The Importance of Exercise in Patients with Diabetes

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Exercise is considered a cornerstone in the management of diabetes. It is now widely accepted that exercise is an effective modality for the prevention and treatment of type 2 diabetes (T2DM). The purpose of this review is to provide an overview regarding the clinical effects of physical activity, and to discuss some of the physiological and cellular effects of exercise. Also, we will provide some practical recommendations regarding prescribing exercise to subjects with diabetes.

Effects of Exercise on Glycemic Control

Most studies evaluating the effect of exercise on glucose control in T2DM subjects indicate that physical activity alone (in the absence of weight loss) has a modest effect on glycemia. For example, a meta-analysis of several controlled clinical trials performed in subjects with T2DM, which included data from 12 studies of aerobic exercise training and from 2 resistance training studies, showed that post-exercise hemoglobin A1c (HbA1c) levels were lower in the exercise groups compared with the control groups (7.65% vs. 8.31%)[1]. A subsequent meta-analysis of 14 controlled trials evaluating the effect of aerobic and resistance training showed that exercise leads to a reduction in HbA1c by 0.6%[2]. Importantly, these studies indicate that the improvement in glycemic control caused by exercise is independent of any effect on body weight. Nonetheless, exercise functions best as an adjunct to medical nutritional therapy, by maximizing and helping to sustain reductions in body weight, which leads to a further reduction in HbA1c.

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While exercise, even in the absence of weight loss, can lead to a significant improvement in glucose control in subjects with T2DM, the ability of physical activity to improve glycemia in subjects with type 1 diabetes mellitus (T1DM) is less pronounced. The majority of studies evaluating the effect of exercise on glucose control in T1DM have shown no or small reductions in HbA1c[3,4]. Nevertheless, physical activity confers the typical benefits ascribed to exercise in the general population, including improvements in fitness, cardiovascular and pulmonary function, cholesterol levels, and as adjunct to antidepressant therapy. Therefore, exercise should be encouraged in T1DM subjects. As health-care providers, however, the emphasis should be placed on minimizing the risk of exercise-induced complications. Virtually all T1DM subjects are treated with insulin, and physical activity can increase the risk of hypoglycemia. On the other hand, exercise can precipitate ketoacidosis in under-insulinized T1DM subjects. Some recommendations are provided below aimed at reducing the risk of developing hypoglycemia and metabolic decompensation resulting from exercise.

Exercise and Prevention of Type 2 Diabetes

The initial indication that physical activity could help to prevent T2DM came from association analyses. In the Insulin Resistance and Atherosclerosis Study self-reported frequency of exercise directly correlated with insulin sensitivity[5]. Wei et al also found that a low cardiopulmonary fitness level is associated with a high risk of subsequently developing T2DM[6]. More recent interventional studies have proven that physical activity can delay/prevent the onset of T2DM in glucose intolerant individuals. The Malmo study, performed in Sweden, showed that a lifestyle intervention, which included physical activity, reduced the risk of progression to T2DM from impaired glucose tolerance by 50%[7]. The China Da Qing Diabetes Prevention Study, also performed in glucose intolerant individuals, demonstrated that diet, exercise, and diet plus exercise, resulted in 31, 46, and 42% reductions in the risk of developing T2DM, respectively[8]. In the Finnish Diabetes Prevention Study, an intervention which included physical activity and intensive nutritional counseling reduced the progression to T2DM from impaired glucose tolerance by 58%[9]. The more recent Diabetes Prevention Program, performed in glucose intolerant subjects from North America, evaluated the effect of a lifestyle modification (the goals were to achieve a weight reduction of at least 7% and to exercise at moderate intensity for at least 150 minutes per week) and the effect of metformin at a dose of 850 mg twice daily. After 2.8 year of follow-up, 58 and 31% reductions in the risk to T2DM progression were observed in the intensive lifestyle and metformin groups, respectively[10]. Based on these findings, it has been recommended that individuals at high risk of developing T2DM should perform at least 150 minutes per week of moderate intensity physical activity and to undergo medical nutritional therapy aimed at losing 5-10% of body weight[11], with the purpose of reducing their risk to progress to T2DM.

