

Diabetes and life-styles: role of physical exercise for primary prevention

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Regular physical exercise has been known to be beneficial in the treatment of type 2 diabetes. Epidemiological studies of physical exercise: previous non-randomized studies suggested that a life-style intervention program involving diet and/or exercise reduced the progression of impaired glucose tolerance (IGT) to type 2 diabetes. Recent randomized controlled intervention trials also showed that diet and/or exercise intervention led to a significant decrease in the incidence of diabetes among those with IGT. Endocrinological and metabolic effects of exercise: in well controlled diabetic patients, physical exercise promotes utilization of blood glucose and lowers blood glucose levels. On the other hand, in poorly controlled diabetic patients with ketosis, physical exercise results in further rises in blood glucose, free fatty acids and ketone body concentrations. Long-term gentle regular jogging increases insulin action in respect of both carbohydrate and lipid metabolism despite no influence on body mass index or maximal oxygen uptake. A significant correlation was observed between Δ MCR (insulin sensitivity) and average daily steps ($P < 0.005$). Our recent data suggested that the improvement of insulin action by physical exercise was attributed, at least in part, to the increase in insulin-sensitive GLUT4 (glucose transporter 4) on the plasma membrane in skeletal muscle. In conclusion, as an adjunct to other forms of therapy, mild regular physical exercise will play an important role in primarily preventing type 2 diabetes.

Type 2 diabetes: Primary prevention: Physical exercise: Insulin sensitivity: GLUT4

In Japan, most diabetic patients are non-insulin dependent (type 2) (Sato, 1988). Decreased insulin secretion and insulin resistance play important roles in the occurrence and progression of type 2 diabetes (Olefsky & Kolterman, 1981). Insulin resistance is exacerbated by aspects of modern, westernized life-styles such as overeating, sedentary state and stressful daily life (Goodyear & Smith, 1994). Recently the notion of life-style related diseases has been proposed. Diabetes may occur in those experiencing the above mentioned life-style abnormalities in addition to hereditary disposition (Sato, 1998).

Regular physical exercise improves reduced sensitivity to insulin in life-style related diseases including diabetes (type 2), hypertension and coronary artery disease and continued physical training may be beneficial in the prevention and the treatment of these diseases (Goodyear & Smith, 1994; Sato, 1998; Department of Health and Human Services, 1996).

Epidemiological studies of physical exercise

Disease prevention has been considered at three levels: primary (avoiding disease occurrence), secondary (early detection and reversal) and tertiary (prevention or delay of complications). Physical exercise could potentially contribute to all of these three levels (King & Kriska, 1992).

Previous non-randomized studies suggested that adherence to a life-style intervention program of diet and/or exercise reduced the progression of impaired glucose tolerance (IGT) to type 2 diabetes (Eriksson & Lindgärde, 1991; Helmrich *et al.*, 1994). King & Kriska (1992) showed that in general activities with greater intensities are associated with poorer compliance and post intervention compliance to life-style activities is better than high-intensity aerobic programs. Recent randomized controlled intervention trials in Norway (Torjesen *et al.* 1997) and China (Pan *et al.* 1997) showed that diet and/or exercise

Abbreviations: BMI, body mass index; BW, body weight; GIR, glucose infusion rate; GLUT4, glucose transporter 4; IGT, impaired glucose tolerance; MCR, metabolic clearance rate of glucose; VO_2 max, maximal oxygen uptake.

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intervention led to a significant decrease in the incidence of diabetes among those with IGT.

Endocrinological and metabolic effects of exercise

The principal purpose of physical exercise for primary prevention and the treatment of type 2 diabetes is to improve insulin resistance (Sato, 1988; Goodyear & Smith, 1994).

