Effects of Exercise on Insulin Sensitivity in Humans

JOHN T. DEVLIN, MD

Physical exercise is promoted as one of the primary therapeutic strategies available to increase insulin sensitivity in individuals deemed at risk from insulin resistance and its attendant hyperinsulinism. Subjects with non-insulin-dependent diabetes mellitus (NIDDM) and impaired glucose tolerance (IGT) represent the major clinical population in which physical training is promoted as a treatment modality to improve insulin sensitivity. This manuscript reviews both the acute effects of muscular contractions and the effects of physical training on insulin sensitivity in NIDDM and insulin-dependent diabetic (IDDM) human subjects. Additionally, the effects of localized (regional) muscular contractions on insulin-mediated glucose disposal in previously exercised and nonexercised muscle groups will be discussed briefly.

Insulin resistance is a hallmark of non-insulin-dependent diabetes mellitus (NIDDM), and therapeutic strategies (such as dietary-induced weight loss and physical exercise) are targeted at ameliorating this defect (1). In insulin-dependent diabetes (IDDM), exercise is also able to increase skeletal muscle sensitivity to insulin, and adjustments in dietary intake and/or insulin dosages are required to accommodate changes in physical activity level in order to prevent metabolic complications of either hypoglycemia or worsening hyperglycemia and ketosis (2,3).

Multiple loci of cellular insulin resistance have been identified in NIDDM, including decreased number or altered structure/function of the insulin receptor (4), decreases in glucose transporter number and activity (5), and impairments in the activities of key intracellular enzymes (e.g., pyruvate dehydrogenase and glycogen synthase) under euglycemic conditions (6,7). The mechanism(s) of contraction-induced increases in skeletal muscle glucose transport are incompletely understood at present, but do not involve the same tyrosine-kinase-dependent mechanism that is activated by insulin binding to its membrane receptor (8). This study will focus on the role of muscular contractions to increase whole-body insulin sensitivity in NIDDM humans, and the ability to overcome impaired insulin sensitivity in this group by physical training. The role of exercise in managing IDDM will be briefly discussed, with particular reference to the potentially adverse metabolic effects of exercise during periods of moderate insulinopenia.

PHYSICAL TRAINING IN NIDDM — Early studies on the effects of training in NIDDM failed to show significant improvements in diabetic control (assessed by fasting plasma glucose concentrations) and only variable improvements in oral glucose tolerance (9,10; Table 1). This failure in early studies has generally been attributed to the low intensity of exercise used and the prolonged time interval between the last bout of exercise and the testing period.

Subsequent work by other investigators (11–14) showed improvements in glycemic control (assessed by fasting glucose and/or glycated hemoglobin concentrations) following 6–12 wk of physical training in NIDDM utilizing work loads of ≥60% of maximal aerobic capacity ($\dot{V}O_{2\ max}$). Schneider et al. (11) demonstrated that improvements in oral tolerance were greater at 12 h than 72 h after the last bout of exercise and suggested that much of the "training effect" on glucose metabolism was caused by a carryover effect from the last bout of exercise.

The mechanism of training-induced improvement in insulin sensitivity has been largely ascribed to increased skeletal muscle glucose disposal during and after exercise. Bogardus et al. (14) demonstrated, using the insulin clamp technique, that obese NIDDM subjects had greater improvements in insulin-stimulated glucose disposal following combined diet and exercise therapy than after dietary treatment alone. This difference was entirely explained by increased nonoxidative glucose disposal, taken to reflect increased glucose storage as glycogen in the previously exercised muscles.

A period of as short as 1 wk of intense physical training (68% $\dot{V}O_{2\ max}$) has been shown capable of improving oral glucose tolerance in NIDDM men (15). Of interest, the two subjects in this study who did not demonstrate improvement had relative insulin deficiency.

ACUTE EFFECTS OF EXERCISE IN NIDDM — Training-induced improvements in glucose tolerance in nondiabetic athletes were shown to be lost within 10 days of stopping physical training by Heath et al. (16), whereas studies using the insulin clamp tech-

FROM THE METABOLIC UNIT, UNIVERSITY OF VERMONT COLLEGE OF MEDICINE, BURLINGTON, VERMONT.
ADDRESS CORRESPONDENCE TO JOHN T. DEVLIN, MD, DIABETES CENTER, MAINE MEDICAL CENTER, 22 BRAMHALL STREET, PORTLAND, ME 04102.

