Exercise in the Treatment of NIDDM
Applications for GDM?

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Physical training is associated with lower plasma insulin concentrations and increased sensitivity to insulin in skeletal muscle and adipose tissue of individuals with non-insulin-dependent diabetes mellitus (NIDDM). The benefits of exercise to individuals with NIDDM in terms of increased insulin sensitivity could be applied to reversing the insulin resistance associated with gestational diabetes mellitus (GDM). Exercise may also benefit women with GDM by acting as an adjunct to diet in preventing excessive weight gain and preventing or decreasing the severity of hypertension and/or hyperlipidemia during pregnancy. Regular physical exercise should be considered as a potential approach to the prevention and treatment of GDM. *Diabetes* 40 (Suppl. 2):175–78, 1991

Although the pathogenesis of gestational diabetes mellitus (GDM) is not fully understood, the syndrome has many similarities to non-insulin-dependent diabetes (NIDDM) that becomes manifest during the course of pregnancy. Like NIDDM, there are at least three factors that play a significant role in the development of GDM: a genetic predisposition to the disease; a decrease in the action of insulin in insulin-sensitive tissues, including adipose tissue, skeletal muscle, and the liver; and a defect in pancreatic β-cell function. The development of impaired glucose tolerance or GDM depends on the interplay of insulin resistance and the capacity of β-cells to secrete insulin in a timely and adequate fashion to maintain normal glucose homeostasis. The degree of insulin resistance that develops in a given individual during pregnancy will depend on the hormonal milieu and other factors such as age, obesity, and the level of physical activity and probably genetic factors. Likewise, β-cell function may also be determined by multiple factors.

Because physical exercise has both acute and long-term effects on insulin sensitivity, insulin secretion, and glucose metabolism in both nondiabetic and diabetic subjects, there has been considerable interest in the possibility that regular exercise and/or physical training may be useful approaches to the prevention or treatment of GDM in predisposed patients. However, only limited experimental data are available on the effects of physical training programs in the treatment of GDM (1).

To provide background information on the potential risks and benefits of exercise in the treatment of GDM and the rationale for pursuing further studies of exercise as a potential therapeutic modality in this disease, I briefly review our knowledge of exercise and NIDDM. Several recent reviews have been published on this topic (2,3).

BENEFITS OF EXERCISE IN NIDDM

Many real and potential benefits of regular physical exercise have been identified for patients with NIDDM (Table 1). Although exercise in nondiabetic individuals has little impact on blood glucose concentrations, moderate-intensity exercise in patients with NIDDM and hyperglycemia is usually associated with a decrease in blood glucose concentrations toward normal. This may be used by patients to help regulate blood glucose on a day-to-day basis and may be a mechanism by which regular physical exercise results in improved long-term diabetic control (4). In addition to the acute blood glucose–lowering effect of exercise, it has been recognized for many years that physical training is associated with lower fasting and postprandial insulin concentrations and apparent increased insulin sensitivity (5,6). Because NIDDM is characterized by insulin resistance in skeletal muscle, adipose tissue, and the liver (7,8), there has been considerable interest in the use of physical training to improve insulin sensitivity and, thus, improve one of the major abnormalities of NIDDM.

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TABLE 1
Benefits of exercise for patients with diabetes

1. Lower blood glucose concentrations during and after exercise
2. Lower basal and postprandial insulin concentrations
3. Improved insulin sensitivity
4. Lower glycosylated hemoglobin levels
5. Improved lipid profile
   - Decreased triglycerides
   - Slightly decreased LDL cholesterol
   - Increased HDL cholesterol
6. Improvement in mild to moderate hypertension
7. Increased energy expenditure
   - Adjunct to diet for weight reduction
   - Increased fat loss
   - Preservation of lean body mass
8. Cardiovascular conditioning
9. Increased strength and flexibility
10. Improved sense of well-being and quality of life

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A third benefit of regular exercise is a reduction of cardiovascular risk factors through improvement of the lipid profile and reduction of hypertension. Physical training is associated with a lowering of serum triglycerides, particularly very-low-density lipoproteins (VLDL) and an increase in high-density lipoprotein subfraction 2 (HDL_2) cholesterol (9). There is also a slight reduction of low-density lipoprotein cholesterol with training (10). Recent studies on the mechanism by which physical training results in lower VLDL and increased HDL_2 concentrations have shown that physically trained skeletal muscle has increased lipoprotein lipase activity compared with untrained muscle. This results in greater extraction of circulating VLDL and increased release of HDL_2 resulting from a transfer of VLDL membrane proteins to HDL_2 particles (11). This improvement in the lipid profile with physical training is observed with running a minimum of 10–12 miles/wk and increases in a dose-response fashion up to distances of ~40 miles/wk (12). Lower levels of physical activity have little, if any, effect on lipid profiles.