Acute effects

During physical exercise, glucose uptake by the working muscles rises to 7–20 times the basal level, depending on the intensity of the work performed. Intensive exercise provokes the release of insulin-counter regulatory hormones such as glucagon and catecholamine secretion. Therefore, blood glucose concentrations may increase after intensive physical exercise. Further, the blood glucose response to exercise in diabetic patients is influenced by multiple factors including the state of metabolic control and the timing of insulin injection. In well controlled diabetic patients, physical exercise promotes utilization of blood glucose and lowers blood glucose levels (Sato, 1988). Recent studies from our laboratory indicated that in obese patients with type 2 diabetes, 30 min of low intensity bicycle exercise significantly enhances the decreased insulin-induced glucose uptake shortly after exercise and might be useful for the treatment of postprandial hyperglycemia (Usui *et al.* 1998).

On the other hand, in poorly controlled diabetic patients with ketosis (minimum fasting blood glucose: 250–300 mg/dl, urine ketone body positive), physical exercise causes a further rise in blood glucose, free fatty acids (FFA), and ketone body concentrations and augments metabolic disturbances (Sato, 1988; Goodyear & Smith, 1994).

Training effects

Continued physical training improves reduced peripheral tissue sensitivity to insulin in IGT and type 2 diabetes.

Physical training and insulin resistance. We have evaluated the effects of physical training in terms of *in vivo* action of insulin, using the euglycemic clamp technique (Sato, 1988; Sato *et al.* 1992). Compared with healthy controls, both obese type 2 diabetic and non-diabetic obese patients were insulin resistant. An inverse correlation existed between glucose infusion rate (GIR, a measure of insulin sensitivity) and body mass index (BMI). On the other hand, insulin sensitivity was increased in highly trained athletes.

To evaluate the effects of mild physical training (walking) combined with diet therapy (1000–1600 kcal/day) on insulin sensitivity in patients with type 2 diabetes, the following studies were performed. Subjects were divided into two groups. Ten patients were managed by diet alone (group D) and fourteen patients practiced dietary restriction and walking at least 10 000 paces/day monitored by pedometers (group DE, $19\,200 \pm 2100$ steps/day). Group D was instructed to maintain a normal daily routine (4500 ± 290 steps/day). Body weight (BW) in both groups D and DE decreased significantly. After training for 6–8 weeks, GIR in group D did not change significantly, while GIR increased significantly in group DE (Fig. 1). A significant correlation was observed between Δ MCR (Δ MCR represents the positive changes in metabolic clearance rate of glucose (MCR) after training) and average daily steps ($r = 0.7257$, $P < 0.005$) (Fig. 2a). A significant correlation as observed between Δ MCR and Δ BW (Δ BW represents BW reduction after training) was also observed ($r = 0.5410$, $P < 0.05$) (Fig. 2b). 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 2 diabetic patients, not only for BW reduction, but also for the improvement of insulin sensitivity (Yamanouchi *et al.* 1995). In addition, these results also showed that the amount of exercise can be determined by use of pedometers carried by patients (Yamanouchi *et al.* 1995).

As for exercise intensity, Mayer-Davis *et al.* (1998) indicated that increased participation in nonvigorous as