Effects of Exercise on Glucose Homeostasis

The effect of exercise to improve glycemia in T2DM subjects is due to a large extent by improving the capacity of the skeletal muscle to metabolize glucose.

The effects of exercise on skeletal muscle glucose metabolism are complex. These effects can be divided in three (figure 1). One effect is the acute, insulin-independent increase in muscle glucose transport that occurs during a single bout of exercise; second, is the enhancement in insulin sensitivity during the period immediately following exercise; and third, refers to the numerous biochemical and cellular adaptations that take place in the muscle fibers after physical training. Obviously, in "real life", these effects overlap and they all contribute to the improvement in glucose metabolism caused by physical activity.

Skeletal Muscle Insulin Resistance

The skeletal muscle is the main site responsible for insulin-stimulated glucose disposal in the body[12]. The effect of insulin to promote disposal of circulating glucose into muscle depends on the translocation of the GLUT4 glucose transporter from an intracellular compartment to the surface of the myofiber. Muscle insulin resistance refers to a state of decreased responsiveness to circulating concentrations of insulin to stimulate muscle glucose transport. Insulin resistance in muscle is one of the earliest findings in subjects with T2DM and obesity. Insulin action is initiated through the binding of the hormone to the extracellular α subunits of the insulin receptor. This leads to the activation of the intracellular tyrosine kinase domain of the receptor β subunit. This causes a series of transphosphorylation reactions which lead to tyrosine phosphorylation of different substrates, including insulin receptor substrate-1 (IRS 1). When IRS1 tyrosine residues are phosphorylated, these serve as docking for phosphatidylinositol 3-kinase (PI 3-kinase). Insulin-stimulated activation of PI 3-kinase leads to GLUT4 translocation and increased glucose transport. The precise

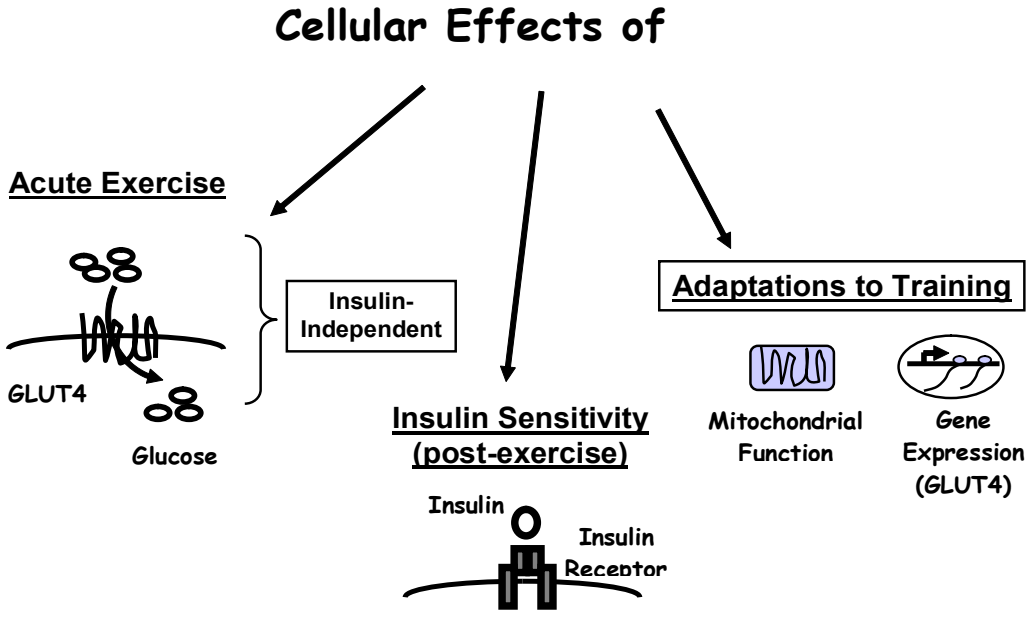

Figure 1. Cellular Effects of Exercise. Physical activity reduces glucose levels by acutely stimulating glucose transport in the muscle (an insulin-independent effect), by enhancing insulin sensitivity in the immediate post-exercise period, and by inducing several adaptations in the muscle.