Another effect of physical training is improvement of mild to moderate hypertension. This occurs independently from weight loss or change in body composition and can result in a decrease in both systolic and diastolic blood pressure of 5–10 mmHg (13,14). Although the mechanism for this effect is not known, it is correlated with a decrease in serum insulin and triglyceride concentrations (15) and may be related to a reversal of the effect of chronic hyperinsulinemia on renal sodium retention.

In addition to improvement in cardiovascular risk factors, regular physical exercise can be an effective adjunct to diet for weight reduction. Combined with calorie restriction, exercise has been shown to result in greater loss of adipose tissue mass and relative preservation of lean body mass (16,17). In some studies, however, particularly with very-low-calorie diets, exercise may not have any significant effect beyond that of diet alone (18,19).

Finally, physical training in patients with NIDDM results in the same general benefits as in nondiabetic individuals. These include increased fitness and physical working capacity, decreased resting heart rate, increased stroke volume, and decreased cardiac work. In addition, there may be psychological benefits, including increased sense of well-being and improved overall quality of life.

RISKS OF EXERCISE IN NIDDM

In addition to the benefits of exercise, several significant risks for patients with NIDDM have been recognized (Table 2). In patients taking insulin or oral hypoglycemic agents, exercise may result in symptomatic hypoglycemia either during or after exercise. In insulin-treated patients, the increased risk of hypoglycemia may persist for up to 24 h after prolonged strenuous exercise (20). In addition, extremely strenuous exercise of short duration may result in a rapid increase in blood glucose concentration that persists for several hours after the exercise is stopped (21). Another risk of exercise in people with NIDDM is precipitation or exacerbation of underlying cardiovascular disease that may have been unrecognized previously. This includes the development of angina pectoris, myocardial infarction, or cardiac arrhythmias. Therefore, adults with NIDDM should have a thorough cardiac evaluation before initiating an exercise program. Degenerative joint disease, particularly of the hips and knees, is more common in obese individuals and may be exacerbated by weight-bearing exercise. Also, patients with sensory neuropathy may experience joint and soft tissue injuries while participating in exercise.

Several complications of diabetes may be aggravated by exercise, and patients with NIDDM should be screened for them before being advised to undertake an exercise program. These complications are usually not present in patients with GDM because of the short duration of the disease. However, all patients should be screened for complications and appropriate precautions taken if they are present. The most important of these is proliferative retinopathy, in which exercise may result in retinal or vitreous hemorrhage. Extremely strenuous exercise or types of exercise associated with Valsalva-like maneuvers are particularly dangerous and should be avoided by patients with proliferative retinopathy. Also, exercise resulting in jarring or

TABLE 2
Risks of exercise for patients with diabetes

1. Hypoglycemia if treated with insulin or oral agents
   - Exercise-induced hypoglycemia
   - Late-onset postexercise hypoglycemia
2. Hyperglycemia after very strenuous exercise
3. Hyperglycemia and ketosis in insulin-deficient patients
4. Precipitation or exacerbation of cardiovascular disease
   - Angina pectoris
   - Myocardial infarction
   - Arrhythmias
   - Sudden death
5. Worsening of long-term complications of diabetes
   - Proliferative retinopathy: vitreous hemorrhage, retinal detachment
   - Nephropathy: increased proteinuria
   - Peripheral neuropathy: soft-tissue and joint injuries
   - Autonomic neuropathy: decreased cardiovascular response to exercise, decreased maximum aerobic capacity, impaired response to dehydration, postural hypotension

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rapid head motion may precipitate hemorrhage or retinal detachment. Physical exercise is also associated with increased proteinuria in patients with diabetic nephropathy (22,23). This is probably the result of changes in renal hemodynamics associated with exercise, and it is not known whether this has any effect on the progression of renal disease. As mentioned above, peripheral neuropathy increases the risk of soft tissue and joint injuries and may be a contraindication to certain types of exercise such as running, jogging, or similar activities in which localized trauma may occur. If autonomic neuropathy is present, the capacity for high-intensity exercise may be impaired due to decreased maximum heart rate and aerobic capacity (24,25). In addition, there may be impaired response to dehydration and problems with postural hypotension. With proper planning and selection of exercise, most of these complications can be avoided, although in some circumstances, physical exercise programs may be contraindicated for the patient with NIDDM.