Table 1—*Effects of physical training on glucose metabolism in NIDDM*

	Physical training			Glycemia		
Ref.	Duration (wk)	Times/wk	$\%\dot{V}O_{2\ max}$	FPG	HbA_{1c}	OGTT*
Ruderman et al. (1979)	12–24	5	—	No δ†	—	No δ (7 days)
Saltin et al. (1979)	12	2	—	No δ	—	Improved
Schneider et al. (1984)	6	3	70–75	No δ	↓	12 h > 72 h
Reitman et al. (1984)	6–10	5–6	60–90	↓	—	Improved (36+ hr)
Trovati et al. (1984)	6	7	50–60	↓	↓	Improved (48+ hr)
Bogardus et al. (1984)	12	3	75 maxHR	↓	—	Improved (6 days)
Krotkiewski et al. (1985)	12	3	80–90	No δ	—	Improved

maxHR, maximal heart rate reserve; FPG, fasting plasma glucose concentration; OGTT, oral glucose tolerance test.
*Numbers in parentheses refer to time interval between testing and last bout of exercise.
†No δ, no change from baseline.

nique demonstrated that increased insulin-stimulated glucose disposal rates in trained athletes had largely disappeared within 60 h of the last bout of exercise (17). In the former study, a single bout of exercise was able to restore the insulin and glucose responses to oral glucose challenge to nearly the lower, "trained" levels (16). These studies further suggested that much of the effects of physical training on muscle insulin sensitivity is the result of repeated acute effects.

We studied the effects of a single bout of high-intensity exercise (85% $\dot{V}O_{2\ max}$), continued to exhaustion (41 ± 10 min), on insulin sensitivity in NIDDM men (18). Twelve hours after exercise, rates of whole-body glucose utilization during physiological hyperinsulinemia 858 ± 113 pM (143 ± 18.8 μU/ml) were significantly increased, compared with the resting state (Fig. 1). The magnitude of increase was comparable with that previously reported following 12 wk of physical training (14). Increased insulin-stimulated glucose disposal was entirely accounted for by nonoxidative glucose disposal, presumable for glycogen resynthesis. Although the activity of glycogen synthase, the rate-limiting enzyme for glycogen synthesis, was normally activated during maximal insulin stimulation 16972 ± 879 pM (3162 ± 293 μU/ml) following exercise, the metabolic clearance rate of glucose in NIDDM remained below that previously reported in normal humans (19,20) (Fig. 2). The latter observation suggested that, despite significant improvements in nonoxidative glucose disposal after high-intensity exercise, a defect in glucose utilization proximal to the glycogen synthase step (e.g., in glucose transport) remained in NIDDM subjects.

The role of skeletal muscle glycogen depletion and repletion in enhancing muscle glucose metabolism after exercise has been clarified by Garetto et al. (20), who described the "two phases" of glycogen resynthesis. In phase I, muscle glycogen is depleted, and glucose utilization by muscle is increased in the presence or absence of insulin. In phase II, glycogen levels have returned to near baseline levels, and only the increase in insulin sensitivity persists.

These studies on the acute effects of exercise on muscle glycogen metabolism help to explain the apparent paradox reported by Schneider et al. (11) (i.e., long-term improvements in glycemia following physical training [assessed by glycated hemoglobin determinations] in the absence of improved fasting plasma glucose concentrations or oral glucose tolerance [at 72 h]). The cycle of repetitive depletion of the glycogen stores, with enhanced glucose disposal for glycogen resynthesis during recovery, may reduce ambient glycemia over the long-term, although producing little effect on glucose concentrations even 48–72 h after the last bout of exercise.

PHYSICAL TRAINING IN IDDM

— Previous studies have generally failed to demonstrate significant improvements in glycemic control (assessed by glycosylated hemoglobin or fasting glucose concentrations) in IDDM after physical training (21,22). However, this may be accounted for by the clinical necessity of either increasing caloric intake or decreasing insulin dosages to prevent hypoglycemia in exercising IDDM subjects. Skeletal muscle insulin sensitivity is improved by physical training, and other cardiovascular risk factors (lipoprotein profiles, blood pressure, and platelet aggregability) may also be improved. For these reasons, attempts should be focused on devising regimens that will allow IDDM subjects to exercise safely and not promote exercise as a means of improved glycemic control.

