Physical Exercise Improves Glucose Metabolism in Lifestyle-Related Diseases

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The beneficial effects of physical exercise on the decreased insulin sensitivity caused by detrimental lifestyle were reviewed based on experimental evidences. In epidemiological studies, disease prevention has been considered at three levels: primary (avoiding the occurrence of disease), secondary (early detection and reversal), and tertiary (prevention or delay of complications). The major purpose of physical exercise for primary prevention and treatment of lifestyle-related diseases is to improve insulin sensitivity. It is known that, during physical exercise, glucose uptake by the working muscles rises 7 to 20 times over the basal level, depending on the intensity of the work performed. However, intense exercise provokes the release of insulin-counter regulatory hormones such as glucagons and catecholamines, which ultimately cause a reduction in the insulin action. Continued physical training improves the reduced peripheral tissue sensitivity to insulin in impaired glucose tolerance and Type II diabetes, along with regularization of abnormal lipid metabolism. Furthermore, combination of salt intake restriction and physical training ameliorates hypertension. In practical terms, before diabetic patients undertake any program of physical exercise, various medical examinations are needed to determine whether they have good glycemic control and are without progressive complications. Because the effect of exercise that is manifested in improved insulin sensitivity decreases within 3 days after exercise and is no longer apparent after 1 week, a continued program is needed. For a safety practice, moderate- or low-intensity exercise is preferable. In conclusion, we have found sufficient evidences that support the theory that, combined with other forms of therapy, mild exercise training increases insulin action despite no influence on body mass index or maximal oxygen uptake. Along with evident benefits in health promotion, moderate-intensity exercise might play an important role in facilitating treatment of various diseases. Exp Biol Med 228:1208–1212, 2003

Key words: lifestyle intervention; Type II diabetes; physical exercise; insulin sensitivity

Insulin resistance is exacerbated by aspects of modern westernized lifestyles such as overeating, sedentariness, and stressful daily life (1). Recently, the Ministry of Health, Welfare and Labor of Japan introduced the notion of lifestyle-related diseases. These diseases may occur in those people experiencing the above-mentioned lifestyle abnormalities in addition to hereditary disposition. Therefore, it is most necessary to teach people about the importance of dietary restriction and an active daily life (2).

Regular physical exercise improves reduced insulin sensitivity in lifestyle-related diseases including Type II diabetes, hypertension, hyperlipidemia, and ischemic coronary disease. Several authors agree that continued physical training may be beneficial for prevention and management of these diseases (2–5).

Epidemiological Studies on Physical Exercise for Preventing Lifestyle-Related Diseases

Disease prevention has been considered at three levels: primary (avoiding the occurrence of disease), secondary (early detection and reversal), and tertiary (prevention or delay of complications) (6).

Nonrandomized Studies. In general, patients with impaired glucose tolerance (IGT), a target group for Type II diabetes prevention, are characterized by having a sedentary lifestyle coupled with poor physical fitness and insulin resistance. It is well known that a higher degree of leisure-time physical activity is associated with a reduced mortality from any cause and from ischemic heart diseases (IHD) in both men and women. In the Malmö study, Eriksson and Lindgärde (7) reported that the mortality rate in middle-aged IGT men was increased in lifestyle changes but that a long-term intervention program, with emphasis on dietary counseling and physical exercise might be successful, resulting in lower-than-expected overall mortality over a 12-year period, due to reduction in deaths from both vascular and

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nonvascular causes. These results are compatible with the hypothesis that if the incidence of Type II diabetes could be reduced, the mortality rate in IGT will fall as well.

Randomized Controlled Intervention Trials. Randomized controlled intervention trials (RCT) in Norway (8) and China (9) showed that diet and/or exercise intervention led to a significant decrease in the incidence of diabetes among those with IGT.

The Finish Diabetes Prevention Study (10) demonstrated that the risk of diabetes from IGT was reduced by 58% in the intervention group that received individualized counseling, which aimed to reduce the total intake of fat and increase the intake of fiber and the level of physical activity. Thus, reduction in the incidence of diabetes was directly associated with changes in lifestyle, leading them to conclude that Type II diabetes could be prevented by changes in the lifestyle of high-risk subjects.

