Exercise therapy in diabetic patients

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Abstract The prevalence of diabetes in the population continues to increase worldwide. The complications of diabetes cause morbidity and mortality, and the cost of managing diabetes has become an important social problem in health economics. Strategies for the prevention and treatment of diabetes are therefore very important, and along with pharmacological and diet approaches, exercise plays a fundamental role. This review outlines the biological and clinical aspects of exercise therapy in patients with diabetes, and highlights the recent advances in research on this topic. The mechanisms by which exercise can reduce insulin resistance are described, along with the effects of exercise on plasma insulin and glucose levels, as well as on changes in muscle fiber types that occur in diabetes. Regarding clinical aspects of exercise in patients with diabetes, recent Japanese practice and physical activity guidelines are discussed, and the latest research into diabetes and exercise, including the role of myokines and the effects of exercise on lifespan and cognition are described.

Keywords : diabetes, exercise, muscle fibers, insulin resistance

Introduction

In 2013, of a global population of approximately 7 billion people, 382 million were estimated to have diabetes mellitus – a rate of approximately one in 201). The rate of diabetes continues to increase in Japan. According to the National Livelihood Survey by the National Health and Nutrition Survey 2011, the percentage of people in whom diabetes is strongly suspected is 15.7% in men and 7.6% in women. The group of people who are impaired glucose tolerance is described as the preliminary group, and the rate in this group is estimated at 33% in men and 23% in women. Overall, approximately one-quarter of the Japanese population either have diabetes or are in this preliminary group.

Diabetes is a disease resulting from insufficient insulin action, and can lead to various complications. Diabetic microangiopathy (neuropathy, retinopathy and nephropathy) and macroangiopathy (cardiovascular disease, cerebrovascular disease and peripheral vascular disease) are well known complications of diabetes; and, in recent years, dementia and cancer have been suggested as new complications. Diabetes has a significant impact on quality of life (QOL) and prognosis, and is a major burden on the healthcare economy.

Diabetes continues to be a global problem, with rates still increasing in many parts of the world. The UN (United Nations) has adopted measures to address this issue, including the implementation of World Diabetes Day, held annually on November 14. Despite these efforts, their effects will still take some time to show a positive impact.

What is diabetes?

Diabetes mellitus is caused by deficient insulin action, and is characterized by chronic hyperglycemia with disturbances in fat and protein metabolism alongside carbohydrate metabolism. The pathogenesis of deficient insulin action falls into two broad categories: impaired insulin secretion and insulin resistance (Fig. 1).

Many factors are involved in insulin secretion. Factors that promote insulin secretion include glucose, some amino acids and fatty acids, glucagon, and gastrointestinal hormones such as gastric inhibitory polypeptide (GIP) and glucagon-like peptide (GLP)-1. GIP and GLP-1 are collectively referred to as incretins, a group of gastrointestinal hormones that stimulate insulin and increase blood glucose levels, and their actions are targets for novel drug therapies for diabetes. Physiologically, the most important factor in insulin secretion is glucose. Insulin secretion can be inhibited by factors including the pancreatic hormone somatostatin, and catecholamine.
Physical exercise plays a major role in the prevention and management of diabetes, even though impaired insulin secretion is not strongly influenced by exercise therapy. In fact, vigorous exercise can suppress insulin secretion via the sympathetic nervous system or catecholamine. However, exercise after a meal can reduce postprandial hyperglycemia, and exercise therapy can play an important role in improving insulin resistance. Insulin resistance is the attenuated uptake of glucose by insulin and can be improved by regular exercise, and increased muscle mass results in increased overall glucose uptake by the muscles. These issues are discussed in more detail later in this review.

**Exercise and metabolism of glucose and insulin**

*Effects of exercise on insulin action.* The effects of exercise on metabolism can be divided into acute and long-term effects. First, we will discuss the acute effects of exercise. The target tissues of insulin are muscle, liver, and adipocytes. In the liver, glucose uptake is via glucose transporter (GLUT)-2, and in muscle cells or adipocytes it is via GLUT-4. GLUT-4 action is insulin dependent. By the action of insulin, glucose that is not used is stored as glycogen in the liver and muscles. Amino acids are synthesized into proteins, and fatty acids synthesized into triglycerides (Fig. 2).