ACUTE EFFECTS OF EXERCISE IN IDDM

— One of the major concerns of exercise in IDDM is hypoglycemia, either during or for several hours after a single bout of exercise. As might be anticipated from the previous considerations, glycogen resynthesis may be anticipated to place IDDM subjects at risk of hypoglycemia for at least 12 h after a single bout

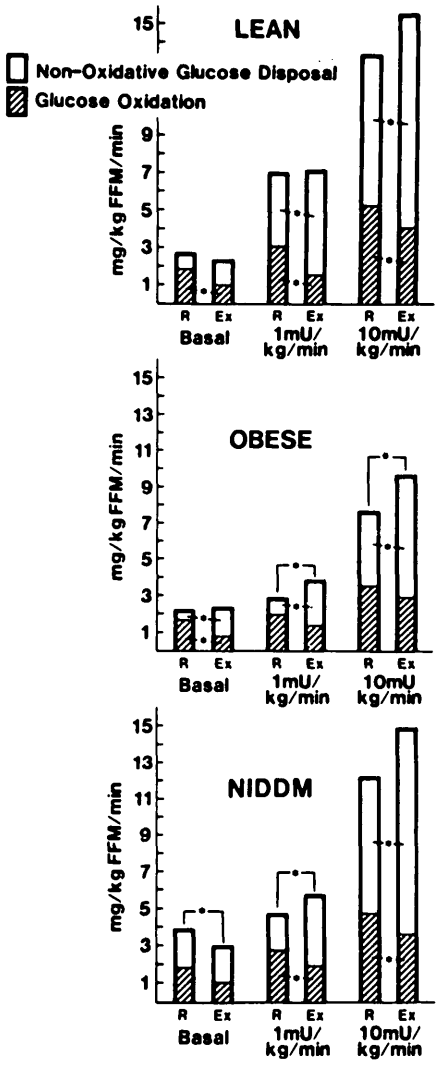

Figure 1—*Glucose disposal rates (mg · kg fat-free mass^{-1} [FFM] · min^{-1}) without (R) and with (Ex) prior exercise in the basal state and during the steady-state periods of the 40 mU · m^{-2} · min^{-1} (low-dose) and 400 mU · m^{-2} · min^{-1} (high-dose) insulin infusions, in lean (top), obese (middle), and non-insulin-dependent diabetes mellitus (NIDDM; bottom) humans. Asterisk indicates significant differences (P < 0.05) in total glucose disposal (top of bars), nonoxidative glucose disposal (side of bars, upper), and glucose oxidation (side of bars, lower), comparing the postexercise (Ex) with the nonexercised (R) state.*

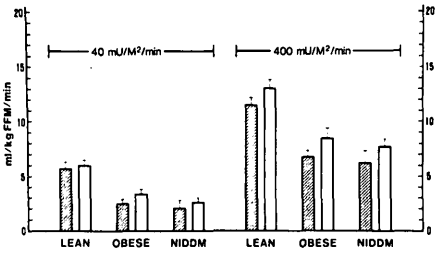

Figure 2—*Metabolic clearance rates (MCR) of glucose in lean, obese, and non-insulin-dependent diabetes mellitus (NIDDM) humans during low-dose (40 mU · m^{-2} · min^{-1}) and high-dose (400 mU · m^{-2} · min^{-1}) insulin infusions, without (hatched bars) and with (open bars) prior exercise. Bars represent means ± SE.*

of exercise, unless food intake or insulin dosages are appropriately adjusted.

IDDM subjects in states of metabolic decompensation resulting from insulin withdrawal plasma glucose ≥ 20 mM (360 mg/dl) are at risk for developing increasing hyperglycemia and ketosis during exercise (2,3), presumably because insufficient insulin is available to counteract the effects of increased counterregulatory hormone concentrations (especially catecholamines and glucagon), which occur during exercise.

We have studied the effects of moderate intensity (50–60% $\dot{V}O_{2\ max}$) bicycle exercise on substrate metabolism during periods of "tight" plasma glucose 6 mM (108 mg/dl) and "loose" 12 mM (216 mg/dl) glycemic control (23). Despite decreasing plasma glucose concentrations during and after exercise on both study days, significant elevations in blood ketone body concentrations occurred during postexercise recovery (to ~2 mM) on the "loose" control study day. This suggests that even modest degrees of insulinopenia, resulting in plasma glucose concentrations of 12 mM (216 mg/dl), may place IDDM subjects at risk of significant ketosis during recovery after exercise.