mechanism by which activation of PI 3-kinase causes GLUT4 translocation is unclear, although several signaling molecules such as phosphoinositide-dependent kinase 1 (PDK1)[13,14], Akt[15,16], protein kinase C (PKC)[17,18], and AS160[19] are thought be involved. In obesity[20] and T2DM[21,22] there is reduced insulin-stimulated GLUT4 translocation[23] which results in impaired muscle glucose disposal[20-22]. This abnormality in glucose transport in insulin resistant muscle has been associated with defects at multiple steps of the insulin signaling cascade, including impaired activation of the insulin receptor, IRS-1, PI 3-kinase[24-28], PKC[18], glycogen synthase[29-32], and AS160 phosphorylation[33]. The underlying cause of these insulin signaling defects is not clear, although accumulating evidence indicates that excessive intramyocellular accumulation of lipid metabolites, such as acyl-CoA, ceramides, and diacylglycerol[34,35], activate kinases which block insulin signaling[36-38]. Taking into account the pivotal role that insulin resistance plays in the pathogenesis of T2DM, developing strategies aimed at restoring insulin signaling defects has been a priority in diabetes prevention and management.

Acute Effect of Exercise

A single bout of exercise is capable of rapidly decreasing blood glucose concentrations in diabetic individuals. The glucose-lowering effect of acute exercise results from increased glucose transport into the contracting myofibers. Acute exercise generally lowers plasma insulin levels, and does not stimulate the insulin signaling cascade[39-41]. Moreover, blockade of the insulin signaling cascade does not affect exercise-stimulated muscle glucose transport[42-45]. These findings clearly establish that acute exercise increases muscle glucose transport through an insulin-independent pathway (figure 2). The cellular intermediaries responsible for contraction-stimulated glucose transport are not fully known. In recent years, activation of the AMP-activated protein kinase (AMPK) has been

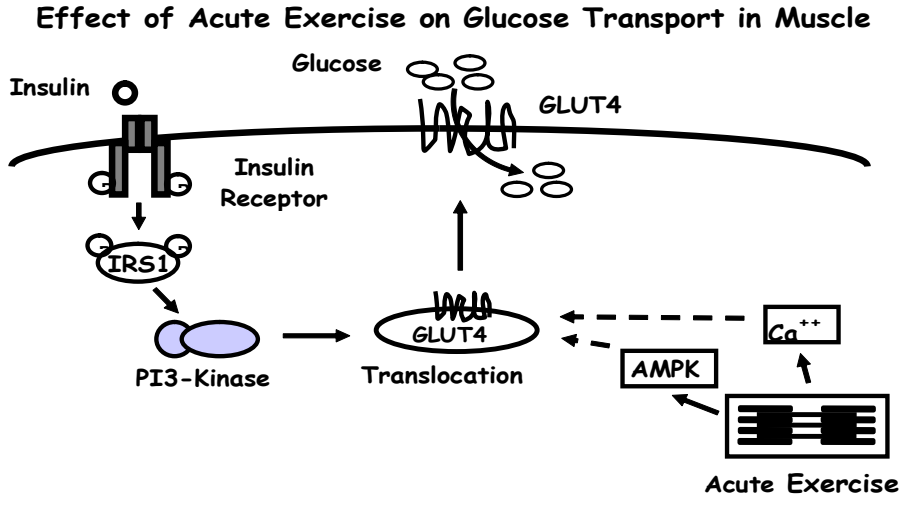

Figure 2. Mechanism of Exercise-induced Glucose Transport in Muscle. Acute exercise increases glucose transport into the contracting myofibers via an insulin-independent pathway. AMPK-and Calcium-regulated pathways have implicated in the mechanism by which acute exercise increases glucose disposal into muscle.

