Does Endurance Training Protect From Lipotoxicity?

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From this issue of Diabetes, Phielix et al. (5) hypothesize that, relative to their untrained counterparts, the high oxidative capacity of endurance-trained athletes attenuates lipid-induced insulin resistance during hyperinsulinemic-normoglycemic clamp tests. Results showed that the athletes’ higher VO2max was associated with greater ex vivo muscle mitochondrial capacity, insulin sensitivity, and carbohydrate oxidation. Lipid infusion reduced glucose disposal by 63% in untrained individuals, thereby confirming previous reports (3), but only by 29% in the athletes. The authors explained the athletes’ reduction in glucose disposal exclusively by diminished carbohydrate oxidation. They interpret the concomitant dephosphorylation of muscle glycogen synthase as stimulation of glycogen synthesis reflecting shunting of glucose into nonoxidative storage as glycogen, in line with the “substrate (glucose:FFA) competition” theory of Randle et al. (6) (Fig. 1). The strength of this article includes combining in vivo and in vitro methods to assess muscle metabolism and signaling without interference from acute exercise effects. Nonetheless, some limitations need to be considered: 1) the nominally higher body weight and plasma FFAs during lipid infusion could have contributed to greater insulin resistance in the untrained participants; 2) indirect calorimetry does not measure tissue-specific nonoxidative metabolism; and 3) assessment of protein expression after prolonged insulin stimulation, which cannot trace the sequence of signaling events.

Endurance training causes various adaptations such as increased muscle capillary density, glucose transporter-4 expression, and mitochondrial mass (7). Phielix et al. confirm this in that maximal oxidative phosphorylation expressed per muscle fiber was enhanced in athletes but not different from the untrained individuals when expressed per mitochondrial content. Nevertheless, baseline ATP synthase flux can be lower in relation to tricarboxylic acid cycle flux, thereby indicating less efficient mitochondrial coupling in athletes (8).

Without lipid infusion, the athletes’ higher insulin sensitivity resulted from increased oxidative, but not nonoxidative, carbohydrate metabolism. In contrast, a comparable group of athletes had augmented nonoxidative glucose disposal, muscle glycogen synthesis activity, and glycogen accumulation (9). Also in sedentary individuals, muscle glycogen synthesis, resulting from increased glucose transport/phosphorylation, accounts for whole-body insulin sensitivity (10). Finally, endurance training improves insulin sensitivity in first-degree relatives of patients with type 2 diabetes by increasing myocellular glucose-6-phosphate and glycogen concentrations (11). These findings indicate that the current study’s observation requires confirmation by direct monitoring of muscle glycogen synthesis and glucose transport/phosphorylation.

Direct monitoring of cellular glucose fluxes would also be important for the article’s main conclusion that lipid-induced insulin resistance is prevented in athletes by shunting glucose toward glycogen storage. This reasoning favors the substrate competition concept of Randle et al. above the alternative mechanism, which relies on “substrate signaling” i.e., the interaction of lipids with insulin signaling. Randle et al. (6) inferred from rodent studies that FFAs increase the intramitochondrial acetyl-CoA/CoA and NADH/NAD+ ratios, leading to pyruvate dehydrogenase inhibition (Fig. 1). Subsequently, glycolytic intermediates and glucose-6-phosphate would accumulate and inhibit hexokinase II (HKII) activity and glucose uptake. The alternative substrate signaling mechanism postulates that myocellular lipid intermediates (diacylglycerol [DAG], ceramides) act as “lipotoxins” to inhibit insulin signaling directly or via activation of novel protein kinase C isoforms (PKC) with subsequent impairment of glucose transport/phosphorylation and reduction in glycogen synthesis (Fig. 1). Indeed, lower increases in glucose-6-phosphate precede lipid-induced reduction in insulin sensitivity and glycogen synthesis in sedentary humans (3). Phielix et al. confirm the reduced nonoxidative glucose disposal in untrained volunteers, whereas only glucose oxidation was lower in the athletes during lipid infusion. They speculate that the higher oxidative capacity of trained muscle allows for more efficient shifting from glucose to lipid oxidation. This would imply a rise in glucose-6-phosphate with decreased glucose uptake and continued glycogen synthesis. However, lipid oxidation was comparable between both groups in this study, and the lipid-induced decline of glucose oxidation was similar in another study (12). In the absence of data on glycolytic intermediates and glucose-6-phosphate, the
operation of substrate competition remains to be proven for lipid-exposed athletes. Supporting substrate signaling, insulin failed to consistently stimulate Akt phosphorylation in both trained and untrained individuals. Nevertheless, glycogen synthase phosphorylation as surrogate of actual glycogen synthesis was decreased only in the athletes. It is noteworthy that increased AMP-activated protein kinase activity could stimulate glucose uptake via glucose transporter-4 translocation independently of insulin. Endurance training also stimulates IMCL synthesis (13), which should diminish myocellular lipotoxins. Phielix et al. state that only untrained humans responded to lipid infusion with an increased total lipid fraction. However, total IMCL do not necessarily reflect true triglyceride turnover in skeletal muscle as surrogate of actual glycogen synthesis was decreased only in the athletes. It is noteworthy that increased AMP-activated protein kinase activity could stimulate glucose uptake via glucose transporter-4 translocation independently of insulin.