Recent results of the Diabetes Prevention Program (DPP; Fig. 1) (11) are more impressive. IGT persons (mean body mass index (BMI): 34.0) were randomly assigned to placebo, metformin (850 mg twice daily), or a lifestyle modification program with the goals of at least a 7% weight loss and physical activity of moderate intensity, such as brisk walking, for at least 150 min per week. After an average follow-up for 2.8 years the lifestyle intervention reduced the incidence of diabetes by 58% and metformin by 31% as compared with placebo. The authors concluded that lifestyle changes and treatment with metformin reduced the incidence of diabetes in IGT persons and that lifestyle intervention was more effective than metformin. The Japan Diabetes Prevention Program (JDPP; directed by Dr. H. Kuzuya, Kyoto National Hospital), supported by the Ministry of Health, Labor and Welfare of Japan, is still under way.

Effects of Exercise on Endocrinological and Metabolic Abnormalities

The principal purpose of physical exercise for the primary prevention and the treatment of lifestyle-related diseases is to improve insulin resistance.

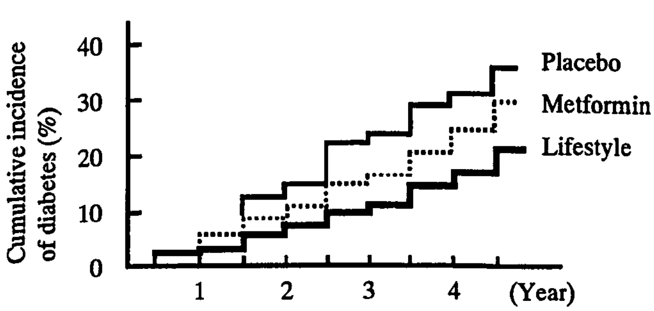

Figure 1. Cumulative incidence of diabetes according to the studied group. The diagnosis of diabetes was based on the criteria of the American Diabetes Association. The incidence of diabetes differed significantly among the three groups ($P < 0.001$ for each comparison) (11).

Acute Effects of Exercise. During physical exercise, the glucose uptake by the working muscles rises 7 to 20 times over the basal level, depending on the intensity of the work performed. Intense exercise provokes the release of insulin-counter regulatory hormones such as glucagons and catecholamines, which ultimately cause a reduction in the insulin action (2).

Effects of Long-Term Physical Training. Continued physical training improves reduced peripheral tissue sensitivity to insulin in IGT and Type II diabetes (5), and also improves abnormal lipid metabolism. Further, the combination of salt intake restriction and physical training ameliorates hypertension.

Physical training and insulin resistance. We have evaluated the effects of physical training in terms of the *in vivo* action of insulin using the euglycemic clamp technique (2, 12). Compared with healthy controls, both obese Type II diabetic and nondiabetic obese patients were insulin resistant. An inverse correlation existed between the glucose infusion rate (GIR, a measure of insulin sensitivity) and the BMI. On the other hand, insulin sensitivity was increased in highly trained athletes.

To evaluate the effects of mild physical training (i.e., walking) combined with diet therapy (1000–1600 kcal/day) on insulin sensitivity in obese patients with Type II diabetes, the following studies were performed. Subjects were divided into two groups: 10 patients were treated by diet alone (Group D) and 14 patients practiced dietary restriction and walking at least 10,000 steps/d monitored by pedometers (Group DE (diet and exercise), 19,200 ± 2,100 steps/day). Group D was instructed to maintain a normal daily routine (4500 ± 290 steps/day). After an intervention period of 6 to 8 weeks, body weight (BW) in both groups was significantly decreased, and GIR in group D did not change markedly, while it increased significantly in group DE. A significant correlation was observed between ΔMCR (ΔMCR represents the positive changes in metabolic clearance rate of glucose (MCR) after training) and average daily steps ($r = 0.7257$, $P < 0.005$). Another significant correlation was observed between ΔBW (ΔBW represents BW reduction after training) and ΔMCR ($r = 0.5410$, $P < 0.05$). These results suggest that walking, which can be safely performed and easily incorporated into daily life, can be recommended as an adjunct therapy to diet treatment in obese Type II diabetic patients, not only for reducing BW, but also for the improving insulin sensitivity (13).