postulated as an important mechanism that mediates increases in glucose transport with exercise. AMPK is an energy-sensing enzyme which functions as a fuel gauge, responding to changes in cellular energy stores[46,47]. When AMPK senses a decrease in high-energy phosphate levels, it switches off ATP-consuming pathways and switches on pathways for ATP synthesis. AMPK activity increases during conditions of ATP such as muscle contraction, hypoxia, and ischemia[48-50]. Exercise rapidly increases the AMP/ATP ratios in skeletal muscle, causing a robust increase in AMPK activity (reviewed in 51). This increase in AMPK activity directly correlates with contraction-stimulated muscle glucose transport[48,52]. Similar to the effects of contraction, chemical activation of AMPK with the compound 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR) increases glucose transport via an insulin-independent mechanism[53,54]. This suggests that AMPK may play an important role in mediating the effects of contraction on muscle glucose transport. Calcium-sensitive mechanisms also have been implicated in contraction-induced glucose transport[55]. Contraction results in increased calcium release from the sarcoplasmic reticulim which results in activation of kinases such as calcimu/calmodulin-dependent protein kinase (CaMK) and PKC which also have been postulated as mediators of glucose transport.

Effect of Exercise on Muscle Insulin Sensitivity

It has been clearly established that muscle insulin sensitivity is enhanced after exercise[21, 56, 57] and affects insulin-sensitive processes such as glucose transport[40, 58, 59] and glycogen synthesis[59,60]. However, the underlying mechanism mediating the increase in muscle insulin sensitivity after exercise is unclear. While acute exercise does not activate proximal insulin signaling events, in the period immediately after exercise, insulin causes a marked increase in phosphotyrosine-associated PI 3-kinase activity, as compared with the effect of insulin alone[45,61]. Yet, in the period after contraction or exercise, insulin-stimulated IRS-1-associated PI 3-kinase activity actually decreases[39, 60] or remains unchanged[45, 61]. This suggests that there is another insulin-stimulated tyrosine phosphoprotein. Studies by Howlett et al suggest that IRS-2 can partially account for the increase in phosphotyrosine-associated PI 3-kinase activity after exercise[62, 63].

Muscle Adaptations Following Physical Training

Exercise training improves insulin-stimulated glucose disposal in T2DM subjects[64]. Whether this is due in part or entirely to reversal of impairments in insulin signaling is unclear. While short term training in insulin resistant subjects[65], and long term training in T2DM individuals[64], improved insulin-stimulated glucose disposal, these programs had no effect the activation of the insulin signaling cascade by insulin, suggesting that training does not reverse abnormalities in insulin signaling. Nonetheless, chronic physical activity leads to several adaptations in muscle, including increases in GLUT4 expression[56, 66], glycogen synthase activity[67], and mitochondrial function[68] (figure 3). These adaptations likely contribute to the insulin-sensitizing effect of exercise training.

Prescribing Exercise to Diabetic Subjects

As mentioned above, exercise is a key element in the treatment of T2DM and also should be encouraged