In conclusion, application of lipid infusion in athletes sheds new light on muscle metabolism, but future studies are needed to identify the sequence of events leading to lipotoxic effects not only on muscle but also on liver metabolism. This will contribute to improved characterization of subgroups at risk for type 2 diabetes as well as identification of innovative targets for the treatment of insulin resistance.

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REFERENCES

1. American Diabetes Association. Executive summary: Standards of medical care in diabetes—2012. Diabetes Care 2012;35(Suppl. 1):S4–S10
2. Boden G, Chen X, Ruiz J, White JV, Rossetti L. Mechanisms of fatty acid-induced inhibition of glucose uptake. J Clin Invest 1994;93:2438–2446
3. Roden M, Price TB, Perseghin G, et al. Mechanism of free fatty acid-induced insulin resistance in humans. J Clin Invest 1996;97:2850–2865
4. Goodpaster BH, He J, Watkins S, Kelley DE. Skeletal muscle lipid content and insulin resistance: evidence for a paradox in endurance-trained athletes. J Clin Endocrinol Metab 2001;86:5755–5761
5. Phielix E, Meex R, Ouwens DM, et al. High oxidative capacity due to chronic exercise training attenuates lipid-induced insulin resistance. Diabetes 2012;61:2472–2478
6. Randle PJ, Garland PB, Hales CN, Newsholme EA. The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1963;1:785–789
7. Holloszy JO. Biochemical adaptations in muscle. Effects of exercise on mitochondrial oxygen uptake and respiratory enzyme activity in skeletal muscle. J Biol Chem 1967;242:2278–2282
8. Befroy DE, Petersen KF, Dufour S, Mason GF, Rothman DL, Shulman GI. Increased substrate oxidation and mitochondrial uncoupling in skeletal muscle of endurance-trained individuals. Proc Natl Acad Sci USA 2008;105:16701–16706
9. Ebeling P, Bourey R, Koranyi L, et al. Mechanism of enhanced insulin sensitivity in athletes. Increased blood flow, muscle glucose transport protein (GLUT-4) concentration, and glycogen synthase activity. J Clin Invest 1993;92:1623–1631
10. Samuel VI, Shulman GI. Mechanisms for insulin resistance: common threads and missing links. Cell 2012;148:852–871
11. Perseghin G, Price TB, Petersen KF, et al. Increased glucose transport-phosphorylation and muscle glycogen synthesis after exercise training in insulin-resistant subjects. N Engl J Med 1996;335:1357–1362
12. Matzinger O, Schneiter P, Tappy L. Effects of fatty acids on exercise plus insulin-induced glucose utilization in trained and sedentary subjects. Am J Physiol Endocrinol Metab 2002;282:E125–E131
13. Bergman BC, Perreault L, Hunerdosse DM, Koehler MC, Samel AM, Eckel RH. Increased intramuscular lipid synthesis and low saturation relate to insulin sensitivity in endurance-trained athletes. J Appl Physiol 2010;108:1134–1141
14. Brehm A, Krssak M, Schmid AI, Nowotny P, Waldhäusl W, Roden M. Increased lipid availability impairs insulin-stimulated ATP synthesis in human skeletal muscle. Diabetes 2006;55:136–140
15. Nielsen J, Mogensen M, Vind BF, et al. Increased subsarcolemmal lipids in type 2 diabetes: effect of training on localization of lipids, mitochondria, and glycogen in sedentary human skeletal muscle. Am J Physiol Endocrinol Metab 2010;298:E706–E713
16. Jeppesen J, Jordy AB, Sjøberg KA, et al. Enhanced fatty acid oxidation and FATP4 protein expression after endurance exercise training in human skeletal muscle. PLoS ONE 2012;7:e20391