*Effects of exercise on glucose and insulin fluctuation.* At rest, fatty acids are the main energy source in muscles. Glucose oxidation accounts for only 10% of the energy produced in skeletal muscles, whereas 85% to 90% is from fatty acids. When exercise begins, muscles use both glucose and fatty acids, corresponding to the duration and intensity of the exercise. First, the breakdown of glycogen in muscle begins, and subsequently, within minutes of the onset of exercise, uptake of glucose and oxygen into muscle tissue increases. During mild exercise, the muscles use fatty acid as the major energy source. During higher intensity exercise, the muscles use glucose from stored glycogen and blood glucose as the main energy sources (Fig. 3). In healthy individuals, blood glucose levels are kept constant during exercise because the amount of glucose uptake from the blood is approximately equal to the amount of glucose released from the liver. Insulin suppresses glycogenolysis and gluconeogenesis and the release of glucose from the liver, and glucagon has the opposite effect to insulin. Exercise increases levels of catecholamines and activates the sympathetic nervous system, as well as leading to the breakdown of triglycerides in adipose tissue and the release of fatty acids into the circulation. As a result, insulin secretion is suppressed, glucagon secretion is promoted and blood glucose levels remain essentially constant.

It can be seen, therefore, that multiple complex neurologic and hormonal responses are involved in glucose homeostasis during exercise, but the central component of glucose regulation is insulin.

In people with diabetes, plasma insulin levels will vary, and exercise may increase blood glucose levels in some cases and cause hypoglycemia in others. If blood insulin concentrations are low, glucose uptake by muscles is attenuated. Moreover, when glucagon levels are high, glucose is released from the liver, leading to increased blood
Insulin is an anabolic hormone

Target organs

- muscle
  - Glucose uptake
  - Glycogenesis

- liver
  - Glucose uptake
  - Glycogenesis
  - Glucogenesis
  - Glucose output

- adipocyte
  - Lipogenesis
  - Lipolysis

Fig. 2 Insulin action in target organs.

Mechanisms of glucose uptake by muscle

There are two pathways of glucose uptake by muscles: insulin-stimulated glucose uptake and non-insulin-dependent action.

In muscles, insulin binds to insulin receptors on the cell surface. This leads to the activation of the phosphatidylinositol 3-kinase (PI3-kinase) pathway and the translocation of intracellular GLUT-4 to the cell surface, thereby causing the uptake of circulating glucose into the muscle. In the same way, exercise acutely increases glucose transport into the contracting muscle via GLUT-4 translocation to the plasma membrane, but insulin and exercise use distinct signaling pathways in muscles. AMP-activated protein kinase (AMPK) is activated in the pathways leading to exercise-stimulated glucose uptake, which stimulates glucose transport in the absence of insulin. It can be said that exercise assists the insulin action and exercise has an insulin sparing effect.

Exercise and insulin resistance

In addition to other benefits of exercise, prolonged physical training can improve insulin resistance. The mechanisms may be linked to augmented translocation of GLUT-4 to the plasma membrane, increased GLUT-4 expression, and increased numbers of mitochondria in muscle cells. Improved muscle blood flow because of enhanced capillary networks may also contribute to this mechanism. Regular exercise also increases energy consumption and reduces obesity. This is important because reduction of visceral fat reduces the detrimental adipocytokines such as tumor necrosis factor (TNF)-α and resistin, and increases beneficial adipocytokines such as adiponectin. Weight loss can be achieved by diet therapy, but diet therapy alone does not improve insulin resistance. Improvement of insulin resistance following exercise lasts 48 hours, reduces over 3 days and almost disappears a week following exercise. Therefore, to maintain the insulin sensitizing effect achieved with exercise, it is nec-
necessary to exercise every other day. A simultaneous benefit is the increase in muscle caused by resistance training, whereby the capacity of glucose uptake is increased and glucose metabolism improves\(^4\).

**Diabetes, exercise and muscle fibers**

**Muscle fibers.** Skeletal muscle comprises heterogeneous types of fibers with different morphological, functional, and metabolic properties\(^5\). Muscle fibers are generally classified as type I (slow twitch) and type II (fast twitch); and type II fibers are further classified into type IIA, type IIB and type IIC fibers. Oxidative enzyme activity is higher in type I, IIA, and IIC fibers, whereas glycolytic enzyme activity is higher in type IIA, IIB, and IIC fibers.

Skeletal muscles are classified into two types: slow muscle and fast muscle (Table 1). Slow muscles, e.g. the adductor longus and soleus muscles, exhibit activity of relatively low intensity and long duration, which is required for performing functions against gravity, such as

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Fig. 4  Effects of exercise on plasma glucose levels.