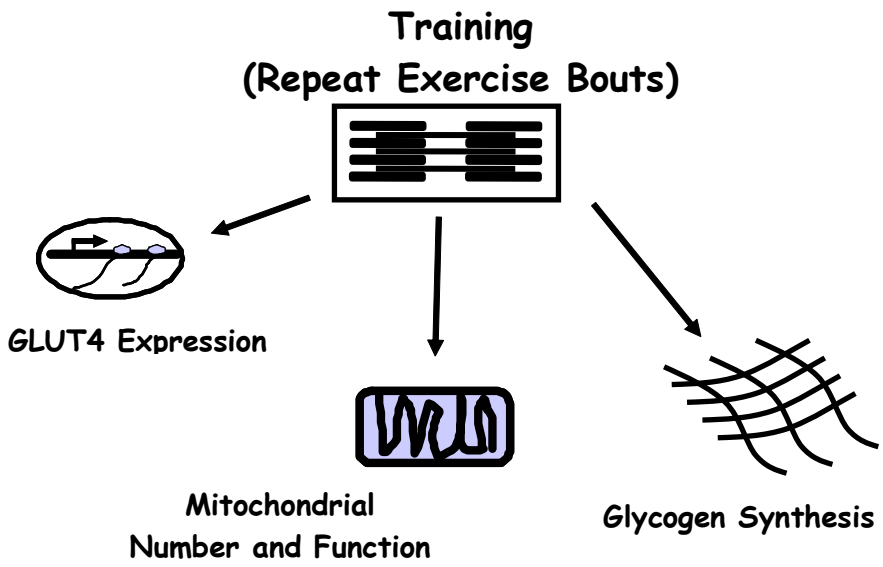

Figure 3. Adaptations to Exercise Training. Repeated bouts of exercise induce several adaptations in the muscle. Some of these adaptations include, increased gene expression of proteins such as the GLUT4 glucose transporter, increased number and function of mitochondria, and increased activity of glycogen synthase. Collectively, these adaptations lead to improvements in glucose metabolism.

in T1DM individuals. Nevertheless, before prescribing exercise, it is prudent to take some precautions. For example, individuals should be evaluated carefully for the presence of macro- and microvascular complications which, in some instances, can be exacerbated by exercise. In addition, there are some contraindications to exercise, including unstable coronary artery disease, uncontrolled hypertension, and active/proliferative retinopathy.

Evaluation of the Cardiovascular System

Before undertaking a physical activity program which involves more than habitual walking, a graded exercise test with electrocardiogram should be considered in certain individuals[11]:

- T1DM and T2DM with age > 35 years
- T2DM with more than 10 years duration (if age > 25 years)
- T1DM with more than 15 years of duration (if age > 25 years)
- Presence of additional risk factors for coronary artery disease
- Presence of microvascular disease (retinopathy or nephropathy)
- Presence of peripheral vascular disease
- Presence of autonomic neuropathy

In subjects that display nonspecific changes in the electrocardiogram in response to exercise, or who have nonspecific ST and T wave changes on the resting electrocardiogram, other exams such as radionuclide stress testing may be indicated.

Peripheral Arterial Disease (PAD)

Some signs and symptoms are indicative of the possible presence of PAD, such as cold feet, intermittent

claudication, decreased or absent pulses, hair loss, and atrophy of subcutaneous tissue. Measurement of the ankle-brachial index (ABI) and doppler ultrasonography are important tools for the documentation of PAD. In subjects in which PAD is detected, screening for coronary artery disease through stress testing is indicated. Once active coronary artery disease has been ruled out, a low-intensity physical activity program which does not elicit pain/claudication is appropriate for subjects with PAD.

Retinopathy

Strenuous physical activity can precipitate serious events such as vitreous hemorrhage and traction retinal detachment in subjects with proliferative diabetic retinopathy or severe non-proliferative diabetic retinopathy. These individuals should avoid anaerobic exercise and activities that increase systolic blood pressure, such as straining, jarring or Valsalva-like maneuvers. A more detailed guideline regarding activities that are acceptable and discouraged in subjects with different severities of retinopathy has been proposed by the American Diabetes Association and the American College of Sports Medicine[69].

Peripheral Neuropathy

Weight-bearing exercise can lead to skin breakdown, infection, and joint destruction in individuals with decreased sensation to pain. Therefore, weight-bearing activities such as prolonged walking, treadmill running, and jogging, are not recommended for subjects with advanced peripheral neuropathy with sensation loss[11]. Other non-weight-bearing exercises, including swimming, cycling, rowing, and arm exercises are more appropriate for these subjects[11].

Autonomic Neuropathy

Autonomic neuropathy can lead to abnormal responses during exercise, such as decreased cardiac responsiveness to exercise, orthostatic hypotension, impaired thermoregulation due to impaired skin blood flow and sweating, and impaired thirst[11]. Diabetic subjects with cardiac autonomic neuropathy are at an increased risk for sudden death and silent myocardial ischemia. Therefore, before undertaking an exercise program, subjects with autonomic neuropathy are generally evaluated for the presence of coronary artery disease with imaging tests such as thallium myocardial scintigraphy.

Nephropathy

Physical activity can increase urinary protein excretion. Nonetheless, there is no evidence of an association between exercise and progression of diabetic nephropathy. Thus, there are no specific exercise restrictions in diabetic individuals with nephropathy.