Joseph *et al.* (14) showed that short-term (4 weeks) energy restriction resulting in moderate decreases in BW and fat mass (FM) did not improve insulin sensitivity; the addition of resistance training to hypoenergetic diet preserved muscle mass but provided no synergistic effect on insulin action. The authors concluded that a greater change in BW or FM might be necessary to observe a significant improvement in insulin action. Janssen *et al.* (15) also reported that weight loss was associated with reductions in metabolic risk factors in obese women. However, the improvement in the metabolic profile was not enhanced by the addition of aerobic or resistance exercise. Furthermore, Liao *et al.* (16) compared the effects of diet plus endurance exercise with the effects of diet plus stretching exercise in the control group. They concluded that lifestyle modification consisting of a reduction in dietary fat intake and a regular participation in endurance exercise reduced BMI and improved body composition and body fat distribution, and thus, might delay or prevent Type II diabetes in Japanese Americans with IGT. The above-mentioned findings are in accordance with our previous data (13).

The effects of exercise on the improvement of the metabolic profile have been controversial so far, but combination of dietary restriction and regular physical exercise might be effective in delaying or preventing Type II diabetes, at least in Japanese people. As for exercise intensity, the majority of studies in which the effects of physical training were analyzed used high-intensity exercise such as bicycle ergometer or running graded up to 70% to 90% of the VO_2 max. McAuley *et al.* (17) showed that modest levels of dietary and exercise recommendations did not improve significantly the insulin sensitivity, but a more intensive program did. Therefore, they emphasized that intensive lifestyle changes were necessary to improve insulin sensitivity. However, previous studies from our laboratory showed that long-term gentle jogging increased insulin action despite no influence on BMI or $\dot{V}O_2$ max (18). Recently, Laaksonen *et al.* (19) also reported that high-risk men engaging in currently recommended low levels of leisure-time physical activity (LTPA) were less likely to develop the metabolic syndrome than sedentary men.

These results lend additional support to the current public recommendations for increased moderate-intensity physical activity on most days (3).

We have further reported that aerobic exercise such as walking was more effective than anaerobic exercise such as weight-lifting in increasing the *in vivo* insulin sensitivity (20). Our most recent studies suggested that the combination of aerobic and resistance exercise (PACE training) is more efficient in improving insulin sensitivity and responsiveness, at least for the decreased insulin action brought about by aging (Fig. 2). Resistance training alone was proven to be not so effective (21). Our colleagues, Nagasawa *et al.* (22), also reported that the training effects represented by improved insulin sensitivity declined within 3 days and almost disappear after 7 days of detraining.

Finally, although no significant change in body mass was found when exercised groups were compared with control groups, a meta-analysis of controlled clinical trials on the effects of exercise in patients with Type II diabetes showed that exercise training reduced HbA_1c by an amount that should decrease the risk of diabetic complications (23).

Mechanisms of training effects. The training effects represented by *in vivo* improved insulin action are attributed chiefly to changes in muscular factors such as increased muscle volume, increased rate of blood flow to the exercising muscle, and changes in the insulin receptor and post-receptor mechanisms (1). Glucose transport is the rate-limiting step in muscle glucose utilization and is carried out by the glucose transport proteins present on the cell membrane (1). Over the past several years considerable progress has been made in understanding the molecular mechanism responsible for the effects of physical exercise on glucose metabolism in skeletal muscle. It is well established that the glucose transporter 4 (GLUT4) translocation is an important cellular mechanism through which exercise enhances skeletal muscle glucose uptake (24).