Fig. 5  Mechanism of glucose uptake by muscle. GLUT-4, glucose transporter-4; PI3-kinase, phosphatidylinositol 3-kinase.
walking and maintaining posture. Conversely, fast muscles such as the extensor digitorum longus and plantaris muscles exhibit activity of relatively high intensity and short duration, required for functions where strength and power are essential. Slow muscles have a high proportion of high-oxidative type I and IIA fibers, exhibit increased lipid storage capacity, insulin binding, insulin-stimulated glucose uptake, and glucose transport protein content compared with fast muscles, which have a high proportion of low-oxidative type IIB fibers. Skeletal muscles exhibit plasticity and undergo hypertrophy or atrophy and/or shifts in fiber type under various conditions, such as growth, ageing, during disease, increased or decreased neuromuscular activity, and exposure to hypoxia5).

Skeletal muscle characteristics in obese or diabetic patients. In general, obese individuals have a decreased proportion of high-oxidative type I fibers and an increased proportion of low-oxidative type II fibers in skeletal muscles6,7). Similarly in diabetic patients, a lower proportion of type I fibers and a higher proportion of type II fibers, especially type II B, are observed8). The altered fiber-type distribution is correlated closely with insulin concentrations, which regulates myosin synthesis in skeletal muscles. A reduced proportion of type I fibers is observed parallel to the progression of insulin resistance; and an altered fiber-type distribution-induced imbalance between glycolytic and oxidative capacities is present in diabetic patients. Decreased oxidative capacity in the skeletal muscles of diabetic patients is the result of a reduced proportion of high-oxidative type I fibers, rather than because of diminished oxidative enzyme activity of individual fibers9-9).

In summary the altered patterns of fiber types in skeletal muscles of diabetic patients may be linked to impaired glucose tolerance and insulin resistance.

Effects of exercise on muscle fibers. Shifts in muscle fiber types occur under a variety of conditions, such as growth, ageing, in disease states, and with increased or decreased muscle activity10,11). Running can also induce muscle fiber type shifts12,13). In obese diabetes model rats, a higher proportion of low-oxidative type I fibers is observed in the soleus muscle compared with that of normal control rats. However, there are no differences in the fiber-type distribution of the soleus muscles between normal control rats and exercised obese diabetes model rats, indicating an improvement in muscle oxidative capacity of exercised obese diabetes model rats. In addition the type I fiber proportion of the soleus muscle is related to running distance in exercised obese diabetes model rats14).

These data suggest that running can inhibit a diabetes-induced type shift of fibers in the skeletal muscles, and induce metabolic improvement.

### Table 1. Muscle fiber types and their morphological, metabolic, and functional properties (cited from literature4).

<table>
<thead>
<tr>
<th>Fiber size (CSA)</th>
<th>Type I (ST)</th>
<th>Type II (FT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiber size (CSA)</td>
<td>Small</td>
<td>Type IIA</td>
</tr>
<tr>
<td>Capillarity</td>
<td>Rich</td>
<td>Type IIB</td>
</tr>
<tr>
<td>Metabolic property</td>
<td>Oxidative capacity</td>
<td>Very high</td>
</tr>
<tr>
<td>Glycolytic capacity</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Functional property</td>
<td>Contractile speed</td>
<td>Slow</td>
</tr>
<tr>
<td>Strength</td>
<td>Weak</td>
<td>Fast</td>
</tr>
<tr>
<td>Fatigue resistance</td>
<td>Very high</td>
<td>High</td>
</tr>
<tr>
<td>Type IIB</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Type IIC1)</td>
<td>High</td>
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Exercise therapy – The Japan Diabetes Society (JDS) guidelines

The Japan Diabetes Society has published the “Evidence-based practice guidelines for treatment of diabetes mellitus in Japan 2013”. In the chapter on exercise therapy there are five statements, which are described below.

1. Exercise therapy: in cases in which a new exercise regimen will be started and in cases with complications.
   - It is necessary to carry out a medical check at the start of exercise therapy. The medical check should include cardiovascular diseases, diabetic microangiopathy (peripheral and autonomic neuropathy, retinopathy, nephropathy), and orthopedic diseases.
   - Even in patients with advanced complications, decreasing sedentary time in daily life is desirable when possible.

2. Exercise therapy: in cases with type 2 diabetes
   - Exercise leads to improvement of various functions, including cardiovascular function, plasma glucose control and lipid metabolism, reduction in blood pressure, and insulin resistance.
   - Aerobic exercise and resistance training are both effective for plasma glucose control. A combined effect is obtained with resistance and aerobic exercise.
   - Even higher effects are observed when exercise therapy is combined with diet therapy.