Exercise Prescription

As discussed above, before initiating an exercise program all diabetic subjects should be evaluated for the presence of micro- and macrovascular complications, and appropriate measures should be taken if these are found. Before initiating an exercise routine subjects should be instructed to first undergo a warm-up period to prepare to body for more intense exercise. Aerobic activity (walking, cycling) for 5-10 minutes at a low intensity is a good way to warm-up. Stretching for 5-10 minutes is also recommended to help decrease the risk of soft tissue injuries. Once the exercise routine is completed, a cool-down period, which is similar to the

warm-up exercise, should be performed for about 5-10 minutes to gradually bring the heart rate down to the pre-exercise level.

To maximize the metabolic and cardiovascular benefits of exercise it is recommended that subjects with T2DM perform aerobic exercise for a minimum of 150 minutes per week at a moderate intensity[11]. This level of exercise intensity usually is defined as 50-70% of the maximum heart rate. Alternatively, subjects can exercise at a high intensity (>70% of maximum heart rate) for at least 90 minutes per week. To calculate the maximum heart rate one deducts the subjects' age from 220. The exercise should be distributed over a minimum of 3 days per week. While there is substantial information indicating that aerobic exercise is beneficial for insulin resistant subjects, there is increasing evidence that resistance training also has beneficial effects on glucose homeostasis. If there are no contraindications to resistance exercise, insulin-resistant subjects should be encouraged to perform resistance exercise three times a week, targeting all major muscle groups. The assistance of exercise physiologists and certified fitness instructors is valuable to help adjust and monitor the exercise.

Physical activity promotes free fatty acid release from the adipose tissue. Therefore, exercise can precipitate ketosis, especially in T1DM subjects who are underinsulinized. In general, exercise should be postponed in any subject whose blood glucose is > 300 mg/dL, and in subjects with blood glucose > 250 mg/dL in the presence of ketosis. Exercise also can induce hypoglycemia in subjects that use sulfonylureas and/or insulin. If the subject takes sulfonylureas and/or insulin, 10-15 g of carbohydrates should be ingested before initiating exercise when the blood glucose level is less than 100 mg/dL. Typically, the insulin dosage also is reduced to help avoid hypoglycemia. These are the instances in which reductions in insulin dose are recommended: exercise for more than 30 minutes, exercise performed during time of peak insulin action, strenuous exercise, and exercise performed to promote weight loss. Reductions in insulin dose by 5 to 30% are recommended, depending on the intensity and duration of exercise[11]. For brief (<30 min) exercise of any intensity, adjustments are usually not needed. Reductions of 5-10% in insulin dose are recommended for low and moderate intensity exercise of intermediate (30-60 min) duration. Reductions of 20% are suggested for moderate intensity exercise of long (>60 min) duration and for high intensity exercise of more than 30 min. Reductions of ~30% may be necessary for subjects that exercise for more than 60 min at a high intensity. The timing of exercise is also important to determine which type of insulin should be adjusted. For subjects that exercise in the morning, the A.M. dose of short acting (Regular) or rapid acting (lispro, aspart, glulilsine.) insulin is reduced. In subjects who will exercise in the afternoon, the P.M. dose of intermediate acting (NPH) insulin is reduced. In general, there is no need to decrease the dosage of long acting (glargine, detemir) insulin.

Summary

Exercise is an essential component in the treatment and prevention of T2DM. Even though exercise per se generally does not lead to significant improvements in glycemia in subjects with T1DM, physical activity does provide other physical and psychological benefits in these individuals. Exercise reduces glucose levels by acutely stimulating glucose transport and metabolism in the

muscle (an insulin-independent effect), by enhancing insulin sensitivity in the immediate post-exercise period, and by inducing several adaptations in the muscle which improve glucose metabolism (increases GLUT4 content and mitochondrial function). Health care providers should encourage exercise in diabetic subjects, but need to first evaluate for the presence of micro- and macro-vascular complications, and take certain measures if these are detected. Finally, one should instruct the subject not to exercise if there is evidence of metabolic decompensation (hyperglycemia, ketosis) and educate them about the measures that will reduce the risk of exercise-induced hypoglycemia.

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