EXERCISE AND INSULIN SENSITIVITY

A possible role for physical exercise as a means to treat the insulin resistance associated with obesity and NIDDM was first suggested ~20 yr ago by Bjorntorp et al. (26). They observed that physically active middle-aged men had significantly lower fasting and postglucose plasma insulin concentrations than age- and weight-matched sedentary men (5). Subsequently, they demonstrated that obese subjects who underwent physical training developed lower plasma insulin levels despite no change in body composition or oral glucose tolerance (6). Since these initial observations, many studies in both humans and animals have confirmed that physical training increases sensitivity to insulin, although the mechanism by which this occurs still is not well understood (7).

Athletes have normal or increased tolerance to oral glucose in conjunction with low basal and glucose-stimulated insulin responses (27), and physical inactivity rapidly results in decreased glucose tolerance (28). Both healthy control subjects and patients with NIDDM have been shown to have a 30–35% increase in insulin-stimulated glucose disposal after physical training when studied by the hyperinsulinemic-euglycemic clamp technique (29). This increase in insulin sensitivity correlates well with the training-induced increase in $\dot{V}O_{2\,max}$ and is thought to be caused primarily by increased glucose uptake by muscle, because no changes have been observed in hepatic glucose production rates (30).

Acute exercise in untrained subjects is also associated with increased insulin sensitivity and glucose metabolism that persists for several hours after the exercise (31). This is related to both the need for replenishment of decreased muscle and liver glycogen stores and to increased glucose metabolism in muscle. After a single bout of exercise in untrained subjects, there is an increase in nonoxidative glucose disposal that persists for at least 12–14 h. This occurs in individuals with normal glucose tolerance as well as in insulin-resistant subjects with impaired glucose tolerance or NIDDM (32).

The increase in insulin sensitivity and responsiveness associated with physical conditioning is rapidly lost when exercise is discontinued. Burstein et al. (28) found that much of the effect is gone within 60 h, and others have demonstrated that the effect is no longer present after 5–7 days without exercise. In a study by Bogardus et al. (18) comparing the effects of a very-low-calorie diet with the same diet plus a physical training program on weight loss and blood glucose regulation in NIDDM, the physically trained group had a significant increase in insulin-stimulated glucose disposal rates, whereas the group treated by diet alone had no change after 3 mo of treatment. The increase in insulin-stimulated glucose disposal in the group treated by diet and physical training was due entirely to an increase in nonoxidative glucose disposal, presumably reflecting increased glycogen synthesis. In this study, the effect of training was demonstrated 5–7 days after the last exercise session, indicating a long-term effect of physical training on insulin-stimulated glucose disposal. In other studies, Mikines et al. (31) have shown that a single bout of exercise increases the sensitivity and responsiveness of insulin-stimulated glucose disposal in untrained individuals. This effect lasts for at least 2 days but is not observed after 5 days. In addition, physically trained subjects have increased insulin action when studied 15 h after their last training session compared with untrained subjects (33). When studied 5 days after the last training session, insulin responsiveness remains increased compared with untrained subjects, suggesting that there is a long-term adaptive increase in whole-body responsiveness to insulin with training.

Despite the increase in insulin-stimulated glucose uptake that can be demonstrated for at least 5–7 days after cessation of exercise in previously trained subjects, patients with NIDDM have generally not been demonstrated to have improved fasting blood glucose concentrations or improved glucose tolerance with training (34,35). This has led some to suggest that physical training is ineffective as a means to improve glucose homeostasis in NIDDM. However, others have observed that physical training is associated with lower glycosylated hemoglobin levels (4). Current interpretation is that this may be the cumulative result of decreased blood glucose concentrations associated with repeated bouts of exercise rather than a specific effect of physical training. Because it is known that exercise usually results in a fall of blood glucose concentrations toward normal in hyperglycemic patients with NIDDM and increased insulin-stimulated glucose disposal can be observed for many hours after a single bout of exercise, it is likely that regular exercise 4–7 days/wk may result in lower average blood glucose and glycohemoglobin concentrations without a significant effect on fasting blood glucose or glucose responses to meals. Thus, the net effect of exercise repeated on a regular basis would be to improve long-term blood glucose control in patients with NIDDM.