We (25) have reported that exercise training prevented the maturation-induced decrease in insulin sensitivity and suggested that an improvement of insulin sensitivity by exercise training was in part attributable to an increase in the insulin-sensitive GLUT4 on the plasma membrane in rat skeletal muscle. Other recent data from our laboratory suggested that the prevention of maturation-induced decreases in the protein content of IRS-1 and PI 3-kinase was involved in the mechanism responsible for the improvement of insulin sensitivity by exercise training; thus, exercise training may affect transcriptional regulation of the IRS-1 gene and posttranscriptional regulation of the PI 3-kinase expression (26).

Kennedy *et al.* (27) provided very interesting evidence that there were separate signaling mechanisms for exercise- and insulin-stimulated glucose transport. They have shown that the exercise-stimulated glucose utilization was mediated and regulated by the 5′AMP-activated protein kinase. On the other hand, Balon and Nadler (28) reported that nitric oxide (NO) might be a potential mediator of exercise-induced glucose transport. Our studies concerning rat C-peptide and glucose utilization also support this theory. Further studies are necessary to clarify more detailed molecular mechanisms in this field.

Practical Methods of Physical Exercise

Indications of Physical Exercise and Medical Check-Up. Before patients undertake programs of physical exercise, various examinations are needed to determine whether they have good diabetic control and are without progressive complications (29).

Type and Intensity of Exercise. The effect of exercise that is manifested in improved insulin sensitivity decreases within 3 days after the last bout of exercise and is no longer apparent after 1 week. As noted previously, moderate- or low-intensity exercise is preferable.

Specifically, moderate-intensity exercise that results in VO_2 max of about 50% (plus heart rate of about 120/min for those in their 50s or younger and about 100/min for those in their 60s and 70s) should be performed for 10 to 30 min at a time (2–3 times a day, preferably after a meal), at least 3 to 5 days a week. The recommended type of exercise is the aerobic one, which uses muscles throughout the whole body (e.g., walking, jogging, radio gymnastic exercise, stationary