REGIONAL EFFECTS OF EXERCISE

— Ahlborg et al. (24) demonstrated that nonexercised muscle (forearm) tissue released three-carbon gluconeogenic precursors (lactate and alanine) during and shortly after exercise at a rate that could not be accounted for by glucose uptake, and suggested that forearm muscle glycogenolysis was the source of these gluconeogenic carbons. We demonstrated that forearm release of three-carbon compounds (lactate, alanine, and pyruvate) remained twofold increased for at least 2–3 h after exercise (25).

Presumably, nonexercised (forearm) muscle glycogenolysis provides gluconeogenic precursors for subsequent glycogen resynthesis in the previously exercised (leg) muscle. We also demonstrated that forearm muscle is insulin-resistant during the 2- to 3-h postexercise period, because insulin-stimulated forearm glucose uptake was not increased during the recovery period, compared with the fivefold increase seen in the resting state. These studies demonstrate that the acute effects of exercise on whole-body glucose metabolism are regional, with increased insulin sensitivity confined to previously exercised muscle groups mediated by local factors (e.g., plasma membrane glucose transporters). The net effect of exercise on insulin sensitivity may be the algebraic sum of the local effects to increase (previously exercised muscle) or decrease (non-exercised muscle) insulin sensitivity in individual muscle groups.

SUMMARY— Physical training programs have been shown to improve glycemic control (fasting plasma glucose and HbA_{1c}) significantly in NIDDM subjects, with the likely mechanism being increased skeletal muscle insulin sensitivity. Increases in muscle glucose disposal after exercise are entirely accounted for by nonoxidative glucose disposal reflecting glycogen resynthesis. Training effects per se are deemed to be small in magnitude compared with the cumulative effects of repeated bouts of glycogen depletion and repletion.

Studies in IDDM subjects gener-

ally have failed to demonstrate improvements in glycemic control following a period of physical training, probably because of associated increases in caloric intake. The major concerns in IDDM are either hypoglycemia, or increasing degrees of hyperglycemia and ketosis in poorly controlled subjects during and after exercise. Even moderate degrees of insulinopenia, resulting in plasma glucose concentrations of 12 mM (216 mg/dl), may result in potentially significant degrees of postexercise ketosis.

The effects of exercise on insulin sensitivity are regional, with increased sensitivity confined to the previously exercised muscle groups, combined with decreased insulin sensitivity in the nonexercised muscles.

Acknowledgments— This study was supported by the National Institutes of Health (NIH) Clinical Investigator Award K08-O1554, a Juvenile Diabetes Foundation Research Grant, and NIH Award GCRC RR-109.