The mechanisms by which exercise and physical training increase insulin sensitivity are not yet fully understood. After a single session of exercise, glucose uptake by skeletal muscle is enhanced for several hours. This occurs without any increase in the binding of insulin to its receptor (36). However, the number and activity of glucose-transporter proteins, particularly the GLUT4 isoform, are increased in plasma membranes of skeletal muscle after exercise (37). In

addition, glycogen synthase activity is increased, resulting in increased synthesis of glycogen and increased nonoxidative disposal of glucose (32).

During training, the binding of insulin to its receptor is slightly increased in adipose tissue but not in muscle. However, both tissues have a substantial increase in the total number of glucose transporters and an enhanced response of glucose transport to insulin stimulation (38). It appears that a major effect of physical training is to increase the capacity for glucose transport into muscle and adipose tissue in response to insulin stimulation. Other factors, such as increased capillary density in muscle and increased intracellular glucose metabolism, may also be important in the adaptation to training.

CONCLUSIONS

Based on current knowledge, it seems rational to consider regular physical exercise as a potential approach to the prevention and treatment of GDM. The large body of literature demonstrating that physical training is associated with lower plasma insulin concentrations and increased sensitivity to insulin in skeletal muscle and adipose tissue strongly suggests that it may be useful in reversing the insulin resistance associated with the development of GDM. Regular exercise may also be useful in preventing excessive weight gain during pregnancy, which may contribute to the development of hyperinsulinemia and insulin resistance. Likewise, there may be beneficial effects of exercise in preventing or decreasing the severity of hypertension and/or hyperlipidemia during pregnancy, both conditions clearly associated with hyperinsulinemia. Prospective studies on the effects of exercise in the prevention and treatment of GDM are certainly indicated and much needed.