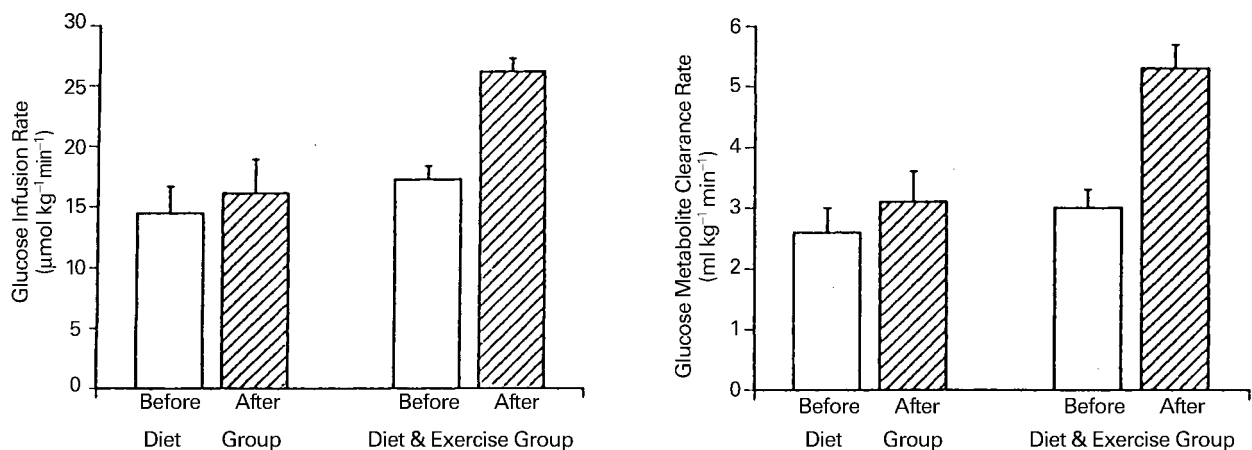


Fig. 1. GIR and glucose MCR before and after training periods in Type 2 diabetic patients managed by diet alone (group D) or by diet and exercise (group DE). A 2×2 repeated-measure analysis of variance showed significant effects of exercise (time \times exercise, $P = 0.0005$) in the improvement of MCR (Yamanouchi *et al.* 1995).

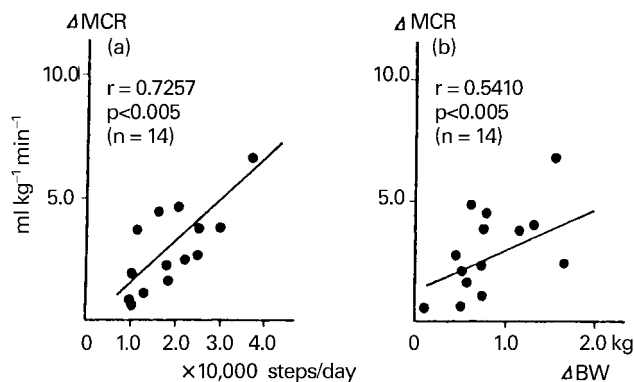


Fig. 2. Correlation between ΔMCR and mean steps/day (a) and between ΔMCR and (b) ΔBW (Yamanouchi *et al.* 1995).

well as overall and vigorous physical activity (at least 30 min of moderate intensity (3–6 Mets) physical activity on most, preferably all, days of the week) was associated with increase in insulin sensitivity estimated by the method of minimal model. We have already reported that long-term gentle jogging increases insulin action despite no influence on BMI or maximal oxygen uptake (VO_{2max}) (Oshida *et al.* 1989).

These results lend further support to current public health recommendations for increased moderate-intensity physical activity on most days (Mayer-Davis *et al.* 1998).

Studies from our laboratory further showed that aerobic exercise such as walking was more effective than anaerobic exercise such as weight-lifting in increasing *in vivo* insulin sensitivity (Oshida *et al.* 1991). Our more recent studies suggested the combination of aerobic and anaerobic exercise (PACE training) is more efficient in improving insulin sensitivity and responsiveness at least for the decreased insulin action caused by ageing (Kitamura *et al.* 2000). Our colleagues Nagasawa *et al.* (1990) also reported that training effects represented by improved insulin sensitivity decline within 3 days and almost disappear after 7 days of detraining.

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, changes in the insulin receptor and post-receptor mechanisms (Goodyear & Smith, 1994). Glucose transport is the rate-limiting step in muscle glucose utilization and is carried out by the glucose transport proteins on the cell membrane (Goodyear & Smith, 1994). Over the past several years considerable progress has been made in understanding the molecular mechanism for the effects of physical exercise on glucose metabolism in skeletal muscle. It is well established that glucose transporter 4 (GLUT4) translocation is an important cellular mechanism through which exercise enhances skeletal muscle glucose uptake (Hayashi *et al.* 1999).