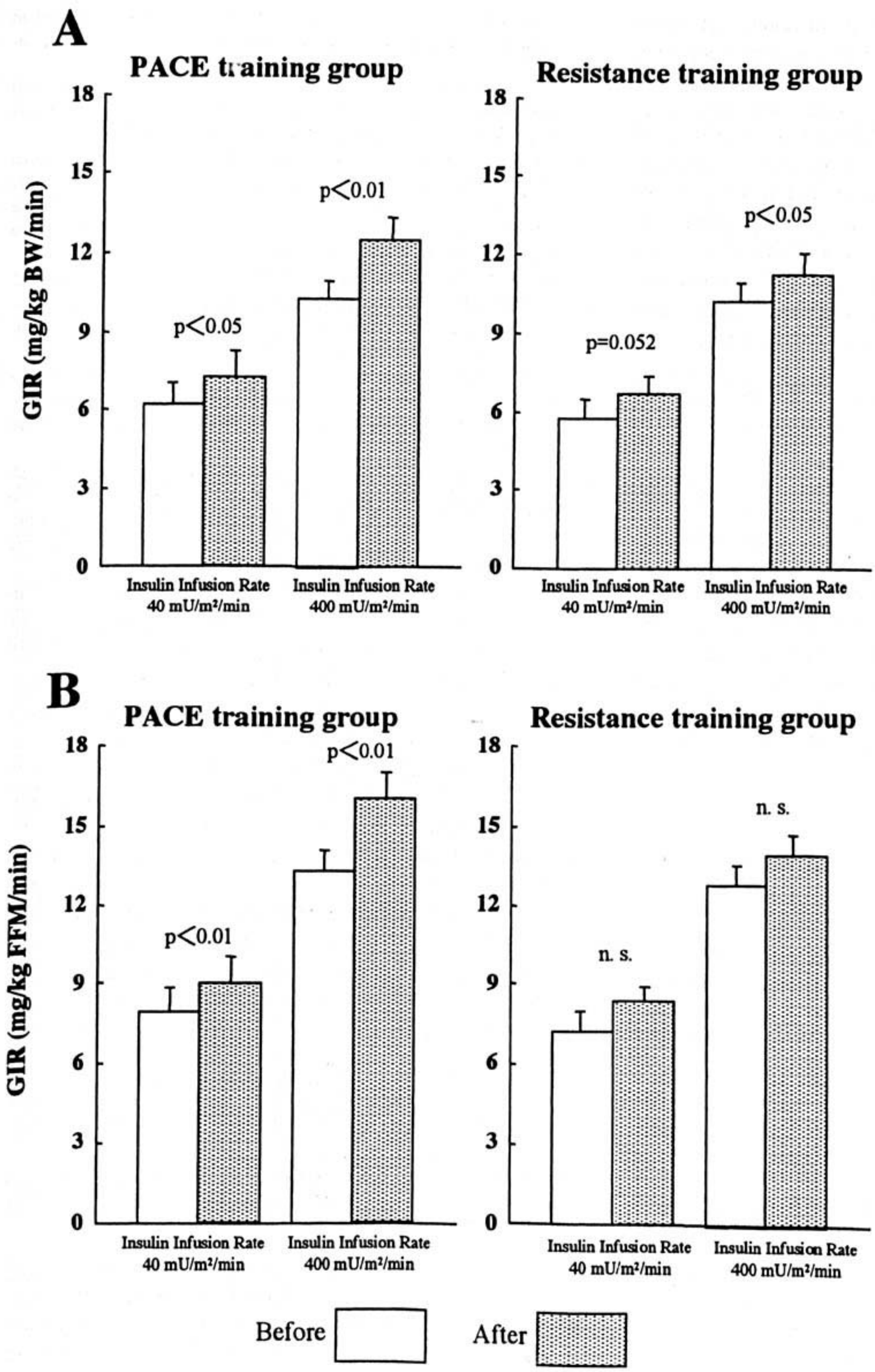

Figure 2. Glucose infusion rate (GIR) for the two insulin infusion rates before and after training expressed as (A) mg/kg BW per min and (B) mg/kg FFM per min. FFM, fat free mass. Values are means ± SE. Steady state plasma insulin levels were 60 to 100 μU/ml at 40 mU/m^2 per min insulin infusion rate and 1100 to 1800 μU/ml at 400 mU/m^2 per min insulin infusion rate (21).

bicycle exercise, and swimming). If resistance exercise is adopted, the level of the load should be low.

Diabetes mellitus is a typical lifestyle-related disease (2). Therefore it is necessary to instruct patients to incorporate some exercise into their daily life (e.g., getting off the bus at a stop before their destination and walking the remaining distance). The use of a pedometer and Life-corder® are useful for motivating patients and for determining how much exercise has been performed. The recorded data should be checked during regular inpatient rounds or in the outpatient clinic, with the goal set at 10,000 steps (or at least 7500 steps) per day (29).

Precautions in Implementing Physical Exercise. The following precautions should be followed:

1. If diet therapy is not followed, good control of blood glucose will not be achieved. Thus, dietary restriction should be instructed.
2. Usually, exercise should be performed after meals.
3. In patients undergoing insulin therapy, the insulin dose should be reduced before exercise. If the exercise practice extends over a prolonged period of time, dietary supplementation is necessary before, during, and after this period. If hypoglycemia occurs during exercise, a cola drink or glucose (pet sugar) dissolved in lukewarm water should be taken. Cookies, cheese, and milk are suitable before and after exercise to prevent hypoglycemia.
4. General precautions including the use of sport shoes and incorporation of warm-up and cool-down exercises should be given (29).

Conclusion

Along with benefits in health promotion, moderate-intensity exercise seems to be useful in facilitating treatment of various diseases. Interventions that are most clearly beneficial during the preclinical phase are those that affect the risk for lifestyle-related diseases. We hope that, with higher-quality guidelines that promote an approach to less intense and more time-efficient regular physical exercise, all people have the opportunity to join some kind of joyful and healthful physical activity.

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