to elucidate exactly how exercise-related alterations in lipids, amino acids, inflammatory markers, and mitochondrial function may serve to optimize cardiometabolic risk. For instance, the extent to which exercise is associated with BCAA levels independent of its relation to insulin sensitization or weight loss remains uncertain. 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. 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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None.

### References


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