References

1. DeFronzo RA, Ferrannini E, Koivisto V: New concepts in the pathogenesis and treatment of noninsulin-dependent diabetes mellitus. *Am J Med* 74 (Suppl. 1A): 52–81, 1983
2. Wahren J, Hagenfeldt L, Felig P: Splanchnic and leg exchange of glucose, amino acids, and free fatty acids during exercise in diabetes mellitus. *J Clin Invest* 55:1303–14, 1975
3. Berger M, Berchtold P, Cuppers HJ, Drost HJ, Kley HK, Müller WA, Wiegelman W, Zimmerman-Telschow H, Gries FA, Kruskemper HL, Zimmerman H: Metabolic and hormonal effects of muscular exercise in juvenile type diabetes. *Diabetologia* 13:355–65, 1977
4. Taylor SI, Kadowaki T, Kadowaki H, Accili D, Cama A, McKeon C: Mutations in insulin-receptor gene in insulin-resistant patients. *Diabetes Care* 13:257–79, 1990
5. Kahn BB, Charron MJ, Lodish HF, Cushman SW, Flier JS: Differential regulation of two glucose transporters in adipose cells from diabetic and insulin treated diabetic rats. *J Clin Invest* 84:404–11, 1989
6. Mandarino L, Consoli A, Thorne R, Kelley D: Effect of hyperglycemia on oxidative and nonoxidative glucose metabolism in noninsulin-dependent diabetes mellitus (NIDDM): role of pyruvate dehydrogenase and glycogen synthase. *Diabetes* 37 (Suppl. 1):77A, 1988
7. Bogardus C, Thuillez P, Ravussin E, Vasquez B, Narimiga M, Azhar S: Effect of muscle glycogen depletion on in vivo insulin action in man. *J Clin Invest* 72: 1605–10, 1983
8. Rosen OM: After insulin binds. *Science* 237:1452–58, 1987
9. Saltin B, Lindgärde F, Houston M, Hörlin R, Nygaard E, Gad P: Physical training and glucose tolerance in middle aged men with chemical diabetes. *Diabetes* 28 (Suppl. 1):30–32, 1979
10. Ruderman NB, Ganda OP, Johansen K: Effects of physical training on glucose tolerance and plasma lipids in maturity onset diabetes mellitus. *Diabetes* 28 (Suppl. 1):89–92, 1979
11. Schneider SH, Amorosa LF, Khachadurian AK, Ruderman NB: Studies on the mechanism of improved glucose control during regular exercise in type 2 (non-insulin-dependent) diabetes. *Diabetologia* 26:355–60, 1984
12. Reitman JS, Vasquez B, Klimes I, Nagulesparan M: Improvement of glucose homeostasis after exercise training in non-insulin-dependent diabetes. *Diabetes Care* 7:434–41, 1984
13. Trovati M, Carta Q, Cavalot F, Vitali S, Banaudi C, Greco Lucchina P, Fiocchi F, Emanuelli G, Lenti G: Influence of physical training on blood glucose control, glucose tolerance, insulin secretion, and insulin action in non-insulin-dependent diabetic patients. *Diabetes Care* 7:416–20, 1984
14. Bogardus C, Ravussin E, Robbins DC, Wolfe RR, Horton ES, Sims EAH: Effects of physical training and diet therapy on carbohydrate metabolism in patients with glucose intolerance and non-insulin-dependent diabetes mellitus. *Diabetes* 33:311–18, 1984
15. Rogers MA, Yamamoto C, King DS, Hagberg JM, Ehsani AA, Holloszy JO: Improvement in glucose tolerance after 1 week of exercise in patients with mild NIDDM. *Diabetes Care* 11:613–18, 1988
16. Heath GW, Gavin JR III, Hinderliter JM, Hagberg JM, Bloomfield SA, Holloszy JO: Effects of exercise and lack of exercise on glucose tolerance and insulin sensitivity. *J Appl Physiol* 55:512–17, 1983
17. Burstein R, Polychronakos C, Toews CJ, MacDougall JD, Guyda HJ, Posner BI: Acute reversal of the enhanced insulin action in trained athletes. *Diabetes* 34: 756–60, 1985
18. Devlin JT, Hirshman M, Horton ED, Horton ES: Enhanced peripheral and splanchnic insulin sensitivity in NIDDM men after single bout of exercise. *Diabetes* 36:434–39, 1987
19. Devlin JT, Horton ES: Effects of prior high-intensity exercise on glucose metabolism in normal and insulin-resistant men. *Diabetes* 34:973–79, 1985
20. Garetto LP, Richter EA, Goodman MN, Ruderman NB: Enhanced muscle glucose metabolism after exercise in the rat: the two phases. *Am J Physiol* 246:E471–75, 1984
21. Wallberg-Henriksson H, Gunnarsson R, Henriksson J, DeFronzo R, Felig P, Östman J, Wahren J: Increased peripheral insulin sensitivity and muscle mitochondrial enzymes but unchanged blood glucose control in type 1 diabetics after physical training. *Diabetes* 31:1044–50, 1982
22. Zinman B, Zuniga-Guajardo S, Kelly D: Comparison of the acute and long term effects of physical training on glucose control in type 1 diabetes. *Diabetes Care* 7:515–19, 1984
23. Devlin JT, Scrimgeour A, Brodsky I, Fuller S: Protein turnover after exercise in IDDM: effect of glycemic control (Abstract). *Diabetes* 39 (Suppl. 1):282, 1990
24. Ahlborg G, Felig P: Lactate and glucose exchange across the forearm, legs, and splanchnic bed during and after prolonged leg exercise. *J Clin Invest* 69:45–54, 1982
25. Devlin JT, Barlow J, Horton ES: Whole body and regional fuel metabolism during early postexercise recovery. *Am J Physiol* 256:E167–72, 1989