3. Exercise therapy: in cases with type 1 diabetes
   - Any exercise should be possible in patients without advanced complications and with good glycemic control. In these cases, predation (to eat extra) or adjustment of insulin doses are required.
   - The long-term effect of exercise on glycemic control is not yet clear, but exercise decreases cardiovascular risk factors and improves quality of life.

4. Exercise therapy: in cases receiving drug therapy
   - In patients with insulin therapy, self-monitoring of blood glucose should be carried out. According to glucose levels, predation before or during exercise and adjustment of insulin doses are required.
   - In cases receiving oral antidiabetic drugs, reduced doses may be necessary in some instances.

5. General cautions regarding exercise therapy in diabetic patients
   - Observe both feet carefully, and choose shoes that fit well and provide cushioning for the sole of the foot.
   - Do not exercise when glycemic control is poor (positive ketonuria, even in type 1 and type 2 diabetes).
   - In cases where plasma glucose levels are under 100 mg/dL before exercise, ingestion of easily-absorbed carbohydrate (80–160 kcal) is desirable. In patients receiving oral antidiabetic drugs or insulin treatment, in particular, hypoglycemia may occur during exercise, on the day of exercise, or the day after.
   - Increase the physical activity in a stepwise fashion in daily life.
   - Have warm-up and cooling-down periods before and after exercise.
   - In general, recommended goals of exercise are as follows:
     - Frequency: every day if possible, or at least three times per week.
     - Intensity: moderate degree.
     - Type: aerobic exercise.
     - Duration: 20-60 min.

In diabetic patients, there are cases where exercise is contraindicated or restricted (Table 2).

Clinical issues of exercise

Exercise intensity[^15,16]. The intensity of exercise can be evaluated by oxygen consumption, heart rate during exercise, and using the subjective exercise intensity questionnaire (Borg Coefficient Scale)^[^17]. In general, moderate-in-

Table 2. Inhibited or restricted exercise therapy.

1. Poor metabolic condition (fasting plasma glucose: >200 mg/dL, moderate or severe ketonuria)
2. Fresh retinal bleeding with proliferative retinopathy
3. Renal failure (serum creatinine: males >2.5 mg/dL, females >2.0 mg/dL)
4. Ischemic heart disease or cardiopulmonary diseases
5. Bone or joint diseases
6. Acute infection
7. Diabetic gangrene
8. Severe diabetic autonomic neuropathy

Even in these cases, try to avoid limiting physical activity in daily life when possible.
tensity exercise is recommended for middle-aged diabetic patients. Moderate intensity is evaluated as follows: 40-60% of maximal oxygen consumption (VO2max), approximately 50-70% of heart rate at rest to maximum, and subjectively "moderately tired" according to the Borg Coefficient Scale. Maximum heart rate can be estimated as 220 – age. Heart rate at 50% exercise intensity is evaluated as (138 − age) ÷ 2. When diabetic patients have autonomic neuropathy or are elderly, risks are associated with using heart rate as an indicator of exercise intensity.

Types of exercise. Exercise can be classified into static and dynamic movement exercise. Static exercise is where the individual stays in the same location, and dynamic exercise involves changes in location. In addition, dynamic exercise is divided into aerobic and anaerobic exercise. Static exercise is so-called muscle training, also known as resistance exercise. Static exercise is also divided into two types. One is isometric exercise, where muscle contraction is sustained, and the other is isotonic exercise, where muscle contraction is repeated.

Conventionally, aerobic exercise is recommended for diabetic patients. Adults with diabetes should be advised to perform at least 150 min per week of moderate-intensity aerobic physical activity (50-70% of maximum heart rate), spread over at least 3 days per week with no more than two consecutive days without exercise. However, recently the utility of resistance exercise has attracted attention. Resistance exercise increases muscle strength and muscle mass and improves insulin resistance, resulting in improved glycemic control. One set of resistance exercise comprises 10-15 repetitions that includes the major muscles. It is desirable to increase the level of resistance and number of repetitions gradually. In the absence of contraindications, adults with diabetes should be encouraged to perform resistance training at least twice per week.

It is convenient to go to a gym for exercise, but to maintain exercise therapy, the philosophy "anywhere, anytime, even by oneself" is fundamental.

Physical activity as exercise plus non-exercise activity thermogenesis

Some diabetic patients do not undertake exercise therapy as they perceive it to be difficult or they do not have the available time. As a starting point it is important to reduce the amount of time spent sitting inactively, and to encourage moving the body in any way.