Our recent data suggested that the improvement of insulin action by physical training was attributed, at least in part, to the increase in GLUT4 protein in muscle plasma membrane (Fig. 3) (Nakai *et al.* 1996). Dela *et al.* (1993)

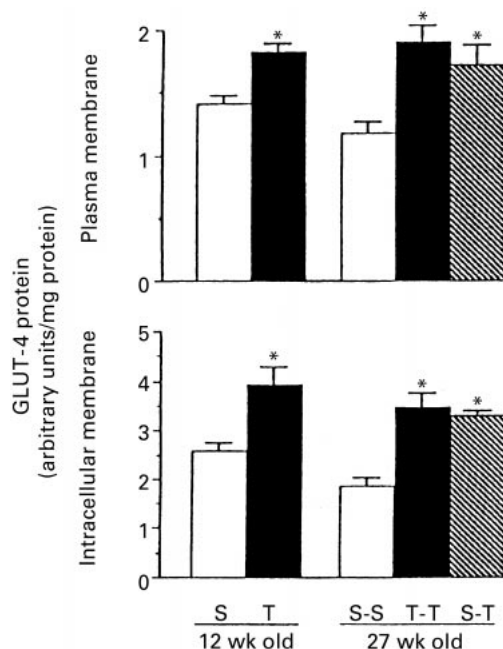


Fig. 3. Concentrations of GLUT-4 protein in skeletal muscle plasma membrane (top) and intracellular membrane (bottom) for 12-week-old sedentary (S) and exercise-trained (T) rats; and for 27-week-old sedentary rats (S-S) and rats allowed to exercise before maturation (T-T) and after maturation (S-T). Signals of immunoreactive GLUT4 were measured with a Bio Imaging analyzer. Values are means \pm SE for six rats. *Significant difference from sedentary rats at same age ($P < 0.05$) (Nakai *et al.* 1996).

also showed that muscle GLUT4 protein and mRNA increased both in patients with type 2 diabetes and in control subjects in response to physical training.

Kennedy *et al.* (1999) provided the very interesting evidence that there are separate signaling mechanisms for exercise- and insulin-stimulated glucose transport. They have also shown that the exercise-stimulated glucose utilization is mediated and regulated by 5'AMP-activated protein kinase (Kennedy *et al.* 1999). On the other hand, Balon & Nadler (1997) reported that nitric oxide may be a potential mediator of exercise-induced glucose transport. Our studies concerning rat C-peptide and glucose utilization also support this theory (Li *et al.* 1999). Further studies are necessary to clarify more detailed molecular mechanisms in this field.

Practical method of physical exercise

Types and combination of physical exercise. A typical physical exercise program consists of (1) systemic dynamic exercise such as walking, jogging, jumping ropes for acquiring strength and overall physical fitness (aerobic), (2) static exercise such as expander stretching for acquiring muscle strength, and (3) gymnastics as warming-up/cooling down exercises. Instead of a combination of these three types of exercise, one could perform gymnastics for at least 10 minutes, walk for at least one subway station or bus stop, and climb up and down the stairs instead of taking elevators (Sato, 1988).

Amount and intensity of physical exercise. We recommend a gradual increase in the amount of exercise from walking or jogging to moderate intense aerobic exercise (pulse rate 120/min for 30–50 years old, 100/min for 60–70 years old) for 10–60 min in the morning and evening with 40–60 % maximal oxygen uptake at least 3–5 times/week.

Utilization rates of glucose and free fatty acid as an energy source for the muscles are almost the same during the exercise of less than moderate degree. With increases in the intensity of exercise, the rate of glucose utilization increases, and glucose alone is used as the energy source at maximal rate of physical exercise. Therefore, excessively intense physical exercise is not recommended for diabetic patients who would benefit from utilization of fat stored in the adipose tissues in addition to training of the muscle (Sato, 1988; Goodyear & Smith, 1994; Sato, 1998).

The amount of exercise can easily be determined by use of a pedometer carried by the patient with instructions to walk at least 10 000 paces a day (7500 steps minimum), and by checking the result at the outpatient clinic or during the daily round for an inpatient. A calorie counter[®] is also useful (Sato, 1988, 1998).

Conclusion

The role of physical exercise for the primary prevention and the treatment of diabetes mellitus has been reviewed. Physical exercise should not be considered separately from other treatments, and full effects can be expected only when dietary therapy, physical exercise, and medication are combined optimally. We would like to emphasize that the amount of exercise should be increased gradually.

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