Insulin sensitivity in skeletal muscle: “Use it or lose it, fast”

John P. Kirwan

1Department of Pathobiology, Lerner Research Institute, Cleveland Clinic; and 2Department of Physiology & Biophysics, Case Western Reserve University, Cleveland, Ohio

There is general agreement that physical activity is a sine qua non for overall physical and mental health (7). Despite this accepted axiom there is much scientific debate regarding the effect of physical activity on specific elements of health, particularly obesity-related diseases such as type 2 diabetes, and insulin resistance. Typically, high levels of physical activity are associated with robust metabolic health, heightened insulin sensitivity, low levels of atherogenic lipids, and well-controlled glucose regulation. In contrast, inactivity is associated with weight gain, obesity, insulin resistance, type 2 diabetes, and cardiovascular disease (5). Before the last two decades the latter was viewed as an age-related phenomenon with activity levels declining as people advanced to middle and old age. However, as society moved into the computer age, our technological successes have been counterbalanced by a decline in the amount of physical activity in our daily lives. The effects of reducing ambulatory activity on metabolic health are highlighted in a paper coauthored by Danish and US scientists and published in this issue of the Journal of Applied Physiology (3).

Krogh-Madsen and colleagues (3) performed a novel investigation on the effects of reducing daily ambulatory activity (from 10,000 to ~1,300 steps/day) on peripheral and hepatic insulin sensitivity, and related physiological adaptations that included changes in body composition and cardiorespiratory fitness. The subjects were young, lean, healthy men, and the investigators used state-of-the-art procedures, including euglycemic hyperinsulinemic clamps and isotope tracers to measure insulin sensitivity, muscle biopsies to evaluate functional changes in insulin signaling proteins in skeletal muscle, dual-energy X-ray absorptiometry (DEXA) to determine changes in body composition, and accelerometry and pedometry to monitor physical activity. The study was performed in a real-life, free-living setting, but with careful oversight to ensure compliance with diet and exercise. After 2 wk of reduced activity, energy expenditure was reduced, body weight increased, and lean body mass in the trunk and legs began to show decline. These changes in body composition were accompanied by a ~6–7% reduction in cardiorespiratory fitness, and most importantly, a 17% drop in peripheral insulin sensitivity. This loss in insulin sensitivity was reflected in a marked decrease in insulin-stimulated phosphorylation of Akt in skeletal muscle.

Although some of the observations reported by Krogh-Madsen were known from earlier detraining and bed rest studies, the context within which these changes occurred in the present study are particularly noteworthy (1, 4, 8). Specifically, the reduction in physical activity from ~10,000 steps/day, the activity levels broadly recommended by the Institute of Medicine (http://www.iom.edu/Global/News%20Announcements/Twelve-Tips-to-Take-Charge-of-Your-Health.aspx), to ~1,300 steps/day, the approximate step count for many sedentary Americans today. It is clear from these data that even if one starts out healthy and achieving expected goals for physical activity, declines in metabolic health are swift and significant, and likely to place an individual at metabolic risk within weeks of adopting a very sedentary lifestyle. Sustaining such a sedentary lifestyle for months or years would be expected to lead to further declines in insulin sensitivity, but perhaps even more important, is likely to lead to clinically significant weight gain and accumulation of abdominal adiposity and lipid deposition in muscle, liver, pancreas, and heart. The eventual outcome is significant morbidity associated with chronic disease states, including type 2 diabetes mellitus (T2DM) and cardiovascular disease. The speed with which one moves to the initial level of metabolic risk is highlighted by the data reported for these young men.

While the directionality of these data are troubling from a health perspective, the magnitude of change in all of the key outcome measures needs to be kept in perspective. Yes, there were weight gain and declines in insulin sensitivity, but these outcomes are still far from levels associated with obesity and T2DM. And yes, these data are troubling because it appears that even young healthy individuals cannot buffer the effects of a sedentary lifestyle for 2 wk. However, we do not know how quickly these individuals can rebound; it is likely to be equally rapid. There is evidence that adding an hour of exercise to a normally sedentary lifestyle results in a ~25% increase in insulin sensitivity, and weight changes similar in magnitude, but opposite in direction (2). Therefore, there is the likelihood that even though short periods of low levels of physical activity are detrimental, these declines can be overcome. In this light, it would have been of great interest if the subjects in this study had been followed for an additional 2 wk, during which they reverted to their normal levels of activity. Perhaps such a study will be forthcoming from this group or others in the near future.

The investigators are to be complimented on the quality of the study design and the thoroughness of their approach to the question. However, this first step points to a need for further study on the mechanisms contributing to the reduction in glucose disposal following such a short period of relative inactivity. Some insight could be gained from examining the associations between changes in glucose disposal and changes in lean body mass, or maximal oxygen consumption (VO2max). Perhaps a multivariate regression approach with a larger sample size would help in this regard. Further thought might also be given to a more detailed study of energy expenditure using a doubly labeled water approach. A potentially confounding aspect of this study is that it is difficult to understand how body weight and lean mass fell during a period when energy expenditure decreased by ~500 kcal/day while subjects “maintained their...
usual dietary habits.” In this context, data on fat-mass and total body water would have been informative. Going forward, more complete diet control and a more intensive approach to addressing energy balance will be needed in order to fully understand the mechanisms at play. Finally, one is left to wonder what is happening at the level of the muscle. The reduction in Akt phosphorylation suggests decreased insulin signaling, which in turn is consistent with decreased insulin-mediated glucose uptake. More detailed investigation of the insulin signaling pathway and GLUT4 translocation, and of the intracellular fate of glucose (viz., oxidative and nonoxidative pathways) will be needed to address this question.

One further comment: in a separate publication the authors have also shown that the adoption of this sedentary lifestyle is also associated with increases in visceral fat and abnormalities in lipid metabolism (6). Thus the effects are not limited to insulin sensitivity and cardiorespiratory fitness. This rather broad decline in metabolic function is a cause for concern and the message needs to be fully assimilated. As physiologists, we are well aware of the plasticity of skeletal muscle and the ability to model and remodel to accommodate specific metabolic demands. The “use it or lose it” concept is not new; however, the speed at which insulin sensitivity can be lost, and the real-life contextual relevance of the data from Krogh-Madsen et al. (3), provide novel insights to understanding chronic disease development.

REFERENCES