‘Physical activity’ means to use the body in any way. Physical activity is divided into daily life activity and specific exercise. Daily life activity includes commuting, shopping, cleaning, washing, and other activities of daily life. These activities are carried out naturally and have recently been described as non-exercise activity thermogenesis (NEAT). In contrast, exercise means carrying out physical activity in a planned manner in leisure time for health promotion, physical strength improvement, and fun.

NEAT is also important for patients with diabetes. NEAT is associated with improvements in insulin sensitivity, waist circumference, high-density lipoprotein cholesterol levels, blood pressure, and markers of atherosclerosis in patients with type 2 diabetes.

In Japan, the Exercise and Physical Activity Guide for Health Promotion 2006 is recommended for health promotion and the prevention of lifestyle-related diseases by the Ministry of Health, Labour and Welfare. The guideline uses a formula in which MET (metabolic equivalent) is an index for the intensity of physical activity, and EX (exercise) is calculated as METs × hours. For example, standing up is the equivalent of 1.3 METs and normal walking is 3 METs. The guideline recommends 23 EX of vigorous physical activity of ≥3 METs per week, and 4 EX of specific exercise of ≥4 METS per week. The amount of energy consumption can be approximated by the following formula:

\[ \text{Energy consumption} = 1.05 \times \text{EX} \times \text{body weight (kg)} \]

The 2013 Physical Activity Guidelines advocate the “Plus 10” philosophy, i.e., to increase the current level of activity by 10 min or to reduce the time spent in a sitting position by 10 min. The indicator of physical activity is the number of steps. In the last 10 years it is estimated that the number of steps taken in all age groups has decreased by approximately 1000 steps per day. This corresponds to about 30 kcal every day, which leads to 1-1.5 kg weight gain in one year. To walk 1000 steps takes approximately 10 min, hence the “Plus 10” slogan of the guideline. The exercise target is 60 min per day in people aged 15-64 years or 40 min per day in people aged over 65 years.

Topics in exercise therapy

Myokines. Skeletal muscle is not just a component of the locomotive system. Recent reports have identified skeletal muscle as a secretary organ. It is reported that muscle cells secrete signaling molecules, which are collectively referred to as myokines. Myokines may exert autocrine, paracrine or endocrine effects, and balance and counteract the effects of adipokines. Particularly in conditions of obesity, adipose tissue secretes adipokines, which cause chronic inflammation and lead to atherosclerosis and insulin resistance. Skeletal muscles secrete myokines that confer some of the health benefits of exercise, and it is thought that some myokines might counteract the harmful effects of pro-inflammatory adipokines (Fig. 6). Molecules now established as myokines include myostatin, leukemia inhibitory factor (LIF), interleukin (IL)-6, IL-7, insulin-like growth factor-1 (IGF-1), fibroblast...
Brain-derived neurotrophic factor (BDNF) and IL-6 are involved in AMPK-mediated fat oxidation and IL-6 enhances insulin-stimulated glucose uptake26. Irisin is a recently discovered myokine that drives growth factor-2 (FGF-2), follistatin-like protein-1 (FSTL-1), and irisin26.

Myostatin is a member of the transforming growth factor-β (TGF-β) superfamily, and inactivation of the myostatin gene in knockout mice results in extensive skeletal muscle hypertrophy24,27. Thus myostatin inhibits muscle hypertrophy, and exercise induces the release of the myostatin inhibitor, follistatin, from the liver.

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brown-fat-like development of white adipose tissue, increases energy consumption, and decreases weight\textsuperscript{30}.

**Physical activity and life span.** A study of over 410,000 people in Taiwan has investigated the relationship between physical activity and life expectancy\textsuperscript{29}. During the 13-year observation period, all-cause mortality, and mortality from cancer, cardiovascular diseases or diabetes were measured. The study found that mortality rates in the group undertaking a low volume of physical activity was lower than in the physically inactive group. The effective threshold of activity was not stated. The report concluded that moderate-intensity exercise for 15 min a day or 90 min a week extended life by an average of 3 years (Fig. 7).

**Physical activity and cognition.** In terms of cognitive function, a study in 120 older adults has reported that aerobic exercise increased the volume of the hippocampus and improved memory function\textsuperscript{30}. Subjects in the intervention group continued aerobic walking three times a week for 1 year; and in the control group the subjects did some stretching exercises. The volume of the hippocampus increased by 2\% in the aerobic exercise group and decreased 1.4\% in the control group. Moreover, spatial memory was significantly better maintained in the intervention group.

In summary, further studies are needed on these issues, but these new findings on the multifaceted benefits of exercise provide good motivation for programs that encourage exercise therapy, particularly in individuals with or at risk of diabetes.

**References**