REFERENCES

1. Jovanovic-Peterson L, Durak EP, Peterson CM: Randomized trial of diet versus diet plus cardiovascular conditioning on glucose levels in gestational diabetes. *Am J Obstet Gynecol* 161:415–19, 1989
2. Horton ES: Exercise and diabetes mellitus. *Med Clin North Am* 76:1301–21, 1988
3. Richter EA, Ruderman NB, Schneider SH: Exercise and diabetes. *Am J Med* 70:201–209, 1981
4. Schneider SH, Amoroso LF, Khachsdurian AK, Ruderman NB: Studies on the mechanism of improved glucose control during regular exercise in type II (non-insulin-dependent) diabetes. *Diabetologia* 26:355–60, 1984
5. Bjorntorp P, Fahlen M, Grimby G, Gustafson A, Holm J, Renstrom P, Schersten T: Carbohydrate and lipid metabolism in middle-aged physically well-trained men. *Metabolism* 21:1037–42, 1972
6. Bjorntorp P, de Jounge K, Sjostrom L, Sullivan L: The effect of physical training on insulin production in obesity. *Metabolism* 19:631–37, 1970
7. DeFronzo RA, Ferrannini E, Koivisto V: New concepts in the pathogenesis and treatment of non-insulin-dependent diabetes mellitus. *Am J Med* 74:52–81, 1983
8. DeFronzo RA: Lilly Lecture 1987: the triumvirate: β-cell, muscle, liver: a collusion responsible for NIDDM. *Diabetes* 37:667–87, 1988
9. Huttunen JK, Lansimies E, Voutilainen E, Ehnholm C, Hietanen F, Pantilla I, Siitonen O, Rauramna R: Effect of moderate physical exercise on serum lipo-proteins. *Circulation* 60:1220–29, 1979
10. Haskell WL: The influence of exercise training on plasma lipids and lipoproteins in health and disease. *Acta Med Scand Suppl* 711:25–37, 1986
11. Kiens B, Lithell H: Lipoprotein metabolism influenced by training-induced changes in human skeletal muscle. *J Clin Invest* 83:558–64, 1989
12. Rotkis TC, Cote R, Coyle E, Wilmore JH: Relationship between high density lipoprotein cholesterol and weekly running mileage. *J Cardiac Rehab* 2:109–12, 1982
13. Boyer J, Kasch F: Exercise therapy in hypertensive men. *JAMA* 211: 1668–71, 1970
14. Choquette G, Ferguson R: Blood pressure reduction in borderline hypertensives following physical training. *Can Med Assoc J* 108:699–703, 1973
15. Krotkiewski M, Mandroukis K, Sjostrom L, Sullivan L, Wetterqvist H, Bjorntorp P: Effects of long-term physical training on body fat, metabolism and blood pressure in obesity. *Metabolism* 28:650–58, 1979
16. Pavlou KN, Steffee WP, Lerman RH, Burrows BA: Effects of dieting and exercise on lean body mass, oxygen uptake and strength. *Med Sci Sports Exercise* 17:466–71, 1985
17. Hill JO, Sparling PB, Shields TW, Heller PA: Effects of exercise and food restriction on body composition and metabolic rate in obese women. *Am J Clin Nutr* 46:622–30, 1987
18. 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
19. Warwick PM, Garrow JS: The effect of addition of exercise to a regimen of dietary restriction on weight loss, nitrogen balance, resting metabolic rate and spontaneous physical activity in three obese women in a metabolic ward. *Int J Obes* 5:25–32, 1981
20. MacDonald MJ: Postexercise late-onset hypoglycemia in insulin-dependent diabetic patients. *Diabetes Care* 10:584–88, 1987
21. Mitchell TH, Abraham G, Schiffrin A, Leiter LA, Marliss EB: Hyperglycemia after intense exercise in IDDM subjects during continuous subcutaneous insulin infusion. *Diabetes Care* 11:311–17, 1988
22. Mogensen CE, Vittinghus E: Urinary albumin excretion during exercise in juvenile diabetes. *Scand J Clin Lab Invest* 35:295–300, 1975
23. Viberti GC, Jarrett RJ, McCartney M, Keen H: Increased glomerular permeability to albumin induced by exercise in diabetes subjects. *Diabetologia* 14:293–300, 1978
24. Storstein L, Jervell J: Response to bicycle exercise testing of long standing juvenile diabetics. *Acta Med Scand* 205:227–30, 1979
25. Hilsted J, Galbo H, Christensen NJ: Impaired cardiovascular responses to graded exercise in diabetic autonomic neuropathy. *Diabetes* 28:313–19, 1979
26. Bjorntorp P, DeJounge K, Sjostrom L, Sullivan L: Physical training in human obesity. II. Effects on plasma insulin in glucose intolerant subjects without marked hyperinsulinemia. *Scand J Clin Lab Invest* 32:42–45, 1973
27. Lohmann D, Liebold F, Heilmann W, Senger H, Pohl A: Diminished insulin response in highly trained athletes. *Metabolism* 27:521–42, 1978
28. Burstein R, Polychronakos C, Toews CJ, MacDougall JD, Guyda JH, Posner BI: Acute reversal of the enhanced insulin action in trained athletes: association with insulin receptor changes. *Diabetes* 34:756–60, 1985
29. Sato Y, Iguchi A, Sakamoto N: Biochemical determination of training effects using insulin clamp technique. *Horm Metab Res* 16:483–86, 1984
30. Rosenthal M, Haskell WL, Solomon R, Widstrom A, Reaven GM: Demonstration of a relationship between level of physical training and insulin-stimulated glucose utilization in normal humans. *Diabetes* 32:408–11, 1983
31. Mikines KJ, Sonne B, Farrell PA, Tronier B, Galbo H: Effect of physical exercise on sensitivity and responsiveness to insulin in humans. *Am J Physiol* 254:E248–59, 1988
32. 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
33. Mikines KJ, Sonne B, Tronier B, Galbo H: Effects of acute exercise and detraining on insulin action in trained men. *J Appl Physiol* 66:704–11, 1989
34. Saltin B, Lindgärd 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
35. Ruderman NB, Ganda OP, Johansen K: The effect of physical training on glucose tolerance and plasma lipids in maturity-onset diabetes. *Diabetes* 28 (Suppl. 1):89–92, 1979
36. Horton ES: Exercise and physical training: effects on insulin sensitivity and glucose metabolism. *Diabetes Metab Rev* 2:1–17, 1986
37. Goodyear LJ, Hirshman MJ, King PA, Thompson CM, Horton ED, Horton ES: Skeletal muscle plasma membrane glucose transport and glucose transporters after exercise. *J Appl Physiol* 68:193–98, 1990
38. Hirshman MJ, Wardzala LJ, Goodyear LJ, Fuller SP, Horton ED, Horton ES: Exercise training increases the number of glucose transporters in rat adipose cells. *Am J Physiol* 257:E520–30, 1989
39. Horton ES: Exercise. In *Therapy for Diabetes Mellitus and Related Disorders*. Lebovitz HE, Ed. Alexandria, VA, Am. Diabetes Assoc., 1991, p. 103–11